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ANNEXURES

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Betel nut and tobacco chewing; potential risk factors of cancer of oesophagus in Assam, India

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Summary Cancer of the oesophagus is the most commonly diagnosed cancer in males in Assam, in north-eastern India, and ranks second for females. The chewing of betel nut, with or without tobacco and prepared in various ways, is a common practice in the region and a case–control study has been designed to study the pattern of risk associated with different ways of preparing and chewing the nuts. 358 newly diagnosed male patients and 144 female have been interviewed together with 2 control subjects for each case chosen at random from among the attendants who accompanied patients to hospital. There were significant trends in risk ratios associated with the frequency of chewing each day, with the duration of chewing in years and with the age at which the habit was started that were apparent for both males and females and which remained significant after allowance was made for other known risk factors, notably tobacco smoking and alcohol consumption. The adjusted ratios, in comparison with non-chewers, were 13.3 M and 5.7 F for chewing more than 20 times a day, 10.6 M and 7.2 F for persons who had chewed for more than 20 years and 10.3 M and 5.3 F for those who had started before the age of 20. Among the different combinations of ingredients that were chewed the adjusted odds ratios were highest for those who had been using fermented betel nut with any form of tobacco (7.1 M and 3.6 F). The risk associated with tobacco smoking and alcohol consumption, which are high in some parts of the world, were less in Assam than those associated with the chewing of betel nut. © 2001 Cancer Research Campaign http://www.bjcancer.com

Keywords: oesophageal cancer; betel nut chewing; tobacco chewing; Assam

Cancer data, from both population-based and hospital-based cancer registries in India, showed the highest incidence of oesophageal cancer to occur in Assam in the north east of the country, followed by Bangalore and Bombay (NCRP, 1984–1989). In Western populations, oesophageal cancer (especially amongst men) seems to be mostly due to a combination of tobacco smoking and alcohol consumption (Tuyns et al, 1977). Poor nutrition may increase susceptibility in many parts of the world and various local factors such as very hot liquids, and the consumption of pyrolysed products such as opium dross in Iran or dottle from the stem of tobacco pipes in South Africa seem to compound the risk and to produce very high rates even in areas where tobacco smoking and alcohol consumption are rare (Munos and Day, 1997; Kinjo et al, 1998). Aetiological studies in India have quantified the risks of oesophageal cancer associated with betel nut chewing and the consumption of alcohol and tobacco in Bombay and Bangalore (Jussawalla, 1971; Jussawalla and Deshpande, 1971; Nandakumar et al, 1996) but no such investigation has been made in Assam where certain ingredients and methods of preparetion of the betel nut quid differ from those common in other parts of India.

In Assam 'raw' ('green'), 'ripe' ('red') and 'fermented' ('underground', 'processed') betel nuts are all chewed. The latter, known locally as 'Bura Tamul', is prepared in a 4–5 foot hole in the ground where ripe betel nuts are left for 3–4 months covered with bark from the betel tree, cow dung and soil. During the period of fermentation the outer fibrous shell of the nuts decays. Chopped or crushed nuts at the different stages of ripening or decay are wrapped in betel leaf and are chewed with or without tobacco. 'Dhapat', dried tobacco leaf that may be treated with lime (calcium oxide), is sometimes added to the betel nut in the quid while a mixture of finely cut and dried, 'raw' or 'ripe' betel nut ('Supari') and finely cut, scented tobacco ('Zarda') is also chewed. In Assam a larger proportion of betel nut is included in the quid and fewer leaves than in the 'pan' which is chewed in Bombay and which includes only a very small quantity of betel nut that is always processed ('fermented'). As in Assam, the Bombay quid may also include tobacco. Dried tobacco chewed alone in Assam is known locally as 'Chadha'. Whatever the composition of the quids, they are usually retained in the mouth for about 20 to 25 minutes but occasionally the mixture may be retained in the mandibular groove during sleep (Bhansle et al, 1979).

A case–control study has been carried out in collaboration with the Dr. Bhubaneswar Barooah Cancer Institute (BBCI) in Guwahati (the largest city in Assam) to investigate the risks associated with the various chewing habits that are practised in the state and to estimate the effect independently of tobacco and alcohol consumption.

METHODS

The BBCI is one of the regional cancer treatment and research centres in India and provides treatment for patients from the 7 north-eastern states, of which Assam is the largest, (total population 31.4 million (1991 Census)). The study was conducted from July 1997 to June 1998 during which period 3720 cases of all types of cancer were registered and 590 new cancer of the oesophagus cases. All suspected cases of cancer of the oesophagus were directed to the social investigator(s) of the project for interview

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before referral to the medical consultant. At the same time information was collected from the attendants who accompanied cancer patients and who provided a readily available and cooperative source of controls from the same socio-economic background as the patients. A final group of matched controls (2 for each patient) were selected by random pairing of the cases with subjects from the pool of controls after matching for sex and age (within ± 5 years).

Only cases confirmed by microscopy and for whom the oesophagus was the primary site of cancer were included in the study. Out of the total cases 93.2% had squamous cell carcinoma, 5.2% had adenocarcinoma and 1.6% other types of cancers. Patients with advanced disease (20), where the tumour had spread so as to obscure the primary site, patients with recurrent cancer (20) and those who were too elderly (12) and who refused to be interviewed (31) were excluded from the study. A total of 502 patients were finally included (358 men and 144 women).

Details of age and sex and various demographic variables were collected in the course of the interviews as well as details of personal habits that included tobacco smoking and the consumption of alcohol as well as chewing practices. A pre-designed, pretested questionnaire was designed specifically for the study. The selection of controls from among the persons bringing the patients to hospital is likely to have minimised differences of socio-economic conditions and also of adequacy of nutrition between the patients and controls and these have not been investigated further.

Analysis of the data was by multiple logistic regression (Breslow and Day, 1980) from which ratios of relative risk (odds ratio = $\exp(\beta)$) and standard errors were derived for betel nut chewing, tobacco smoking and alcohol consumption (with or without stratified adjustment of each factor for the other 2, potentially confounding, habits). In the multifactorial models, the 'other' factors were fitted before the exposure factor of interest.

Estimation of the proportion of cases of a disease attributable to exposure to a particular factor has been done by calculating the 'aetiological fractions' for each variable (Levin, 1953).

RESULTS

The adjusted risks associated with the chewing of betel nut were higher than those for tobacco smoking and alcohol consumption at all levels of consumption (Tables 1–3). However, for all 3 habits there were significantly elevated ORs at high levels of intake or after a long duration of consumption and clear indications of dose–response effects for all 3 habits. The adjusted ORs for persons who chewed more than 20 times a day in comparison with non-chewers were 13.3 for males and 8.4 for females ($P < 0.001$ for both comparisons) (Table 1) whereas the adjusted ORs for smoking more than 20 times a day were 3.7 and 2.5 ($P < 0.001$ and $P = 0.03$) (Table 2) and the adjusted ORs for the highest level of alcohol consumption were 4.8 ($P = 0.05$) for males (drinking more than 10 times a week) and 3.6 ($P = 0.006$) for females (drinking 5–10 times a week) (Table 3).

65% of men in the control population and 38% of women were chewers but only 24% of the men and 3% of the women smoked tobacco and only 24% and 4% consumed alcoholic drinks. In view of the lower population-exposure and of the lower adjusted ORs for the smoking and drinking habits, compared with those for chewing, the detailed results are tabulated (Tables 2 and 3) but are not mentioned further in the text.

Table 1 Risk estimates of betelnut chewing habits and dose–response parameters with or without adjustment for smoking and alcohol

Chewing Characteristics	Male					Female				
	Ca/Co	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value	Ca/Co	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value
Non-chewer	30/249	1				34/153	1			
Chewers	328/457	5.8 (2.3–10.2)	< 0.001	2.6 (1.3–7.4)	0.045	110/135	3.7 (1.6–10.3)	< 0.001	1.9 (0.02–7.8)	0.062
Frequency (per day)										
1–4	60/169	2.9 (1.3–8.4)	< 0.01	2.3 (0.2–8.4)	0.041	25/60	1.9 (0.89–5.3)	0.093	1.5 (0.07–5.7)	0.093
5–10	71/170	3.5 (1.9–10.4)	< 0.001	2.5 (0.7–9.6)	0.021	17/34	2.3 (1.02–8.4)	< 0.05	1.7 (0.02–6.4)	0.072
11–20	80/77	8.6 (3.9–15.3)	< 0.001	4.8 (1.3–8.4)	< 0.001	38/25	6.8 (2.5–13.8)	< 0.001	2.3 (0.5–6.5)	0.031
20 +	117/51	19 (9.4–28.2)	< 0.001	13.3 (4.5–24.6)	< 0.001	30/16	8.4 (4.3–19.6)	< 0.001	5.7 (2.5–17.6)	< 0.001
Duration (years)										
<10	51/180	2.4 1.1–8.2	< 0.05	1.8 (0.09–7.1)	0.083	25/71	1.6 (1.2–6.8)	0.087	1.2 (0.07–5.2)	0.143
10–19	64/165	3.2 1.8–10.5	< 0.001	1.9 (0.06–5.5)	0.068	42/49	3.9 (1.4–8.5)	< 0.01	1.7 (0.03–6.1)	0.082
20 +	213/122	14.5 5.6–23.9	< 0.001	10.6 (5.6–17.3)	< 0.001	43/15	12.9 (2.0–18.8)	< 0.001	7.2 (2.6–14.2)	< 0.001
Age start (years)										
<20	154/90	14.2 (5.4–26.3)	< 0.001	10.3 (3.1–19.7)	< 0.001	49/27	8.2 (2.5–20.8)	<0.001	5.3 (2.1–18.2)	< 0.001
20–29	142/178	6.6 (2.3–12.4)	< 0.001	4.8 (1.4–9.5)	< 0.001	40/30	6 (1.1–15.6)	<0.001	3.9 (1.5–7.8)	< 0.001
30+	32/199	1.3 (0.8–5.8)	0.075	0.8 (0.07–4.2)	0.371	21/78	1.2 (0.9–6.7)	0.064	0.5 (0.02–6.1)	0.561

Ca = cases; Co = controls; OR = odds ratio

Table 2 Risk estimates of smoking habits and dose–response parameters with or without adjustment for chewing and alcohol

Smoking characteristics	Male					Female				
	Ca/Co	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value	Ca/Co	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value
Non-smokers	198/544	1				129/278	1			
Smokers	160/172	2.6 (1.2–8.1)	0.031	1.2 (0.03–6.5)	0.07	15/10	3.2 (1.9–10.5)	0.04	1.8 (0.05–5.8)	0.34
Frequency (per day)										
1–4	20/50	1.1 (0.05–4.5)	0.72	0.85 (0.04–3.5)	0.46	3//3	2.2 (0.9–9.4)	0.058	1.6 (0.3–4.5)	0.43
5–10	35/48	2 (0.02–5.8)	0.31	1.3 (0.03–3.7)	0.68	5//4	2.7 (1.3–10.4)	0.052	1.8 (0.8–6.2)	0.34
11–20	47/41	3.1 (1.5–8.6)	0.006	2.5 (1.4–7.5)	0.007	4//2	4.3 (1.8–15.8)	< 0.001	2.1 (0.6–10.3)	0.04
20 +	58/33	4.8 (2.5–12.5)	< 0.001	3.7 (1.8–8.5)	< 0.001	3//1	6.4 (3.6–20.5)	< 0.001	2.5 (0.8–8.5)	0.03
Duration (years)										
<10	38/68	1.5 (0.4–6.5)	0.65	0.68 (0.04–3.5)	0.69	5//6	1.8 (0.4–4.2)	0.48	0.6 (0.03–5.1)	0.15
10–19	56/53	2.9 (0.8–8.3)	0.07	1.5 (0.4–4.6)	0.31	7//3	5 (2.6–12.2)	< 0.001	2.7 (0.9–10.8)	0.03
20 +	66/51	3.6 (1.4–11.5)	0.005	2.8 (0.3–6.5)	0.09	3//1	6.5 (3.2–18.3)	< 0.001	3.2 (1.5–9.5)	0.007
Age at start (years)										
< 20	84/45	5.1 (1.4–14.50)	< 0.001	4.4 (1.8–16.3)	< 0.001	6//2	6.5 (2.3–14.5)	< 0.001	2.3 (0.6–9.2)	0.02
20–29	46/56	2.2 (0.6–9.5)	0.15	1.7 (0.7–8.5)	0.59	6//3	4.3 (1.8–11.4)	< 0.001	2.1 (0.9–8.7)	0.004
30 +	30/71	1.2 (0.04–5.6)	0.35	0.8 (0.03–4.5)	0.76	3//5	1.3 (0.9–8.8)	0.46	0.4 (0.07–3.9)	0.48
Type of smoking										
Bidi	72/55	3.6 (1.8–9.5)	0.007	2.8 (1.3–7.4)	0.76	7//3	5 (2.1–12.6)	< 0.001	2.4 (1.3–8.3)	0.006
Cigarette	56/73	2.1 (1.3–8.6)	0.35	1.5 (0.8–6.3)	0.46	5//3	3.6 (1.4–8.9)	0.004	1.8 (0.06–8.6)	0.08
Others	32/44	1.9 (0.8–6.3)	0.61	1.2 (0.5–7.8)	0.58	3//4	1.6 (0.7–4.5)	0.21	0.7 (0.07–6.3)	0.43

Consideration of the duration of chewing habits and of the age at which the habit was taken up (Table 1) shows adjusted ORs of 10.6 and 12.9 for men and women who had been chewing for more than 20 years and of 10.3 and 5.3 for those who started the habit before the age of 20 ($P < 0.001$ in each instance).

The risks associated with the different types of quid that are chewed are shown in Table 4. The highest adjusted risks for men are associated with the chewing of betel nut together with tobacco (both Dhapat (OR 7.1, $P < 0.01$ where fermented betel nut is used and OR 3.1, $P < 0.01$ where green or red betel nut is used) and Zarda (OR 6.6, $P < 0.001$)). For men who chew tobacco alone (Chadha) the risk is also elevated (OR 4.9, $P < 0.001$). The pattern for women is similar but not identical. However, the numbers are smaller than those for men and so the ORs are likely to be less stable.

For both men and women the adjusted risks associated with the chewing of betel nut without tobacco are lower than those where tobacco is used, especially when the tobacco is added to fermented nut (OR 7.1, $P < 0.01$ for men and 3.6, $P < 0.001$ for women). The ORs associated with taking just green or red betel nut are 1.9 for males and 0.5 for females, neither differing significantly from the risk in non-chewers. For chewers of fermented betel nut without tobacco there is a slightly raised risk for males (OR 2.3, $P < 0.05$) and no elevation of risk for females (OR 0.8, $P = 0.351$).

The risks for persons who spit out the juices of the quid contrasted with those who swallow them and for those who retain the quid in the mouth for longer periods of time are given in Table 5. For males there is a clear trend in increasing risk from those who spit or swallow sometimes (adjusted ORs of 1.4 and 1.6 that are not significantly different from the risk in non-chewers) to those who both swallow the juices and retain the quid in the mouth (OR 6.3, $P < 0.001$). For women the pattern is less clear but the numbers who retain the quid in the mouth with or without swallowing are very few.

The combined effect of betel nut chewing and smoking as well as chewing and alcohol drinking are shown in Table 6 and Table 7. The highest risks for men (OR = 15.3) and women (OR = 27.4) were found to be associated when fermented betel nut was used in combination with tobacco and bidi smoking. A combination of fermented betel nut with tobacco and non-commercial alcoholic drinks showed a highly elevated risk (OR = 18.5 M and OR = 13.5 F).

The risks for persons who practice different combinations of the three habits are given in Table 8. For both men and women, the highest risks are among those who practice all three, chewing betel nut, smoking tobacco and consuming alcoholic drinks, (ORs 13.6 and 11.8); and then among those who chew and smoke (ORs 8.4 and 8.1). The ORs for chewing and drinking are also elevated but to a slightly lesser extent (ORs 5.5 and 7.6). The risks associated with the practice of just one of the habit again show chewing (ORs 3.4 for men and 3.5 for women) with a higher risk than smoking (ORs 1.9 and 2.5) or drinking (ORs 1.4 and 1.7).

Table 3 Risk estimates of alcohol habits and dose–response parameters with or without adjustment for chewing and smoking

Alcohol characteristics	Male					Female				
	Ca/Co	OR (95% CI)	P value	Adj OR (95% CI)	P value	Ca/Co	OR (95% CI)	P value	Adj OR (95% CI)	P value
Non-alcohol drinker	189/544	1				126/276	1			
Alcohol drinker	169/172	2.8 (0.9–6.3)	0.085	2.2 (0.8–7.5)	0.15	18/12	3.3 (1.5–9.5)	0.04	1.3 (0.07–7.6)	0.06
Frequency (per week)										
< 1	31/56	1.6 (0.06–4.8)	0.073	1.5 (0.05–9.2)	0.27	4//4	2.2 (0.8–5.6)	0.058	1.6 (0.05–4.5)	0.08
2–4	37/55	1.9 (0.06–6.3)	0.065	1.4 (0.07–7.2)	0.23	6//5	2.6 (0.4–7.3)	0.052	1.5 (0.06–6.2)	0.08
5–10	63/43	4.2 (1.8–10.6)	0.009	2.8 (0.06–8.3)	0.082	8/3	5.8 (2.4–11.7)	< 0.001	3.6 (0.9–6.3)	0.006
10 +	38/18	6.1 (2.7–14.8)	< 0.001	4.8 (1.9–11.7)	0.005	0/0	0	0	0	0
Duration (years)										
<10	42/70	1.7 (0.7–5.6)	0.61	1.3 (0.08–8.5)	0.72	7//6	2.6 (0.4–6.3)	0.004	1.5 (0.09–5.4)	0.31
10–19	69/76	2.6 (0.9–7.2)	0.04	2.1 (0.4–9.3)	0.08	5//4	2.7 (0.8–7.8)	0.002	1.3 (0.03–8.4)	0.53
20 +	58/26	6.4 (2.6–14.5)	< 0.001	5.1 (0.1–7.5)	< 0.001	6//2	6.6 (3.1–16.3)	< 0.001	3.1 (0.2–12.2)	0.006
Age at start (years)										
< 20	47/14	9.7 (3.6–20.7)	< 0.001	7.3 (2.8–16.7)	< 0.001	4//1	8.8 (3.2–18.5)	< 0.001	3.2 (1.4–8.2)	0.007
20–29	52/56	2.7 (0.8–8.3)	0.002	1.8 (0.9–5.4)	0.075	6//4	3.3 (1.3–11.6)	0.006	1.7 (0.02–9.4)	0.46
30 +	70/102	1.9 (0.8–4.5)	0.07	1.3 (0.3–4.6)	0.15	8//7	2.5 (0.9–6.8)	0.031	1.4 (0.03–6.1)	0.51
Type of alcohol										
Non-commercial alcoholic drinks	63/40	4.5 (2.6–6.0)	< 0.001	2.4 (0.5–9.6)	0.007	9//5	3.9 (1.7–6.8)	0.003	1.9 (0.07–7.5)	0.09
Process drinks	52/64	2.3 (0.9–4.2)	0.04	1.8 (0.5–6.3)	0.08	5//4	2.7 (0.8–5.9)	0.008	1.5 (0.02–9.5)	0.35
NCAD + PAD	54/68	2.2 (0.7–3.3)	0.05	1.6 (0.4–7.5)	0.09	4//3	2.9 (1.6–6.7)	0.006	1.7 (0.06–5.4)	0.62

NCAD = Non-commercial alcoholic drinks; PAD = Process alcoholic drinks.

Table 4 Risk estimates of different habits of betel nut chewing with additives

Chewing practices	Male					Female				
	Ca/Co	OR (95% CI)	P value	Adj OR (95% CI)	P value	Ca/Co	OR (95% CI)	P value	Adj OR (95% CI)	P value
Non-chewer	30/249	1				34/153	1			
Chadha	68/84	6.7 (2.7–16.9)	< 0.001	4.9 2.8–11.6	< 0.001	15/8	8.4 (2.4–18.8)	<0.001	3.4 1.3–5.6	<0.001
BL + R/G BN	50/120	3.5 (1.3–9.8)	< 0.001	1.9 0.08–6.3	0.089	20/56	1.6 (0.9–8.5)	0.073	0.5 0.03–3.7	0.422
BL + UG BN	65/132	4.1 (2.2–10.5)	< 0.001	2.3 0.7–8.4	< 0.05	15/32	2.1 (1.6–10.2)	0.062	0.8 0.06–4.6	0.351
BL + R/G BN + D	40/62	5.4 (2.4–15.2)	< 0.001	3.1 1.3–6.7	< 0.01	25/14	8 (2.2–13.6)	<0.001	4.3 1.5–9.7	<0.001
BL + UG BN + D	82/54	12.6 (5.7–23.8)	< 0.001	7.1 3.5–6.7	< 0.01	25/16	7 (3.2–17.2)	<0.001	3.6 1.4–9.2	<0.001
BL + S BN + Z	23/15	12.7 (5.8–26.3)	< 0.001	6.6 2.8–10.5	< 0.001	10//9	5 1.6–11.4	<0.001	2.2 0.4–6.3	<0.05

BL = Betel leaf; R/G = Red/green; UG = Underground; BN = Betel nut; D = Dhapat; S = Supari; Z = Zarda.

Table 5 Risk estimates of practice of spitting, keeping in mouth and swallowing of betel quid after chewing

Type of chewing	Male					Female				
	Ca/Co	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value	Ca/Co	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value
Non-chewer	30/249	1				34/153	1			
Spitting	9//38	1.9 (1.2–5.7)	0.072	1.4 (0.06–5.2)	0.091	25/30	3.8 (1.5–7.3)	< 0.001	1.7 (0.09–5.6)	0.062
Partially swallow	34/85	3.3 (1.8–9.6)	< 0.001	1.6 (0.04–6.2)	0.167	30/46	2.9 (1.2–8.6)	< 0.01	3.1 (1.2–9.6)	< 0.001
Swallowing	72/105	5.7 (2.3–8.4)	< 0.001	3.9 (1.3–9.2)	< 0.001	45/50	4.1 (2.2–10.6)	< 0.001	4.3 (1.9–8.6)	< 0.001
Keeps in mouth	35/35	8.3 (3.2–11.4)	< 0.001	5.9 (2.3–11.9)	< 0.001	8//7	5.1 (2.6–14.2)	< 0.001	3.1 (1.2–9.8)	< 0.01
Swallow + Keeps in mouth	92/80	9.5 (3.2–15.9)	< 0.001	6.3 (1.4–13.2)	< 0.001	2//2	4.5 (1.6–9.2)	< 0.001	2.9 (1.6–7.4)	< 0.01

Table 6 Risk estimates of different combinations of betel nut chewing and smoking (adjusted for alcohol)

	Male					Female				
	Ca/Co	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value	Ca/Co	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value
NCh & NSm	26/227	1				31/142	1			
Chadha	20/39	4.5 (2.7–8.3)	0.003	3.2 (1.6–9.5)	0.004	8//5	7.3 (2.4–13.5)	< 0.001	6.2 (2.4–12.1)	< 0.001
Chadha+BSm	12//17	6.2 (2.6–10.4)	0.001	5.7 (1.8–10.3)	0.01	4//3	6.1 (3.2–12.9)	< 0.001	5.1 (1.9–10.3)	< 0.01
Chadha+CSm	11//19	5.1 (2.4–9.8)	0.001	4.3 (2.1–9.6)	0.003	3//3	4.6 (2.7–10.3)	0.004	3.7 (1.8–6.5)	0.006
BL+R/GBN	22/63	3 (1.5–7.2)	0.02	2.4 (1.2–5.5)	0.09	12//40	1.4 (0.4–5.6)	0.4	0.5 (0.01–4.3)	0.52
BL+R/GBN+BSm	20/35	5 (2.3–10.6)	< 0.001	4.3 (2.6–8.3)	0.01	6//10	2.7 (1.3–7.5)	0.07	1.4 (0.02–5.2)	0.41
BL+R/GBN+CSm	14/30	4.1 (1.8–10.8)	< 0.001	3.2 (1.8–6.7)	0.005	4//10	1.8 (0.6–6.3)	0.5	0.8 (0.06–3.8)	0.66
BL+UGBN	34/68	4.4 (1.8–9.3)	0.002	2.6 (1.4–6.5)	0.008	10//26	1.8 (0.3–4.5)	0.31	1.2 (0.05–4.6)	0.48
BL+UGBN+BSm	20/34	5.1 (2.1–10.5)	< 0.001	4.3 (2.3–9.8)	0.007	3//5	2.7 (1.6–7.6)	0.15	1.9 (0.2–5.7)	0.26
BL+UGBN+CSm	19/37	4.5 (2.3–8.6)	< 0.001	3.8 (1.7–10.5)	0.006	2//4	2.3 (1.5–9.6)	0.21	1.5 (0.3–7.6)	0.37
BL+R/GBN+D	20/32	5.5 (1.6–9.8)	< 0.001	4.8 (2.6–10.3)	< 0.001	16/15	4.9 (2.5–9.6)	< 0.001	3.8 (1.3–8.5)	0.004
BL+R/GBN+D+BSm	17/20	7.4 (2.1–11.3)	< 0.001	6.5 (2.8–11.6)	< 0.001	7//3	10.7 (3.3–13.7)	< 0.001	8.5 (2.6–16.3)	< 0.001
BL+R/GBN+D+CSm	12//19	5.5 (1.3–10.4)	< 0.001	5 (1.8–10.8)	< 0.001	3//2	6.9 (2.8–12.6)	< 0.001	4.5 (1.6–8.4)	< 0.001
BL+UGBN+D	35/20	15.3 (7.1–23.8)	< 0.001	9.5 (3.3–20.8)	< 0.001	12//6	9.2 (3.6–15.4)	< 0.001	6.6 (2.4–11.5)	< 0.001
BL+UGBN+D+BSm	26/9	25.2 (10.3–31.2)	< 0.001	15.3 (4.6–28.7)	0.003	8//1	36.6 (18.5–48.6)	< 0.001	27.4 (14.3–41.5)	< 0.001
BL+UGBN+D+CSm	25/14	15.6 (6.3–21.2)	< 0.001	5.1 (2.4–17.6)	0.006	5//1	22.9 (7.5–42.7)	< 0.001	16.1 (8.1–27.3)	< 0.001
BL+SBN+Z	12//15	7 (2.6–13.3)	< 0.001	5.6 (2.3–10.3)	< 0.001	5//7	3.3 (1.7–8.6)	0.03	1.9 (0.4–6.5)	0.28
BL+SBN+Z+BSm	6//8	6.5 (2.7–12.2)	< 0.001	4.1 (1.8–9.7)	0.005	3//3	4.6 (2.3–10.5)	0.02	2.8 (1.3–7.6)	0.09
BL+SBN+Z+CSm	7//10	6.1 (2.3–13.5)	<0.001	3.7 (1.4–7.6)	0.02	2//2	4.5 (1.9–12.6)	0.005	2.4 (1.1–9.4)	0.04

NCh = Non chewer; NSm = Non smoker; BSm = Bidi smoker; CSm = Cigarette smoker; BL = Betel leaf; BN = Betel nut; R/G = Raw/Green; UG = Underground; D = Dhapat; Z = Zarda.

Table 7 Risk estimates of different combinations of betel nut chewing and alcohol drinking (adjusted for smoking)

	Male					Female				
	Ca/Co	OR (95% CI)	P value	Adj OR (95% CI)	P value	Ca/Co	OR (95% CI)	P value	Adj OR (95% CI)	P value
NCh & NAD	22/218	1				28/149	1			
Chadha	16/35	4.5 (1.6–10.3)	0.003	3.8 (1.9–8.5)	0.003	7//6	6.2 (2.4–15.9)	<0.001	5.8 (2.1–12.4)	< 0.001
Chadha+NCAD	19/28	6.7 (2.8–14.4)	< 0.001	6.1 (2.6–12.8)	0.004	4//3	7.1 (2.8–19.7)	< 0.001	6.3 (2.4–14.3)	< 0.001
Chadha+PA	15/23	6.5 (2.4–15.2)	< 0.001	5.3 (2.2–13.1)	0.002	3//3	5.3 (1.5–16.3)	< 0.001	4.4 (1.7–9.5)	< 0.001
BL+R/GBN	21/53	3.9 (1.4–12.6)	0.008	2.8 (1.3–7.5)	0.06	10//27	2 (0.7–8.5)	0.04	1.4 (0.3–6.5)	0.24
BL+R/GBN+NCAD	26/41	6.3 (2.5–11.4)	0.002	5.6 (2.2–9.6)	0.004	7//20	2 (0.3–10.6)	0.08	1.6 (0.2–9.3)	0.41
BL +R/GBN+PA	14/25	5.5 (1.9–10.8)	< 0.001	4.2 (1.8–10.5)	< 0.001	6//12	2.7 (1.1–9.5)	< 0.01	1.7 (0.6–8.5)	0.15
BL+UGBN	22/58	3.8 (1.2–9.6)	0.004	3.1 (1.6–8.5)	0.002	9//15	3.2 (1.8–11.5)	< 0.001	2.4 (0.9–7.2)	< 0.01
BL+UGBN+NCAD	39/46	8.4 (3.4–14.5)	< 0.001	6.2 (2.4–11.3)	< 0.001	7//10	3.7 (1.3–10.7)	< 0.001	2.1 (1.3–5.4)	0.04
BL+UGBN+PA	20/41	4.8 (1.6–11.2)	0.001	3.6 (1.7–9.5)	< 0.001	5//9	3 (1.5–8.6)	< 0.001	1.9 (0.4–7.5)	0.09
BL+R/GBN+D	21/38	5.5 (2.3–11.8)	< 0.001	5 (1.7–10.6)	< 0.001	8//8	5.3 (1.7–10.8)	< 0.001	4.2 (1.6–10.5)	< 0.001
BL+R/GBN+D+ NCAD	20/26	7.6 (2.8–12.3)	< 0.001	7.3 (2.5–12.8)	< 0.001	7//6	6.2 (2.3–14.2)	< 0.001	5.6 (2.3–12.4)	< 0.001
BL+R/GBN+D+PA	12/22	5.4 (1.8–10.6)	< 0.001	4.8 (1.7–9.3)	< 0.001	5//3	8.9 (2.4–19.8)	< 0.001	7.3 (2.6–10.3)	< 0.001
BL+UGBN+D	26/20	12.9 (3.2–18.5)	< 0.001	10.3 (3.6–20.8)	< 0.001	12//5	12.8 (4.2–20.8)	< 0.001	10.4 (2.6–18.5)	< 0.001
BL+UGBN+D+ NCAD	31/14	21.9 (7.5–32.4)	< 0.001	18.5 (5.6–27.3)	< 0.001	9//3	16 (8.3–26.4)	< 0.001	13.5 (3.1–20.6)	< 0.001
BL+UGBN+D+PA	12//15	7.9 (1.9–14.5)	< 0.001	6.3 (2.5–14.7)	< 0.001	5//2	13.3 (5.4–21.6)	< 0.001	10.6 (3.2–18.2)	< 0.001
BL+SBN+Z	9//6	14.9 (4.6–22.8)	< 0.001	8.4 (2.6–17.5)	< 0.001	7//4	9.3 (3.6–18.5)	< 0.001	8.4 (3.1–16.3)	< 0.001
BL+SBN+Z+NCAD	6//3	19.8 (5.3–28.6)	< 0.001	12.1 (4.3–21.4)	< 0.001	3//2	8 (2.4–17.3)	< 0.001	6.5 (2.7–14.6)	< 0.001
BL+SBN+Z+PA	7//4	17.3 (4.2–24.5)	< 0.001	13.6 (4.6–22.5)	< 0.001	2//1	10.6 (3.5–20.4)	< 0.001	7.3 (1.8–15.3)	< 0.001

NC = Non chewer; NAD = Non alcohol drinker; BL = Betel leaf; BN = Betel nut; R/G = Raw/Green; UG = Underground; D = Dhapat; Z = Zarda; NCAD = Non-commercial alcoholic drinks (local beverages = chulai, rice beer, high spirited country liquor etc.); PA = Process alcohol (foreign beverages = whisky, rum, brandy, beer wine etc.).

DISCUSSION

Betel nut chewing with or without tobacco has been shown to be independently associated with the development of oesophageal cancer in Assam and there are clear dose-related responses that indicate a causal effect. Risks are higher for men than for women and further evidence from the data shows that male chewers start the habit at a younger age, use tobacco more often and chew both more frequently during the day and for longer periods of time. Similar findings have also been reported from elsewhere in India (Jussawalla, 1971, 1981). However, in Assam it has been found that the risk from chewing betel nut and tobacco together is higher than that from betel nut alone and this differs from the earlier findings from Bombay where chewing betel nut alone gave a substantially higher risk, apparently because the juices from the quid with tobacco were usually spat out while those from betel nut alone were habitually swallowed (Jussawalla, 1971).

The betel nut (*Areca catechu* L) has been shown to have carcinogenic potential (Suri et al, 1971; Sharan and Wary, 1992) and 3-methyl nitrosamine propionitrile (MNPN), a potent carcinogen (Nair et al, 1987) and safrole-like DNA adducts (Chen et al, 1999) have been detected in the saliva of betel chewers. Both saliva and the active alkaloid, arecoline, present in the nut have been shown to be genotoxic and mutagenic (Chetia et al, 1996; Chaterjee and Deb, 1999; Mahanta et al, 1999; Saikia et al, 1999). Contamination of areca nuts has also been found by fungi such as *Aspergillus flavus, A. niger* and *Rhisopus* sp. (Bandre, 1983; Borle and Gupta, 1987) which can produce carcinogenic *aflatoxins*.

Clearly the effect of chewing is greatest on the buccal mucosa and many studies have indicated a strong dose–response relationship with tumours of the oral cavity (Blot et al, 1997). However, components of the betel quid are absorbed through the mucous membrane by chewers while some portion is also swallowed so that the oesophagus is also affected. The present study strongly indicates that betel nut chewing is probably the most important risk factor for oesophageal cancer in Assam and shows the need yet again for public education to highlight the risks associated with this deeply entrenched local habit.

Table 8 Risk factors for cancer oesophagus related to isolated and combined habits

Habits	Male					Female				
	Ca/Co	RR (95% CI)	P value	CF	EF	Ca/Co	RR (95% CI)	P value	CF	EF
No habit	32/217	1				26/132	1			
Chew only	67/133	3.4 (1.2–9.5)	0.005	0.18	0.7	78/113	3.5 (1.4–10.3)	0.004	0.54	0.71
Smoke only	27/98	1.9 (0.3–5.6)	0.23	0.08	0.47	5//10	2.5 (0.8–7.3)	0.08	0.03	0.61
Drink only	22/106	1.4 (0.1–4.5)	0.46	0.06	0.29	4//12	1.7 (0.5–5.8)	0.63	0.03	0.41
Chew + Smoke	83/67	8.4 (2.6–14.3)	< 0.001	0.23	0.88	8//5	8.1 (2.3–12.9)	< 0.001	0.06	0.87
Smoke + Drink	28/27	7 (2.1–13.4)	< 0.001	0.08	0.86	4//5	4.1 (1.3–10.3)	0.002	0.03	0.75
Alcohol + Chew	25/31	5.5 (1.9–14.3)	< 0.001	0.07	0.82	12//8	7.6 (2.1–16.3)	< 0.001	0.08	0.86
Chew + Drink + Smoke	74/37	13.6 (4.5–21.3)	< 0.001	0.21	0.93	7//3	11.8 (3.7–21.5)	<0.001	0.05	0.92

Chew = Chew betel nut with or without tobacco; Drink = Drinks alcohol of any form; Ca = Cases; Co = Control; RR = Relative risks; CF = Case fraction (Proportion of all cases in ith category of exposure); EF = Aetiological fraction (EFi = RRi-1/RRi where i is category exposure group).

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Annexure 61

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RISK FACTORS FOR CANCER OF THE OESOPHAGUS IN KERALA, INDIA

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A case-control study of oesophageal cancer was carried out in Trivandrum, Kerala, involving 267 cases and 895 controls. Risk factors studied in males were pan (betel)-tobacco chewing, bidi and cigarette smoking, drinking alcohol and taking snuff. Only pan-tobacco chewing was investigated in females as very few indulged in the other habits. Among males significant associations with higher risk were observed for bidi smoking ($p < 0.001$), bidi plus cigarette smoking ($p > 0.05$) and drinking alcohol ($p < 0.001$). While a significant effect of duration of pan-tobacco chewing ($p < 0.005$) was observed in males, there was no significant trend, the risk first falling then rising as duration of use increased. This was partly due to confounding with smoking. No effect of pan-tobacco use was observed in females. A step-wise model was fitted, retaining only those risk factors which were significant when adjusted for other factors; the risk factors included were duration of pan-tobacco chewing, duration of bidi smoking, daily frequency of bidi and cigarette smoking and alcohol use (yes or no). An adjusted relative risk of 2.03 was observed for a pan-tobacco habit of more than 40 years' duration, of 4.70 for more than 20 years of bidi smoking, of 4.80 for more than 20 bidis/cigarettes per day, and of 2.33 for regular alcohol use (in each category relative to a baseline of those never indulging in the relevant habit).

Tobacco smoke and alcohol are major risk factors for cancer of the oesophagus in Western countries (Wynder and Bross, 1961; Tuyns, 1983; Day *et al.*, 1982; IARC, 1988; La Vecchia and Negri, 1989). The risk is reported to be considerably higher when both habits are practised. Epidemiological studies, however, have provided only limited clues regarding risk factors for this disease in high-incidence regions such as northern Iran and north-central China, where alcohol and tobacco appear to play a negligible role. Dietary and nutritional factors, thermal irritation and soil-related factors have been implicated in the aetiology of oesophageal cancer in these regions (Li, 1982; Yang, 1980; Muñoz *et al.*, 1982; Thurnham *et al.*, 1985; Ghadirian, 1987; Li *et al.*, 1989).

India has a low to medium incidence of this type of cancer (Muir *et al.*, 1987), age-adjusted incidence rates varying from 6 to 11.4 per 100,000 in various registration regions of the National Cancer Registry Project (NCRP) of India (ICMR, 1985). Approximately 4,500 new cancer cases are seen annually at the Regional Cancer Centre, Trivandrum, and carcinoma of the oesophagus accounts for 4.5% of these. It is the 4th commonest cancer among males and 8th commonest among females in our Centre. Since there is no population registry in Trivandrum, incidence rates for this region are not available. An apparently higher frequency of oesophageal cancers has been reported in Kashmir as compared to hospital figures in the rest of the country (Siddiqi and Preussman, 1989). Previous case-control studies from Bombay have identified bidi smoking, pan chewing and pan-tobacco chewing as major risk factors for oesophageal cancer in India (Jussawallah and Deshpande, 1971; Jayant *et al.*, 1977; Notani, 1988). The present study addresses the role of pan-tobacco chewing, bidi smoking, cigarette smoking, alcohol and nasal snuff inhalation in oesophageal cancers in Southern India.

MATERIAL AND METHODS

At the Regional Cancer Centre, Trivandrum, 267 patients with cancer of the oesophagus were seen during the years 1983–1984. These patients were interviewed by the social workers of the hospital cancer registry to elicit information on their habit pattern. Histological confirmation was obtained in 67% of the patients, and the rest were diagnosed by radiological means only. Since this was a hospital-based study, there were no restrictions regarding the patients' residence. In most cases the details were obtained by direct interviewing of the patient and in 10 cases from a surrogate such as spouse or relative. A structured questionnaire was used to collect information on demographic, educational, marital, occupational and habit patterns. No detailed information on dietary factors was collected. Daily frequency, duration of the habit in years and the age at which the habit was initiated were ascertained. Habits investigated were pan (a mixture of betel leaf, sliced dry/fresh areca nut and aqueous shell lime) chewing, pan-tobacco (a mixture of pan plus natively cured dry tobacco leaves/stem) chewing, bidi (a native cigarette of coarse tobacco in a dry temburni leaf) smoking, cigarette smoking, alcohol drinking and nasal snuff (a fine home-ground tobacco powder) inhalation.

Controls (895) were selected from patients contemporaneously seen at the cancer centre (271 patients) for conditions not diagnosed as malignant or pre-cancerous lesions and from those attending the teaching hospitals of the medical school with diagnoses of acute respiratory, gastro-intestinal and genito-urinary infections (624 patients). They were also interviewed by the social workers to obtain information on the habits described above.

Few subjects reported irregular indulgence in habits, and for these subjects exact daily frequency, duration and age at starting the habit were not known. These are referred to as occasionally indulging in the habits.

Statistical analysis was by unconditional logistic regression producing odds ratio (OR) estimates of relative risk and deviance Chi-squared tests for effect. Dose-response was evaluated by tests for trend. A forward step-wise procedure was used to construct a multivariate model of risk eliminating those habits which had no effect on risk when adjusted for other habits (Armitage and Berry, 1987; Breslow and Day, 1980). The effect of occasional use was assessed separately. All analyses incorporated adjustment for age and religion (Hindu, Muslim or Christian).

RESULTS

Table I shows frequencies of cases and controls by age, sex and religion. Since only 4 males (all controls) and 6 females (3 cases and 3 controls) chewed pan alone, this variable was not analysed further. The only habit indulged in by females in substantial numbers was pan-tobacco chewing. Data were therefore analysed separately for males and females, in the latter case restricting attention to pan-tobacco.

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TABLE I – FREQUENCIES OF CASES AND CONTROLS BY AGE, SEX AND RELIGION

Factor	Category	Cases	Controls	Total
Age	<40	8	58	67
	40–49	43	189	232
	50–59	89	306	395
	60–69	88	236	324
	70+	39	106	145
Sex	Male	207	546	753
	Female	60	349	409
Religion	Hindu	191	544	735
	Christian	51	201	252
	Muslim	25	150	175

Omitting occasional users, relative risks, 95% confidence intervals and results of significance tests in relation to frequency of habits, are shown in Table II. Significant effects were noted in males for bidi smoking, bidi and cigarette smoking and alcohol drinking, higher frequency of use being associated with increased risk. No significant effects were associated with smoking cigarettes alone, taking snuff (although few subjects indulged in this habit) or pan-tobacco chewing. In female subjects there was no significant effect of pan-tobacco chewing.

Corresponding results for duration of habit are given in Table III. Snuff is not included as there were too few regular users for further subdivision of snuff-taking. Results were similar to those observed for habit frequencies except that, in males, we observed a significant effect of duration of pan-tobacco chewing. No consistent risk gradient was apparent, the relative risk rising falling and rising again as duration increased. This was partly explained by confounding with bidi smoking (see "Discussion"), as measured by raw numbers of bidis smoked per day. Risk was also assessed by total lifetime exposure to habits, but this was no more predictive than duration or frequency of habit.

Effects of occasional use are shown in Table IV. The relative risks associated with bidi smoking and alcohol drinking are higher than those for regular use, suggesting that these occasional users under-reported their consumption. The significant effect of occasional use of snuff suggests that there may also be an effect of regular use which is not significant, though the number of snuff users was small. There is also a significant association of occasional pan-tobacco chewing with high risk.

Effects of starting the habit after age 20, compared to starting before age 21, were studied based on analysis only of those who regularly indulged in each habit. Snuff was excluded due to the small number of regular users. The relative risks associated with a late age at starting bidi (RR = 0.26), bidi and cigarette (RR = 0.29) and alcohol habits (RR = 0.28) are low, consistent with the observed effects of duration. Late age at commencing pan-tobacco chewing is similarly associated with lower risk (RR = 0.21), again indicating that the effect of duration observed above requires explanation.

Table V shows the results of step-wise logistic regression, which resulted in a model with 4 factors: duration of bidi smoking, daily frequency of bidi and cigarette smoking, alcohol use (yes or no), and duration of pan-tobacco chewing. Relative risk estimates are similar to those adjusted only for age and religion (see Tables II and III). Note that the estimates in Table V are also adjusted for trends of risk with exact numbers

TABLE II – FREQUENCIES, RELATIVE RISKS AND RESULTS OF SIGNIFICANCE TESTS WITH RESPECT TO DAILY HABIT FREQUENCIES

Habit and daily frequency	Case	Control	Relative risk	95% C.I.	p^1	p^2
(a) Males						
Pan-tobacco chewing					NS	NS
Never	122	360	1.00	—		
<5 p.d.[3]	23	61	0.96	(0.56, 1.64)		
5–9 p.d.	33	80	1.03	(0.64, 1.64)		
10+ p.d.	11	40	0.64	(0.31, 1.31)		
Bidi smoking					$p < 0.001$	$p < 0.001$
Never	88	402	1.00	—		
≤10 p.d.	45	65	2.84	(1.80, 4.46)		
11–20 p.d.	45	55	3.48	(2.18, 5.54)		
21+ p.d.	24	20	5.22	(2.72, 10.00)		
Cigarette smoking					NS	—
No	198	499	1.00	—		
Yes	9	46	0.56	(0.26, 1.19)		
Bidi and cigarette smoking					$p < 0.005$	$p < 0.001$
Never	157	459	1.00	—		
≤10 p.d.	10	33	0.90	(0.42, 1.90)		
11–20 p.d.	16	24	2.02	(1.02, 3.98)		
21+ p.d.	24	30	2.63	(1.46, 4.73)		
Alcohol drinking					$p < 0.001$	—
No	109	438	1.00	—		
Yes	61	71	3.47	(2.29, 5.27)		
Snuff inhalation					NS	—
No	192	532	1.00	—		
Yes	7	7	2.39	(0.81, 7.04)		
(b) Females						
Pan-tobacco chewing					NS	NS
Never	30	168	1.00	—		
<5 p.d.	8	92	0.50	(0.21, 1.16)		
5–9 p.d.	14	63	1.20	(0.59, 2.45)		
10+ p.d.	3	22	0.70	(0.19, 2.56)		

[1]Global test for a difference in risk among the categories.–[2]Test for a linear trend in risk.–[3]p.d. = per day.

TABLE III – FREQUENCIES, RELATIVE RISKS AND RESULTS OF SIGNIFICANCE TESTS WITH RESPECT TO DAILY HABIT DURATIONS (IN YEARS)

Duration	Case	Control	Relative risk	95% C.I.	p^1	p^2
(a) Males						
Pan-tobacco chewing						
Never	122	360	1.00	—	p 0.005	NS
≤10	8	13	1.83	(0.72, 4.63)		
11–20	8	54	0.42	(0.19, 0.91)		
21–30	10	49	0.51	(0.25, 1.06)		
31–40	19	40	1.15	(0.63, 2.10)		
41+	22	25	2.02	(1.03, 3.94)		
Bidi smoking						
Never	88	402	1.00	—	$p < 0.001$	$p < 0.001$
≤20	7	22	1.62	(0.65, 4.02)		
20+	107	118	3.75	(2.61, 5.36)		
Cigarette smoking						
Never	198	499	1.00	—	NS	NS
≤20	2	18	0.45	(0.10, 2.05)		
21+	7	28	0.60	(0.25, 1.42)		
Bidi and cigarette smoking						
Never	157	459	1.00	—	$p < 0.05$	$p < 0.01$
≤20	9	23	1.60	(0.69, 3.67)		
20+	41	64	1.84	(1.18, 2.85)		
Alcohol drinking						
Never	109	438	1.00	—	$p < 0.001$	$p < 0.001$
≤20	11	24	2.28	(1.05, 4.91)		
20+	50	47	3.99	(2.50, 6.35)		
(b) Females						
Pan-tobacco chewing						
Never	30	168	1.00	—	NS	NS
≤10	5	48	0.57	(0.20, 1.58)		
11–20	5	49	0.55	(0.19, 1.54)		
21–30	6	48	0.68	(0.26, 1.76)		
31–40	5	19	1.41	(0.46, 4.32)		
41+	4	13	2.17	(0.58, 8.12)		

[1]Global test for trend.–[2]Test for linear trend in risk.

TABLE IV – FREQUENCIES, RELATIVE RISKS AND RESULTS OF SIGNIFICANCE TESTS WITH RESPECT TO OCCASIONAL INDULGENCE IN HABITS

Factor	Category	Cases	Controls	R.R.	95% C.I.	p
(a) Males						
Pan-tobacco	Never	122	360	1.00	—	$p < 0.001$
	Occasional	18	5	10.18	(3.60, 28.74)	
Bidi	Never	88	402	1.00	—	$p < 0.01$
	Occasional	5	4	7.48	(1.74, 32.02)	
Cigarette[1]	Never	198	499	—	—	NS
	Occasional	0	1	—	—	
Bidi and cigarette[2]	Never	157	459	—	—	—
	Occasional	0	0	—	—	
Alcohol	Never	109	438	1.00	—	$p < 0.001$
	Occasional	37	37	4.01	(2.36, 6.79)	
Snuff	Never	192	532	1.00	—	$p < 0.05$
	Occasional	8	7	3.59	(1.20, 10.67)	
(b) Female						
Pan-tobacco	Never	30	168	1.00	—	$p < 0.05$
	Occasional	5	4	5.82	(1.42, 23.77)	

[1]Estimation impossible due to sparse data. Not significant by Fisher's exact test.–[2]No estimation or testing possible.

of bidis smoked and pan-tobacco quids chewed per day, in order to account for the confounding mentioned above. No significant heterogeneity by age was observed for any risk factor.

DISCUSSION

One surprising result of this study was the absence of a strong effect of pan-tobacco chewing. Indeed, in males, durations of between 11 and 30 years of the chewing habit seemed to confer a lower risk than never chewing. The absence of effect may be due to the predominant habit in this region of spitting out the quid and its extracts with saliva rather than swallowing it, thus preventing carcinogens from coming into contact with the oesophageal epithelium. The unexpectedly low risks observed in some categories of duration of pan-tobacco chewing are partly caused by confounding with bidi smoking. No increase in risk was found for the only possible risk habit (pan-tobacco chewing) examined in women. A study of the dietary and nutritional factors might identify the risk

TABLE V – RELATIVE RISK ESTIMATES AMONG MALES AND RESULTS OF SIGNIFICANCE TESTS FOR THE FOUR FACTORS RESULTING FROM FORWARD STEPWISE LOGISTIC REGRESSION

Factor	Category	R.R.[1]	95% C.I.	p^1
Bidi duration	Never	1.00	—	$P < 0.001$
	≤20 yrs	2.10	(0.75, 5.87)	
	20+ yrs	4.70	(2.79, 7.89)	
Bidi and cigarette daily frequency	Never	1.00	—	$P < 0.001$
	≤10 p.d.	1.85	(0.80, 4.29)	
	11–20 p.d.	3.85	(1.67, 8.85)	
	21+ p.d.	4.80	(2.34, 9.83)	
Alcohol	No	1.00	—	$P < 0.001$
	Yes	2.33	(1.52, 3.55)	
Pan-tobacco duration	Never	1.00	—	$P < 0.05$
	1–10 yrs	2.18	(0.71, 6.70)	
	11–20 yrs	0.48	(0.19, 1.21)	
	21–30 yrs	0.51	(0.20, 1.25)	
	31–40 yrs	1.02	(0.44, 2.38)	
	41+ yrs	2.23	(0.82, 5.99)	

[1]All estimates and tests adjusted for the effects of the other 3 factors.

factors in women. A case-control study on diet and oesophageal cancer is progressing at the moment in our Centre. Although those who chew are more likely to smoke than non-chewers, their consumption of bidis per day was lower. In male smokers who do not chew, the average number of bidis smoked per day was 19, whereas in those smokers who also chewed the average was 12. This was also observed for bidi and cigarette smoking.

Tobacco smoking in the form of bidi smoking and bidi plus cigarette smoking have emerged as independent risk factors for cancer of the oesophagus. This is in agreement with the results of previous studies in India. Jussawalla and Deshpande (1971) reported a relative risk of 2.9 with bidi smoking. Using the data of Jussawalla and Deshpande (1971), Jayant *et al.* (1977) calculated an "aetiologic fraction" (attributable risk) of 54% for smoking. Notani (1988) reported relative risks of the order of 4 and 4.7 when compared with hospital and population controls, respectively.

As expected, alcohol has emerged as an independent risk factor for this disease. Only 2 studies from India have assessed alcohol as a risk factor in this disease. Jussawalla and Deshpande (1971) reported relative risks of 12 and 18 for men who drank alcohol as well as chewing tobacco and for those who drank and smoked, respectively, compared to men who neither drank alcohol, chewed tobacco nor smoked. Notani (1988), using multi-variate regression analysis, reported relative risks varying from 1.5 to 2.7 with alcohol and observed no association between alcohol consumption and cancer in those over 60 years old. Many studies from Western countries have also identified alcohol as a major risk factor. Alcoholic beverages consumed by members of low socio-economic groups in many parts of India are qualitatively different from those consumed in Western countries, prepared with greatly varying local ingenuity and with diverse ingredients, albeit with an ethanol content varying only from 40% to 50%.

There was no significant heterogeneity of the effect of smoking between drinkers and non-drinkers. The implication of this is that the relative risk for both habits can be obtained by multiplication of the relative risks in Table V. Thus, for example, the relative risk associated with drinking and the highest category of bidi and cigarette smoking is $2.33 \times 4.80 = 11.18$. This high combined relative risk is consistent with previous results.

Regarding the reliability of the data, the prevalence of habits in our controls was comparable to that found in other Indian studies (Sankaranarayanan *et al.*, 1989). We would, however, expect some misclassification in both cases and controls, particularly for alcohol use. It is therefore likely that true relative risks are higher than those observed. Further, the high risks associated with occasional habit use suggest that there has been some underestimation of habits.

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Annexure 62

Original Article

Oesophageal Carcinoma - A Study of Risk Factors (Emphasis on Nutrition) in a Teaching Hospital of Kumaon Region of Uttarakhand

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Abstract

Background: Cancer oesophagus is common in India and is the third leading cause of cancer death in males and fourth in females. Various factors are responsible for it and present study was undertaken to study the various risk factors with stress on nutritional factors associated with it.

Methods: Ninety-four cases of oesophagus cancer and matched equal number of healthy individuals (control) constituted the study. They were assessed for their dietary pattern during the preceding 10-15 years with the help of standard food frequency questionnaire method. Information regarding consumption of alcohol, smoking and tobacco chewing with or without betel leaf was taken in detail.

Results: Seven hundred and eighty upper GI endoscopy revealed 94 (12.05%) cases of oesophageal carcinoma. Histopathology revealed squamous cell carcinoma in 87 cases (92.50%), adenocarcinoma in 6 cases (6.30%) and one with mixed picture of adenocarcinoma and squamous cell carcinoma. Sixth (36.17%) and 7th (23.40%) decade of persons were mainly affected with male to female ratio of 2.1: 1. They were mostly of lower socio-economic (82.90%) status. Various risk factors came across were less consumption of green and leafy vegetables and fruits and consuming more spicy fried and hot food and beverages. Increased risk was seen more often with consumption of alcohol (neat and without or less salad and snacks), smoking beedi and cigarette, and tobacco chewing with or without betel leaf. It is directly related to amount, frequency, mode and duration of use.

Conclusions: Malignancies in general are result of multiple factors and interaction of several environmental factors. One factor cannot be blamed but combination of factors increases the risk of oesophageal carcinoma. Nutritional factor is also one of the major contributing factor increasing the risk of oesophagus cancer.

Introduction

Cancer of the gastro-intestinal tract is a major health problem throughout the world. In India, the gastrointestinal cancers constitute between 15 to 25% of all cancer burdens and is more commonly seen in Karnataka, Tamil Nadu, Kerala and also reported from Assam and Kashmir.[1] Oesophageal cancer is the third leading cause of cancer death in male and fourth in females and the incidence is low in rural India.[2] The importance of diet and nutrition in the etiology of many malignancies has gained a wide acceptance. The nutrition in oesophageal cancer etiology has also been stressed. Main stress has been laid as lack of fresh green vegetables and less intake of vitamin-A, C and riboflavin.[3] Fungal infections and consumption of very hot beverages has also been suggested as risk factors in China, Singapore and Iran.[3,4]

The incidence of oesophageal cancer in India is in increasing tendency but very limited data is available, especially on the association of nutritional factors with oesophageal carcinoma. The present study was undertaken with the objective to study the risk factors (nutritional) associated with oesophageal carcinoma in the Kumaon region of Uttarakhand, India.

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Material and Methods

The present study was based on 780 cases, on whom the upper gastro-intestinal endoscopy was performed, from January 2005 to December 2006 for various indications at the Gastro-enterology Unit of Dr. Sushila Tiwari Memorial Forest Hospital, Haldwani.

Amongst these 780 patients, 94 (12.05%) of them were of oesophageal carcinoma who constituted the present study and have fulfilled the following criteria.[1,4,5]

- Endoscopic appearance typical to oesophageal carcinoma.
- Histopathological proved cases of oesophageal carcinoma.
- Not undergone any treatment i.e. chemotherapy or radiotherapy.
- In good mental health to reply the questionnaire.
- Not suffered from any major chronic illness in the past before the diagnosis so as to assure the actual pattern of diet without any modification.

The control group constituted of healthy individuals who were accompanying the patients and other individuals attending the hospital with patients. Control group were matched with age, sex and socio-economic status etc., and had not suffered from any major illness in the past.

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These patients and control individuals were subjected to thorough clinical examination and relevant investigations. All of them were subjected to pre-tested and semi-structured questionnaire so as to get following information.

1. Socio-economic profile

Information was collected regarding occupation, education, income, religion and place of residence (Kuppuswamy's classification).[6,7]

Table 1 : Socio-demographic pattern

	Oesophageal carcinoma (n = 94)		Control (n = 94)	
	No.	%	No.	%
Age (in years)				
⇨ 31-40	18	19.14	18	19.14
⇨ 41-50	20	21.27	17	18.08
⇨ 51-60	34	36.17	32	34.10
Above 60	22	23.40	27	28.60
Minimum age	34		32	
Maximum age	72		71	
Mean±S.D.	54.6±9.6		52.2±7.8	
Sex				
⇨ Males	64	68.08	64	68.08
⇨ Females	30	31.91	30	31.91
Male: Female ratio	2.1:1		2.1:1	
Socio-economic status				
Upper class	06	06.38	06	06.38
Upper middle class	10	10.63	08	08.51
Lower middle class	42	44.68	41	43.61
Lower class	36	38.29	39	41.48
Educational status				
Illiterate	32	34.04	36	38.29
Upto junior high school	42	44.68	41	43.61
Upto intermediate	17	18.08	15	15.95
Graduate	03	03.19	02	02.12

2. Nutritional or Dietary History

Type of diet and its constituents consumed during the last 10-15 years prior to diagnosis of oesophageal carcinoma (food frequency questionnaire method) was enquired in detail.[7] Commonly consumed food items were categorized in certain group: e.g., cereals, pulses, legumes, vegetables, fruits, milk and its products and non-vegetarian items. Frequency and intake amount was assessed e.g., days per week, once fortnight and month etc. They were asked about the hotness (temperature) of beverages and food items consumed and stress has been laid on amount, frequency, temperature, spicy and fried nature of intake items.

3. Intoxicant Consumption History

They were asked about consumption of alcohol regarding (amount per day, type, frequency and whether with water, salad and snacks etc.) similarly they have been also asked for smoking beedi, cigarette and chewing of tobacco in its different forms.

The collected data were subjected to conventional statistical analysis. Chi-square test was employed for comparison between case and the control group. The test was performed at 95% confidence limits. $P<0.05$ and $P<0.01$ considered to be significant.

Results

Majority of the patients were from 6th (36.17%) and 7th (23.40%) decade of life (Table 1) with age varied from 34 to 72 years (mean = 54.67±9.6 years) and male to female ratio of 2.1: 1. During the period of 2 years, 780 upper gastrointestinal endoscopies were performed and 94 of them (12.10%) came out to be suffering from oesophageal carcinoma. The specimen taken on histopathology revealed squamous cell carcinoma in 87 cases (92.50%), adenocarcinoma in six cases (6.30%) and one

Table 2 : Dietary status (relative risk factors)

Type of diet with frequency of intake	Oeso-carcinoma (n = 94)		Control (n = 94)		Odds ratio	CI 95%		'p' value
	No.	%	No.	%		LL	UL	
Vegetarian Diet								
1. Underground & ground vegetable								
⇨ Daily to 4/ week	36	38.29	55	58.51	1.000	-	-	
⇨ 3/ week to 1/week	48	51.06	36	38.29	0.655	0.466	1.486	*
⇨ Occasional or nil	10	10.63	03	03.19	0.262	0.145	2.149	
2. Green leafy vegetable								
⇨ Daily to 4/ week	22	23.40	44	46.80	1.000	-	-	
⇨ 3/ week to 1/ week	54	57.44	41	43.61	0.552	0.420	1.422	*
⇨ Occasional or nil	18	19.20	09	09.57	0.364	0.257	1.618	
3. Fruits								
⇨ Daily to 4/ week	04	4.25	5	46.80	1.000	-	-	
⇨ 3/ week to 1/ week	22	23.40	22	43.61	0.800	0.215	3.837	
⇨ Occasional or nil	68	72.34	67	09.57	0.788	0.232	3.505	
4. Milk & Milk products								
⇨ Daily to 4/ week	50	53.19	46	48.93	1.000	-	-	
⇨ 3/ week to 1/ week	28	29.78	36	38.29	1.398	0.726	1.841	
⇨ Occasional or nil	16	17.02	12	12.78	0.815	0.518	1.617	
Non- Vegetarian								
1. Meat, chicken Fish etc.								
⇨ Daily to 4/ week	23	24.46	02	02.12	1.000	-	-	
⇨ 3/ week to 1/ week	45	47.87	14	14.89	0.467	0.109	4.740	**
⇨ Occasional or nil	26	27.65	78	82.97	4.500	0.304	12.142	

* = $p<0.05$; ** = $p<0.01$

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Table 3 : Nature of edible articles consumed (relative risk factors)

Nature of food articles	Oeso-carcinoma (n = 94)		Control (n = 94)		Odds ratio	CI 95%		'P' value
	No.	%	No.	%		LL	UL	
Spicy food/snacks etc.								
⇨ Mild or almost nil	20	21.27	42	44.68	1.000	-	-	**
⇨ Moderate spicy	44	46.80	38	40.42	0.905	0.522	1.755	
⇨ Too spicy	30	31.91	14	14.89	0.489	0.342	1.571	
Fried food								
⇨ Almost nil	19	20.21	50	53.19	1.000	-	-	**
⇨ Yes	75	79.78	44	46.80	0.571	0.481	1.280	
Temperature								
⇨ Tea or Coffee								
• Warm	20	21.27	52	55.31	1.000	-	-	**
• Hot	50	53.19	28	29.78	0.258	0.285	1.085	
• Too Hot	24	25.53	14	14.89	0.269	0.250	1.281	
⇨ Snacks and/or meals								
• Room temperature	10	10.63	66	70.96	1.000	-	-	**
• Warm	38	40.42	16	17.02	0.263	0.210	1.496	
• Hot	46	48.93	12	12.76	0.163	0.165	1.254	

* = $p < 0.05$; ** = $p < 0.01$

patient of mixed picture of squamous and adenocarcinoma. It was mostly seen in lower middle (44.68%) and lower (38.29%) class of persons who were educated upto junior high school level (44.68%). Nearly 67 cases (71.30%) were unskilled or semi-skilled working class.

Dietary Habits

The staple diet in this region is rice (patients 46.80%, control 38.30%) and wheat (cases 34.10%, controls 43.70%), but at times they used to take mixed diet. There was significant difference between patients and controls regarding intake of vegetables (Table 2). They were mostly taking underground or ground level growing vegetable three times a week or occasionally (41.48% control, 61.69% cases) and leafy vegetables (53.18% control and 76.60% cases). The insignificant difference was seen in the use of dairy products and fruits (68 cases or 72.20%). Significantly, more patients were taking non-vegetarian preparations from daily (24.46%) to three times a week or once a week (47.87%), which was spicy in nature.

Significant role of the nature of diet has been observed in the present series of cases (Table 3). Most of the patients were taking either too spicy (31.91%) or moderately spicy (46.80%) meals and majority of them were fond of taking hot (53.19%) to very hot (25.53%) tea, coffee and meals (warm 40.42%, hot or too hot 48.93%).

Table 4 reveals the significantly more consumption of intoxicants by oesophageal cancer patients. They were consuming more alcohol (patients 74.50% control 48.90%) and 32 of them were chronic alcoholic i.e., all the 24 hours they were under the effect alcohol intoxication. Quite a good number of them were consuming neat alcohol (37.14%) or alcohol with little amount of water and salad etc. (34.30%) and amount was more than 200 ml per day (55.26%). During alcohol intake or otherwise, they were smoking beedi, more than one bundle per day (34.00%) or cigarettes, more than one packet per day (21.30%) (Table 4) or both depending on availability (9.60%). Tobacco chewing was present in 54 cases (57.50%) either alone (34.00%) or with betel leaf (23.36%).

As evident from Table 4 the prevalence of combination of various risk factors i.e, alcohol, smoking, tobacco chewing, spicy and hot food, snacks, beverages played a significant role. In all these combinations alcohol, smoking and tobacco chewing played a significant role and alcohol intake (70 cases or 74.4%) was on top. This was followed by temperature of the beverages, food and snacks and their spicy nature (74 cases or 78.78%).

Discussion

In India malignancy of gastro-intestinal tract is more common specially in Kerala, Tamil Nadu, Karnataka followed by Assam and Kashmir, but no actual prevalence data is available.[1,5] Few studies reported the occurrence rate between 15 to 25% of all cancer burden and Coimbatore Government Hospital, Tamil Nadu had the registration rate of 8-12 cases of oesophageal carcinoma every month. In our hospital based study on upper gastro-intestinal endoscopy we detected 94 cases of oesophageal carcinoma out of 780 upper gastro-intestinal endoscopies giving the incidence of 12.05%. As reported in literature,[1, 5, 8-10] we too detected squamous cell carcinoma in 92.50% of cases. Maximum number of cases were seen in 6th decade of life with male to female ratio from 2:1 to 3.5:1[5,6,12] and same was observed in our present study (6th decade of life- 36.17%, mean age = 54.60 ± 9.60 years) with male to female ratio of 2.1:1.

Cancer in general, is multifactorial in origin and several environmental interactions are possible. It is not easy to quantify the contribution of diet to cancer risk. Mumbai study[13] revealed the 2.62 times higher risk when vegetables specially leafy vegetables were less commonly consumed or almost nil. A diet rich in green leafy vegetables and fruits was found to be less often associated with oesophageal carcinoma.[5,10,14,16] Various nutritional factors have been implicated in causation of oesophageal carcinoma. In the present study, most of the patients (61.90%) were consuming less green and/or leafy vegetables and fruits. It is just because of lack of knowledge and poverty. The potentiality of anticancerous property of green and leafy vegetables is due to carotenoids, vitamin-C and E, selenium, folic acid, dietary fibres, alium compounds, plant sterols, indols, flavinoids etc. These agents have complementary as well as overlapping mechanism of action, detoxification action of enzymes, inhibition of nitrosamines formation and helping the binding of carcinogens in the gastro-intestinal tract and anti-oxidant effects.[5,12,14,15] It is said that these compounds has also immunologic properties which may influence carcinogenesis.[14,15]

Table 4 : Relative risk factors in relation to intoxicants consumed

Type of diet with frequency of intake	Oeso-carcinoma (n = 94)		Control (n = 94)		Odd ratio	CI 95%		'p' value
	No.	%	No.	%		LL	UL	
A. Alcohol								
1. Amount per day								
⇨ Occasional or nil	24	25.53	48	51.06	1.000	-	-	
⇨ Upto 200 ml/day	18	19.14	36	38.29	1.000	0.449	2.226	
⇨ 200-500 ml/day	27	28.72	10	10.63	0.185	0.192	1.206	**
⇨ >500 ml/day	25	26.54	-	-	0.010	0.008	2.354	**
2. Frequency								
⇨ Occasional or almost nil	24	25.53	48	51.06	1.000	-	-	
⇨ Intermittent 2-4/week	38	40.42	36	38.29	0.666	0.426	1.650	*
⇨ Chronic drinker (almost every day)	32	34.04	10	10.63	0.220	0.217	1.235	**
3. Mode of drinking								
⇨ Mixed with water or soda and with snacks etc.	20	28.57	04	8.69	1.000	-	-	*
⇨ Mixed with water & salad	24	34.28	12	26.08	1.625	0.431	3.538	
⇨ Neat	20	28.57	30	65.21	0.500	0.198	2.764	**
B. Smoking								
1. No smoking	15	15.90	29	30.8	1.000	-	-	*
2. Beedi smoking per day								
⇨ Mild i.e., upto 1 bundle	10	10.60	16	17.10	0.768	0.313	2.543	
⇨ Moderate 1-3 bundles	20	21.20	15	15.40	0.360	0.246	1.676	*
⇨ Heavy more than 3 bundles	12	12.80	07	07.50	0.280	0.181	1.833	**
Total	42	44.60	38	40.5				
3. Cigarette smoking per day								
⇨ Mild i.e., upto 1 packet	08	08.50	10	10.70	0.600	0.252	2.547	
⇨ Moderate 1-3 packets	11	11.70	05	05.40	0.218	0.146	1.823	*
⇨ Heavy more than 3 packets	09	09.60	04	04.20	0.213	0.131	2.000	*
Total	28	29.80	19	20.30				
4. Both depending on availability								
⇨ Moderate	04	04.20	05	05.40	0.600	0.182	3.533	
⇨ Heavy	05	05.40	03	03.10	0.288	0.119	2.851	
Total	09	09.60	08	08.50				
C. Tobacco chewing								
1. Alone								
⇨ Occasional	10	10.60	05	05.30	0.385	0.209	2.085	
⇨ Daily	22	23.40	02	02.20	0.070	0.070	1.419	**
2. With betel leaf								
⇨ Occasional	07	07.40	20	21.20	2.198	0.542	3.656	
⇨ Daily	15	15.96	15	15.90	0.769	0.391	2.038	
Total	54	57.50	42	44.70				

* = p<0.05; ** = p<0.01

Kashmir studies[16,17] attributed to contamination of raw food-stuffs with N-nitroso compounds along with use of spicy hot food items and salted tea. Low socio-economic status and consumption of very hot beverages, smoked fish, fried and pickled vegetables and red chilli have been associated with oesophageal carcinoma.[18] Table 1 and 3 of present study reveals the same thing which has contributed to the cancer oesophagus. Chitra et al[10] stressed more on the use of chilli and pickles in food.

Intoxicant consumption specially alcohol in its various forms is a well established factor in the genesis of oesophagus cancer.[5,10] Alcohol and alcoholic beverages possess some carcinogenic chemicals and contaminants which are known to produce carcinogenic effect and few of them need to mention are N-nitroso compounds, mycotoxins, urethane, tannins and pesticide residues.[5,10,19,20] It is the quality, quantity, concentration and duration of consumption, which matters in causation of oesophageal carcinoma. In present 94 cases, 74.50% of them were consuming alcohol and 34.04% of them were chronic alcoholic who were all the 24 hours under alcoholic effect and consuming it for more than 3 years (mean duration = 4.2±1.5 years). Twenty six of them were taking neat alcohol and that too mostly without snacks etc. It seems that alcohol in these cases is one of the main risk factor. This observation is also supported by Notani and Jayanti from India and others.[5-10,11,13]

This series of cases revealed the significant role of beedi and/or cigarette smoking in oesophageal carcinoma. Amount, frequency and duration of smoking has direct relationship with oesophageal carcinoma even though its role in bronchogenic carcinoma is well established. During alcohol intake especially when it is taken along with other persons they used to smoke more. Seventy nine (84.00%) cases were smoking beedi (44.60%) and/or cigarette (29.80%) for more than 3 years and some of them (27.80%) were chain smokers. It has been observed that smoking, mainly cigarettes, increases the risk of oesophageal carcinoma by 1.95 times in India and developed countries.[5,10,11] In India and especially in the Kumaon region of Uttarakhand, the

practice of beedi smoking is comparatively more prevalent than cigarette smoking as they are mostly of lower socio-economic group (82.90%) and this seems to increase the risk of oesophageal carcinoma.

Tobacco chewing with or without betel- leaf has been reported to be an important risk factor in oesophageal carcinoma in Karnataka,[10] Assam[21] and other parts of India[5,22] and reported 2.5 to 2.8-fold increase in cancer risk amongst tobacco chewing and smokers which is directly related to amount, frequency and duration of use. We too observed the same as it is clear from Table 4 and identified the chewing of tobacco with or without betel leaf as one of the contributing factor in causation of cancer oesophagus.

Malignancies in general and that too of the gastro-intestinal tract are said to be multifactorial in origin and interaction of several environmental factors. The present study revealed the same i.e., an association of cancer oesophagus with alcohol, smoking, tobacco chewing with or without betel leaf and lack of protective food i.e. green and leafy vegetables, fruits and whole grains. It can be said that food which is lacking in green vegetables, leafy vegetables, fruits and ingestion of fried, spicy and hot food and beverages, played an important role in increasing the risk of oesophageal carcinoma. It can be said that lack of protective food (green and leafy vegetables, fruits etc.) has also played a possible contributory factor in the aetiology of oesophageal carcinoma.

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Cancer Epidemiology, Biomarkers & Prevention

Tobacco Use and Stomach Cancer in Mizoram, India

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Special Section

Tobacco Use and Stomach Cancer in Mizoram, India

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Abstract

The incidence of stomach cancer in India is lower than that of any other country around the world. However, in Mizoram, one of the north-eastern state of India, a very high age-adjusted incidence of stomach cancer is recorded. A hospital-based case-control study was carried out to identify the influence of tobacco use on the risk of developing stomach cancer in Mizoram. Among the cases, the risk of stomach cancer was significantly elevated among current smokers [odds ratio (OR), 2.3; 95% confidence interval (95% CI), 1.4-8.4] but not among ex-smokers. Higher risks were seen for *meiziol* (a local cigarette) smokers (OR, 2.2; 95% CI, 1.3-9.3). The increased risk was apparent among subjects who had smoked for ≥30 years. The increased risk was significant with 2-fold increase in risk among the subjects who smoked for ≥11 pack-years. The risk increased with increasing cumulative dose of tobacco smoked (mg). *Tuibur* (tobacco smoke–infused water), used mainly in Mizoram, was seemed to increased the risk of stomach cancer among current users in both univariate and multivariate models (OR, 2.1; 95% CI, 1.3-3.1). Tobacco chewer alone (OR, 2.6; 95% CI, 1.1-4.2) showed significant risk. Tobacco use in any form [smoking and smokeless (*tuibur* and chewing)] increased the risk of stomach cancer in Mizoram independently after adjusting for confounding variables. (Cancer Epidemiol Biomarkers Prev 2005;14(8):1892–6)

Introduction

Stomach cancer is one of the most common cancers in the world with an estimated 876,000 new cases reported in 2000 (1). Stomach cancer is highest among male in the population of Changle in China (age-adjusted rate = 145.0 per 10^5; ref. 2). Among females, it is highest in the population of Yamagata in Japan (age-adjusted rate = 38.9 per 10^5; ref. 2). However, the rates of stomach cancer in India are lower in comparison with other countries around the world (3). In India, earlier studies showed relatively higher incidence of stomach cancer among males in Chennai during 1997 to 1998 (age-adjusted rate = 13.2 per 10^5) and among women it is next to cancer of the breast (age-adjusted rate = 7.0 per 10^5; ref. 4). However, recent studies in Mizoram, showed very high incidence of stomach cancer (5).

Mizoram is situated between 92.15′ to 93.29′ E longitude and 21.58′ to 24.35′ N latitude and virtually land locked and situated between Myanmar in the east and Bangladesh in the west. The Mizo people have their ancestral origin in China (6). Tobacco smoking rate in Mizoram is very high among adults (7). A peculiar habit of using "tuibur" (tobacco smoke–infused water) has also been observed in Mizoram. The habit of chewing betel quid, containing fresh betel nut, slaked lime wrapped in betel leaf is also widespread in Mizoram. Tobacco is often used. Dried tobacco mixed with lime processed with tips of thumb on the palm of other hand into a powder that is place near the gum known locally as "Khaini" also chewed in Mizoram.

Tobacco use in the form of smoking is highly associated with stomach cancer. The people of Mizoram are culturally and ethnically distinct from the other tribes and communities of India. Due to their peculiar smoking habits and use of other tobacco products and high prevalence of stomach cancer in Mizoram, a matched case-control study was carried out at the Aizawl Civil Hospital, Aizawl to investigate influence of tobacco use on cancer stomach.

Tuibur. A number of smoking and smokeless tobacco products are in use all over the world. But unlike other smokeless tobacco products, a unique tobacco smoke–infused water is used in Mizoram and is locally known as *tuibur*. This product is made locally by passing smoke, generated by burning tobacco, through water until the preparation turns cognac in color and has a pungent smell. *In vitro* studies using the allium root test show the toxic nature of *tuibur* (8). Indigenous crude devices are used for the production of *tuibur* on small scale. Users take about 5 to 10 mL *tuibur* orally and keep it in the mouth for some time and then spit it out. Most of the users take it several times a day.

Meiziol. It is a local cigarette made from vaihlo (*Nicotiana dadacum*) tobacco. After plucking, the tobacco leaves are thrashed by feet until the leaves become soft and most of the juices flow out. Then they are dried in the sun or sometimes in a warm place like over the fireplace without applying direct heat. Then they are cut into small pieces and rolled directly using a thin paper. The tobacco content of each *meiziol* is about 0.8 to 1 g. The length of each *meiziol* is 6 to 7 cm.

Materials and Methods

This study was a hospital-based matched case-control study carried out at Aizawl Civil Hospital situated at Aizawl, Mizoram. This hospital serves as a tertiary health care facility and is the only hospital having facility to treat cancer in the state with a population of 891,058 (2001 census). The study was conducted from August 2001 to August 2004 during which 372 new cases (all Mizos) of the stomach cancer were registered. This represented 35.1% of all cancer cases registered in this hospital during the study period (n = 1,060).

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The inclusion criteria of cases were:

1. Newly diagnosed stomach cancer cases confirmed by histopathology,
2. Mizo ethnicity, and
3. Cases diagnosed between August 2001 to August 2004.

The exclusion criteria of cases were:

1. Patients with advanced disease (n = 19), where the tumor had spread so as to obscure the primary site,
2. Patients with recurrent cancer (n = 13),
3. Patients too old to be interviewed elaborately (n = 8), and
4. Patients who refused to be interviewed (n = 3).

A total of 329 patients were finally included (253 men and 76 women) with male-to-female ratio of 3.3:1. Controls were selected from hospital patients suffering from non-malignant disease admitted with either injury, minor eye ailments, or infections of any other type or with osteomuscular diseases. The controls were matched for age (±5 years), sex, and ethnicity. For each case, two controls were selected (n = 665). All the confirmed stomach cancer cases were directed to the social investigator(s) of the project for interview and simultaneously information was also collected from the controls. Trained social investigators were employed for interviewing both cases and controls at hospitals used a pretested questionnaire. The main items included in the questionnaire were age, sex, ethnicity, present and past occupation, income, family history, and details of habits about tobacco use.

Subjects who reported that they were regularly smoking/using tuibur/chewing during the index year were defined as current users, those who reported that they had stopped regular using any habits the year before the index year or before were defined as ex-smokers/ex-users/ex-chewers, and people who reported that they never had smoked before or during the index year were defined as never-smokers or never-users or never-chewers. The cumulative dose of smoking was expressed as pack-years. One pack-year was regarded as the equivalent of 20 cigarettes smoked per day for 1 year. The duration from the year of the cessation to the index year was calculated and categorized into the following intervals: 1 to 9, 10 to 19, and 20 years.

Statistical Analysis. Univariate and multivariate logistic regression were used to analyze data. Conditional maximum-likelihood method (9) was used to estimate the variables of regression models due to matched design and significance was taken at $P \leq 0.05$ (two tailed). Initially, a univariate analysis was done. The crude measure of association between single putative risk factors and stomach cancer was expressed as odds ratio (OR) and its 95% confidence interval (95% CI) was calculated from the SE of the regression coefficient. For controlling confounding variables and other covariables like alcohol drinking, level of education, occupation, income, etc., the data were analyzed by conditional multiple logistic regressions to evaluate the extent to which risk factors are associated independently with stomach cancer in Mizoram. The categories used for each adjusting variable in the logistic regression are frequency per day, age began (years), duration (years), cumulative dose, and years since stopped. The statistical packages used for the analysis were Epi-Info-2002 and SPSS version 12.

Ethical Clearance. The study has been cleared by Institutional Ethical Committee of Regional Medical Research Centre, Dibrugarh.

Results

All the stomach cancer patients (n = 329) were confirmed by histology. Of the 329 cases, 95.7% (n = 315) were having adenocarcinoma of which 75.9% (n = 250) were diffuse type. Antrum and pylorus were the major sites of cancer.

The age and sex profile of the cases and controls is shown in Table 1. The mean age of the cases and controls was 56.8 and 57.1 years, respectively. There were no statistically significant differences between the age of the cases and controls, suggesting that age matching was effective. Of the cases, 76.9% were male and majorities (65.3%) of the stomach cancer were in the age group of 45 to 64 years at the time of diagnosis of stomach cancer. Level of education, income groups, and occupation, which were not matching factors in the study, were also included in all models to control for their confounding effect.

ORs were calculated using non-smokers as reference group to see the association with smoking (Table 2). The ORs of current smokers (OR, 2.3; 95% CI, 1.4-8.4) was found to be statistically significant compared with ex-smokers. Although the 50% reduction in risk had been observed after controlling the other habits and co-factors in the multivariate model, a significant risk had been observed, indicating independent effect on the development of stomach cancer. Statistically significant higher risks were seen for smokers of combined users of tobacco (cigarette and *meiziol*) with OR, 3.1 (95% CI, 2.0-11.1) but among the single type of tobacco users, higher risks were seen for *meiziol* smokers, a local cigarette (OR, 2.2; 95% CI, 1.3-9.3) in the multivariate model in comparison to cigarette smokers. Overall, the excess risk was limited to smokers of >10 *meiziol* per day. Risk also tended to increase with duration and with pack-years, with an OR of ~3 among smokers of ≥30 years and those who smoked ≥20 pack-years. Increasing risk was also observed with the amount of tobacco (mg) smoked increases. Risk tended to decline with years since quitting and with age started smoking and these linear trend were statistically significant ($P < 0.01$).

The risk associated with *tuibur* is mainly seen in Mizoram. Non-users were kept as the reference group to compute the risk estimates. The OR of current *tuibur* user was higher than former *tuibur* users. The likelihood ratio test showed that the risk associated with current *tuibur* users was significantly different from that seen among former *tuibur* users and OR

Table 1. Age distribution and social characteristics of cases and controls

Variables	Cases, n (%)	Controls, n (%)
Age group (y)		
<45	24 (7.3)	52 (7.8)
45-54	97 (29.5)	195 (29.3)
55-64	118 (35.9)	238 (35.8)
65-74	62 (18.8)	124 (18.6)
75≤	28 (8.5)	56 (8.4)
Mean ± SD	56.8 ± 8.4	57.1 ± 8.9
Sex		
Male	253 (76.9)	512 (77.0)
Female	76 (23.1)	153 (23.0)
Male/Female	3.3:1	
Education		
Illiterate	165 (50.1)	195 (29.3)
Up to class XII	122 (37.1)	364 (54.7)
College level or more	42 (12.8)	106 (15.9)
Income		
Low	48 (14.6)	70 (10.5)
Middle	123 (37.4)	288 (43.3)
High	158 (48.0)	307 (46.2)
Occupation		
Office worker	65 (19.8)	180 (27.1)
Skilled worker	26 (7.9)	41 (6.2)
Unskilled worker	49 (14.9)	36 (5.4)
Cultivator	95 (28.9)	200 (30.1)
Others	94 (28.6)	208 (31.2)

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Table 2. Tobacco smoking and risk of stomach cancer

Habits	Cases	Controls	Univariate*, OR (95% CI)	Multivariate†, adjusted OR (95% CI)
Smoking status				
Non-smokers	85	389	1.0 (reference)	1.0 (reference)
Ex-smokers	75	104	3.1 (1.6-11.3)	1.8 (0.4-7.7)
Current smokers	169	157	4.6 (2.7-14.7)	2.3 (1.4-8.4)
Smoking types				
Non-smokers	85	389	1.0 (reference)	1.0 (reference)
Cigarette	13	39	1.8 (0.8-7.2)	1.2 (0.5-14.2)
Meiziol	167	170	4.0 (1.7-10.4)	2.2 (1.3-9.3)
Cigarette + *Meiziol*	64	50	5.9 (2.5-12.1)	3.1 (2.0-11.1)
Smoking frequency/d				
Non-smokers	85	389	1.0 (reference)	1.0 (reference)
<5	15	28	2.3 (0.7-7.2)	1.1 (0.6-5.8)
5-10	114	122	3.6 (1.3-10.4)	1.7 (0.3-8.2)
>10	115	101	4.9 (2.7-13.6)	2.8 (1.3-9.3)
$P_{trend} < 0.0001$				
Age began (y)				
Non-smokers	85	389	1.0 (reference)	1.0 (reference)
≤10	44	46	4.1 (1.4-10.4)	2.1 (0.5-7.1)
11-20	153	142	2.7 (0.7-8.2)	1.3 (0.1-6.2)
>20	47	68	1.9 (0.04-9.1)	1.1 (0.01-8.0)
$P_{trend} < 0.001$				
Smoking duration (y)				
Non-smokers	85	389	1.0 (reference)	1.0 (reference)
≤15	21	45	1.9 (0.4-13.4)	1.1 (0.03-9.4)
16-30	99	111	4.1 (0.8-12.6)	1.8 (0.8-9.5)
>30	124	105	5.4 (2.5-11.5)	2.9 (1.3-11.6)
$P_{trend} < 0.001$				
Pack-years of smoking				
Non-smokers	85	389	1.0 (reference)	1.0 (reference)
<5	20	25	2.1 (1.1-8.3)	1.1 (0.02-6.68)
5-10	73	90	3.1 (1.8-10.4)	1.4 (0.18-6.91)
11-19	60	68	4.0 (1.9-13.8)	2.0 (1.3-10.6)
≥20	91	93	4.5 (2.1-15.5)	2.7 (1.5-15.4)
$P_{trend} < 0.001$				
Tobacco smoked (mg)				
Non-smokers	85	389	1.0 (reference)	1.0 (reference)
<25,000	53	70	2.7 (0.11-5.19)	1.2 (0.05-9.53)
25,000-50,000	61	64	3.6 (0.76-9.17)	1.8 (0.22-8.63)
>50,000	130	142	4.2 (1.21-11.5)	2.1 (1.28-13.9)
$P_{trend} < 0.001$				
Years since stopped smoking				
Non-smokers	85	389	1.0 (reference)	1.0 (reference)
<10	36	36	4.5 (1.5-17.4)	2.3 (1.1-14.2)
10-19	27	33	3.2 (1.2-13.2)	2.1 (1.1-12.9)
≥20	12	35	1.7 (0.54-6.2)	1.1 (0.5-8.4)
$P_{trend} < 0.01$				

*Matched (cases and controls were matched for age and sex) univariate OR estimated by conditional logistic regression analysis.
† Adjusted ORs (adjusted for alcohol drinking, chewing, *tuibur*, level of education, occupation, and income group) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

of former *tuibur* users was not statistically significant in the multivariate model (OR, 1.3; 95% CI, 0.4-2.1). Significant dose-response effects were observed as the intensity of *tuibur* use per day and duration in years increases and decreasing trend was observed for the increase of age of start in the multivariate model with the statistically significant trend ($P < 0.001$) indicating independent effect of the habit. The risk remains for 1 to 10 years after cessation of the habit, although the trend test was not statistically significant. Increased risks were also observed as the use of cumulative dose to amount of *tuibur* (ml) increases with significant trend ($P < 0.001$; Table 3).

Association of different type of chewing habit with stomach cancer has been shown in Table 4. In univariate analysis, both ex-chewers and current chewers had higher risk (2.0-2.2 times) of stomach cancer compared with non-chewers. But in multivariate analysis, after controlling for other habits, statistically non-significant risk was observed compared with non-chewers. On the other hand, the risk of stomach cancer significantly higher (OR, 2.6) even after adjustment in persons who chewing tobacco (smokeless tobacco) only. In addition, there appeared an increase in risk for stomach cancer in late chewers. Increased risks were also observed among the tobacco chewers as the amount of tobacco (in mg; OR, 2.6; 95% CI, 1.2-5.6) increases in a dose-dependent manner.

The risk among persons who practice different tobacco-related habits are given in Table 5. The highest risk showed who practice both *meiziol* and *tuibur* (OR, 2.3; 95% CI, 1.8-3.6). The risk associated with the practice of just one of the habit showed *meiziol* users (OR, 2.2; 95% CI, 1.6-3.1) with a higher risk than *tuibur* (OR, 2.0; 95% CI, 1.5-3.2), betel with tobacco only (OR, 1.7; 95% CI, 0.6-2.9), and betel without tobacco only (OR, 1.3; 95% CI, 0.4-2.0).

Discussion

Tobacco smoking and use of smokeless tobacco, chewing of tobacco and *tuibur*, are common in both the sexes in Mizoram. We found tobacco smoking to be a significant risk factor. The excess risk was largely confined to long-term heavy smokers. Relatively high prevalence of tobacco smoking in Mizoram (7) may have contributed to the high rates of stomach cancer.

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Table 3. *Tuibur* (tobacco smoke–infused water) and risk of stomach cancer

Habits	Cases	Controls	Univariate*, OR (95% CI)	Multivariate†, adjusted OR (95% CI)
Tuibur status				
Non-user	236	557	1.0 (reference)	1.0 (reference)
Former user	37	46	1.9 (1.1-2.8)	1.3 (0.4-2.1)
Current user	56	55	2.4 (1.5-3.4)	2.1 (1.3-3.1)
Frequency/d				
Non-user	236	557	1.0 (reference)	1.0 (reference)
<5	17	28	1.3 (0.4-4.0)	1.1 (0.2-7.2)
5-10	48	55	1.7 (0.3-7.4)	1.3 (0.4-8.2)
>10	28	18	3.3 (1.6-10.7)	2.8 (1.1-11.7)
$P_{trend} < 0.001$				
Age began (y)				
Non-user	236	557	1.0 (reference)	1.0 (reference)
≤19	23	19	3.4 (1.8-16.5)	2.7 (1.3-15.6)
20-29	25	41	2.2 (0.6-12.7)	1.5 (0.6-6.4)
≥30	45	61	1.7 (0.3-8.6)	1.2 (0.8-7.3)
$P_{trend} < 0.0001$				
Duration (y)				
Non-user	236	557	1.0 (reference)	1.0 (reference)
≤15	20	26	1.8 (0.6-4.8)	1.4 (0.05-7.9)
16-30	45	50	2.7 (1.4-6.6)	1.7 (0.3-8.4)
>30	28	25	3.6 (1.7-11.2)	2.4 (1.1-10.5)
$P_{trend} < 0.0001$				
Years since stopped				
Non-user	236	557	1.0 (reference)	1.0 (reference)
<10	15	12	2.4 (1.24-8.54)	1.9 (1.1-6.2)
10-20	18	27	1.6 (0.4-5.27)	0.5 (0.02-6.1)
>20	9	21	1.1 (0.1-4.98)	0.2 (0.07-7.2)
Trend test not significant				
Cumulative dose to amount of tuibur (ml)				
Non-user	236	557	1.0 (reference)	1.0 (reference)
<1,000	45	57	1.8 (0.7-5.2)	0.7 (0.05-8.2)
1,000-2,000	24	27	2.1 (1.1-9.2)	1.3 (0.5-7.5)
>2000	24	17	3.3 (1.7-9.2)	2.1 (1.7-8.6)
$P_{trend} < 0.001$				

*Matched (cases and controls were matched for age and sex) univariate OR estimated by conditional logistic regression analysis.

†Adjusted ORs (adjusted for alcohol drinking, chewing, smoking, level of education, occupation, and income group) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

An increased risk of stomach cancer among smokers has been observed in numerous case-control and cohort studies (10-16) and is consistent with our study too. However, studies from Europe have reported no association between stomach cancer and smoking (17-23). Smoking as a variable risk factor for stomach cancer has also been reported from India (24, 25). However, the present study indicated statistically significant higher risk among current smokers compared with ex-smokers, which is consistent with previous findings (10, 12, 13, 16, 26). Furthermore, we are also reporting smoking of crude tobacco, *meiziol* (local cigarette) in this study, and its association with higher risk. Our study has shown significant dose response relationship with the quantity of smoked like other studies (10, 19, 27-31). Tobacco smoke contains a variety of carcinogen including *N*-nitroso compounds and nitrogen oxides that may promote endogenous formation of *N*-nitroso compounds (32), which have been linked to gastric carcinogenesis (33). IARC has revealed that smoking is causally associated with cancer of the stomach (34). A potential causal role of tobacco in causation of pre-cancerous lesions, in a high-risk area of China, where smoking was found to nearly double the risk of transition to gastric dysplasia (35). Another study (36) carried out in the United States revealed that current smokers had 2.3 times increased risk of dying from stomach cancer compared with non-smokers.

The Third National Cancer Survey of the United States (37) and studies elsewhere reported a non-significant risk of stomach cancer with smokeless tobacco use (31, 38, 39). Our study revealed significant elevated risk among the chewers of tobacco only (smokeless tobacco) and *tuibur* users than the nonusers, which supported the findings of toxicity of *tuibur* (8). There is sufficient evidence that smokeless tobacco causes oral and pancreatic cancer in humans and sufficient evidence of carcinogenicity from animal studies (40). The working group of the IARC monograph concluded that smokeless tobacco is "carcinogenic to humans." It is pertinent to mention here that while keeping *tuibur* in the mouth for sometime, some portion of it also swallowed. Therefore, association of *tuibur* with stomach cancer in Mizoram cannot be ruled out. Of course, further experimental studies are required to confirm the risks of *tuibur* use in Mizoram.

Although our study revealed no significant association between betel quid chewers and stomach cancer like other study (25), a risk (OR, 2.8) had been observed in persons who consumed betel quid along with tobacco and those who were late chewers. However, there are sufficient evidence of betel

Table 4. Chewing of betel nut with or without tobacco and risk of stomach cancer

Habits	Cases	Controls	Univariate*, OR (95% CI)	Multivariate†, adjusted OR (95% CI)
Chewing status				
Non-chewers	131	388	1.0 (reference)	1.0 (reference)
Ex-chewers	83	120	2.0 (1.4-2.9)	1.6 (0.7-2.6)
Current chewers	115	150	2.2 (1.6-3.1)	1.5 (0.5-2.2)
Chewing ingredients				
Non-chewers	131	388	1.0 (reference)	1.0 (reference)
Betel nut + betel leaf	110	189	1.7 (1.2-2.3)	1.2 (0.7-2.1)
Tobacco alone	25	20	3.7 (1.9-7.2)	2.6 (1.1-4.2)
Betel nut + Betel leaf + tobacco	54	56	2.8 (1.8-4.4)	2.0 (1.3-5.3)
Chewing frequency/d				
Non-chewers	131	388	1.0 (reference)	1.0 (reference)
≤3	82	110	1.03 (0.7-1.5)	0.6 (0.1-4.4)
>3	116	160	2.2 (1.5-2.9)	1.4 (1.0-4.3)
$P_{trend} < 0.001$				
Age began (y)				
Non-chewers	131	388	1.0 (reference)	1.0 (reference)
≤10	27	39	2.0 (1.2-3.5)	1.3 (0. 3-1.4)
11-15	53	102	1.5 (0.8-1.9)	0.9 (0.4-1.9)
16-20	68	79	1.5 (1.0-2.3)	0.7 (0.06-3.3)
21-30	30	34	2.6 (1.4-4.5)	1.9 (1.1-3.1)
≥31	20	16	3.7 (1.7-7.7)	2.6 (1.6-5.5)
Trend test not significant				
Years of chewing				
Non-chewers	131	388	1.0 (reference)	1.0 (reference)
≤15	66	96	2.0 (1.3-3.0)	1.2 (0.06-4.4)
16-30	48	64	2.2 (1.4-3.4)	1.3 (0.65-5.4)
>30	72	103	2.0 (1.4-3.0)	1.1 (0.03-6.4)
Trend test not significant				
Years since stopped chewing				
Non-chewers	131	388	1.0 (reference)	1.0 (reference)
<10	44	52	2.5 (1.5-4.0)	1.1 (0.01-6.4)
10-20	25	40	1.8 (1.04-3.2)	0.74 (0.02-4.2)
20<	14	24	1.7 (0.8-3.6)	0.61 (0.03-5.6)
Trend test not significant				
Cumulative dose to chewing of betel nut + betel leaf				
Non-chewers	131	388	1.0 (reference)	1.0 (reference)
<50,000	42	76	1.6 (1.0-2.5)	0.63 (0.05-3.2)
50,000-100,000	60	88	2.0 (1.3-3.0)	1.3 (0.08-5.3)
>100,000	84	68	3.6 (2.4-5.4)	2.3 (1.2-4.5)
$P_{trend} < 0.01$				
Cumulative dose to amount of tobacco chewing (mg)				
Non-chewers	131	388	1.0 (reference)	1.0 (reference)
<20,000	13	18	2.1 (0.9-4.7)	1.5 (0.04-4.8)
>20,000	24	22	3.2 (1.6-6.2)	2.6 (1.2-5.6)

*Matched (cases and controls were matched for age and sex) univariate OR estimated by conditional logistic regression analysis.

†Adjusted ORs (adjusted for alcohol drinking, smoking, using of *tuibur*, level of education, occupation, and income group) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

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Table 5. Different tobacco-related behaviors and risk of stomach cancer

Habits	Cases	Controls	Univariate*, OR (95% CI)	Multivariate†, adjusted OR (95% CI)
Never tobacco/betel user	135	288	1.0 (reference)	1.0 (reference)
Betel with tobacco only	45	50	1.9 (0.8-3.1)	1.7 (0.6-2.9)
Betel without tobacco only	89	126	1.5 (0.6-2.1)	1.3 (0.4-2.0)
Meiziol only	143	130	2.4 (1.7-3.2)	2.2 (1.6-3.1)
Tuibur only	56	53	2.2 (1.4-3.5)	2.0 (1.5-3.2)
Meiziol and *tuibur* only	90	80	2.6 (1.6-3.9)	2.3 (1.8-3.6)
Meiziol and betel with tobacco	67	73	2.0 (1.3-2.9)	1.9 (0.9-4.1)
Meiziol and betel without tobacco	48	58	1.7 (1.1-2.7)	1.6 (0.5-3.2)
Meiziol, *tuibur*, and betel with tobacco	64	66	2.4 (1.3-3.2)	2.1 (1.2-4.1)
Meiziol, *tuibur*, and betel without tobacco	57	60	2.0 (1.3-3.1)	1.8 (0.8-5.1)

*Matched (cases and controls were matched for age and sex) univariate OR estimated by conditional logistic regression analysis.
†Adjusted ORs (adjusted for alcohol drinking, corresponding tobacco user, level of education, occupation, and income group) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

quid with tobacco is carcinogenic to humans in sites other than stomach like oropharynx, hypopharynx, larynx, and esophagus, but betel quid without tobacco is not classifiable as to its carcinogenicity to humans (41).

In conclusion, tobacco users in the form of smoking or smokeless (chewing of tobacco only and *tuibur*) were found risk factor for stomach cancer in our study. The findings add to the growing consensus that tobacco is risk factors for stomach cancer and that efforts aimed at tobacco cessation may eventually help to reduce the burden of stomach cancer, still one of the world's most common malignancies.

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Annexe 54

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Smokeless tobacco use and risk of cancer of the pancreas and other organs

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Limited data are available on the carcinogenicity of smokeless tobacco products in organs other than the mouth. Snus is a smokeless tobacco product widely used in Norway. We studied 10,136 Norwegian men enrolled since 1966 in a prospective cohort study, 31.7% of whom were exposed to snus. The relative risk of pancreatic cancer for snus use was 1.67 (95% confidence interval [CI] = 1.12, 2.50); that of oral and pharyngeal cancer was 1.10 (95% CI = 0.50, 2.41), that of esophageal cancer was 1.40 (95% CI = 0.61, 3.24), and that of stomach cancer was 1.11 (95% CI = 0.83, 1.48). The relative risks of cancers of the lung (either all histological types or adenocarcinoma), urinary bladder and kidney were not increased among snus users. The increase in the relative risk of pancreatic cancer was similar in former and current snus users and was restricted to current tobacco smokers. Our study suggests that smokeless tobacco products may be carcinogenic on the pancreas. Tobacco-specific *N*-nitrosamines are plausible candidates for the carcinogenicity of smokeless tobacco products in the pancreas.
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Key words: smokeless tobacco; pancreatic cancer; lung cancer; epidemiology; N-nitrosamines

Use of smokeless tobacco products is common in many regions of the world and is increasing in the United States and Northern Europe.[1,2] Tobacco chewing is a major risk factor for oral and pharyngeal cancer in Asia,[3,4] but a similar increase in risk has not been shown consistently among users of smokeless tobacco products in the United States or Europe.[5,6] Smokeless tobacco might cause other cancers, in particular those linked to tobacco smoking, but limited data are available.[2,4,5] In particular, an increased risk of pancreatic cancer has been suggested in studies based on few exposed cases.[7,8] A detailed assessment of the risk of pancreatic and other cancers entailed by smokeless tobacco use is needed before conclusions on the overall health risks of this group of products can be reached.

Although tobacco snuff and chewing entail very little exposure to polycylic aromatic compounds, exposure to *N*-nitrosamines is substantial.[9–11] Tobacco-specific nitrosamines are experimental carcinogens and are heavily suspected to cause cancer, in particular adenocarcinoma, in humans.[12]

Snus is a smokeless tobacco product widely used in Norway; it is usually placed behind the upper or lower lip. The average sale of snus in the mid-1960s was around 200 g/year/Norwegian adult. It decreased to 80 g/year in the 1980s, and has remained stable since.[13]

We conducted a detailed analysis of cancer incidence in a cohort of Norwegian men to estimate the risk of cancer of the pancreas and other organs from use of smokeless tobacco products.

Material and methods

The cohort under study consists of 2 groups of subjects: a systematic sample of the general adult population of Norway identified from the 1960 census, and relatives of Norwegian migrants to the United States.[7,14] Study subjects completed questionnaires on lifestyle habits in 1964 and 1967. The participation rate varied by study and location, but was above 75%. The questionnaire collected information on use of smokeless tobacco, as well as information on dietary habits, tobacco smoking, alcohol drinking and anthropometric parameters.

A total of 12,431 men who were alive on 1 January 1966 were included in the study. Information on snus use was missing for 2,295 of them (18.5%); the remaining 10,136 cohort members were classified as regular current users (N = 1,999, 19.7%), regular former users (N = 1,216, 12.0%), or never or occasional users (N = 6,921, 68.3%). The age distribution of subjects with information on snus was very close to that of subjects with missing information (χ^2 test with 7 *d.f.*, p = 1.0). Tobacco smoking was classified as never/current/former smoking of cigarettes/cigars/pipe. Amount of current smoking was classified in 3 categories for cigarettes (1–9, 10–14 and 15+ cigarettes/day) and in 2 categories for cigars and pipe (1–4 and 5+ g/day). Information on amount of smoking was not available for former smokers. No reassessment of snus use or tobacco smoking was carried out during the follow-up.

Cohort members were followed until date of diagnosis of cancer, date of emigration, date of death or 31 December 2001, whichever occurred earliest. The follow-up was carried out *via* linkage with nationwide residence, mortality and cancer incidence registries, using unique personal identification numbers. Fifteen cohort members were lost to follow-up (0.15%). For the purpose of this analysis, we considered the incidence of cancers of the oral cavity and pharynx (ICD7, 141–148), esophagus (ICD7, 150), stomach (ICD7, 151), pancreas (ICD7, 157), lung (ICD7, 162), kidney (ICD7, 180) and urinary bladder (ICD7, 181). In addition, cases of esophageal and lung adenocarcinoma were considered separately. Cases diagnosed on the basis of a clinical examination or death certificate only were excluded. The analysis of pancreatic cancer risk was based on 220,007 person-years of observation. Censoring the follow-up at the time of first diagnosis resulted in a slightly different number of person-years in the analysis of each cancer.

Cox proportionate hazard regression models, including attained age as time variable, were fitted to the data to estimate relative risks (RR) and 95% confidence intervals (CI) of each cancer. The regression models used in the main analysis included terms for never, former and current smoking of cigarettes, cigars and pipe. In sensitivity analyses, alternative approaches were used to control for the potential confounding effect of tobacco smoking. Additional models included a term for body mass index (BMI).

Results

The number of incident cases was 34 for oral and pharyngeal cancer, 27 for esophageal cancer (4 cases of adenocarcinoma), 217

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for stomach cancer, 105 for pancreatic cancer, 343 for lung cancer (of whom 50 cases of adenocarcinoma), 88 for kidney cancer and 238 for bladder cancer.

There was an increased RR of pancreatic cancer among ever users of snus, and the RR of oral and pharyngeal, esophageal and stomach cancer showed a modest, non-significant increase. There was no increase in the RR of lung cancer (all histological types and adenocarcinoma) and of other cancers included in the analysis (Table I). No difference in the RR of pancreatic cancer was evident between former and current use. The number of cases of esophageal adenocarcinoma was too small to justify a separate analysis. Table II shows the RRs of pancreatic and lung cancers for ever snus use, estimated separately according to smoking habit. The number of cases among never and former smokers was small, and there was no evidence of an increased RR of pancreatic cancer in these 2 groups.

Different approaches to control for the potential confounding effect of tobacco smoking resulted in risk estimates that were similar to those reported in Table I. For example, the RR of pancreatic cancer for ever snus use, derived from a model including a continuous term for amount of tobacco smoking, was 1.66 (95% CI = 1.06, 2.62). Further adjustment for body mass index did not affect the RR (not shown in detail).

Discussion

Our study provides evidence for a carcinogenic effect of smokeless tobacco products on the pancreas, thus confirming the findings of an early report from this cohort, which was based on only 14 cases among snus users.[7] None of the other available studies, all from the United States, included more than 10 cases of pancreatic cancer among users of smokeless tobacco products.[8,15–17] Despite the low statistical power, an association was suggested in two of these studies.[8,17]

Arguments in favor of a causal effect of snus on pancreatic cancer in our study are the strong statistical significance, the likely exclusion of selection and information bias because of the prospective nature of the investigation, and the lack of an apparent confounding effect of tobacco smoking and BMI. Residual confounding by tobacco smoking or by other potential risk factors for pancreatic cancer, such as heavy alcohol intake and a diet poor in fruits and vegetables, cannot be completely ruled out. The lack of a corresponding increase in risk of lung cancer detracts from the hypothesis of residual confounding by tobacco smoking.

Lack of information on snus use and tobacco smoking after enrollment in the cohort is a matter of concern, in particular given the long-term follow-up of the study. Given the decrease in the prevalence and use of snus among Norwegian men during the study period, it is likely that change in snus use status mainly affected current users who quit rather than non-users and formed users who took up the habit. Because misclassification is unlikely to have occurred differentially with respect to outcome (*i.e.*, future cases of pancreatic cancer having changed their habits during the follow-up differently from other cohort members), it should have resulted in an underestimate of the difference of carcinogenic effect of snus between current and former snus users. Additional limitations of our study are the lack of information on amount and duration of snus use, which preempted dose-response analyses, and the small number of cases of pancreatic cancer among never and former smokers.

N-nitroso compounds, specifically *N*-nitrosamines, are plausible candidates for the carcinogenicity of smokeless tobacco products in the pancreas. Tobacco-specific nitrosamines have been identified in the pancreatic juice of smokers and, to a lesser extent, of non-smokers.[18] Experimental studies have shown the ability of tobacco-specific nitrosamines to produce pancreatic cancer in exposed rats,[12] and, in one experiment, oral administration of NNK (one of the main tobacco-specific nitrosamines) was more effective in causing pancreatic cancer than other routes of exposure.[19] Furthermore, a high proportion of G to A transitions in K-ras mutations detected in nitrosamine-induced animal pancreatic cancers represents further evidence for a central role of tobacco-specific nitrosamines and other *N*-nitrosamines in pancreatic carcinogenesis, although results on mutations in human cancers are not consistent.[12,20]

The lack of an increased risk of lung cancer among smokeless tobacco users confirms previous reports.[21–23] The relatively large size of the cohort confers a power of 80% to detect as significant a relative risk of 1.28 or greater. The analysis of lung adenocarcinoma was limited by the small number of cases, however, and our study had 80% power to detect as significant a relative risk of 1.85 or greater. We therefore cannot exclude some carcinogenic effect of smokeless tobacco on lung adenocarcinoma.

A weak, non-significant association was detected between use of snus and cancer of the oral cavity. The statistical power of our study for oral cancer was similar to that for lung adenocarcinoma (80% power to detect as significant a relative risk of 1.8–1.9). Chewing of tobacco products is an important cause of oral and pharyngeal cancer in several developing regions of the world, including in particular India,[3,9] other South Asian countries such as Pakistan, Bangladesh and Myanmar,[24–26] Central Asia,[27] and Sudan.[28,29] Studies conducted in the United States provided evidence for a carcinogenic effect of smokeless tobacco products on the oral cavity,[30–33] although these findings were not confirmed by other investigations conducted in the United States[34,35] or in Sweden.[36,37] The inconsistencies of results from previous studies can

TABLE II – RR OF PANCREATIC CANCER AND LUNG CANCER FOR EVER USE OF SMOKELESS TOBACCO (SNUS), ESTIMATED SEPARATELY ACCORDING TO SMOKING STATUS

Smoking	Pancreatic cancer			Lung cancer		
	Cases	RR[1]	95% CI	Cases	RR[1]	95% CI
Never smokers	3	0.85	0.24–3.07	3	0.96	0.26–3.56
Former smokers	14	1.37	0.59–3.17	7	0.64	0.24–1.68
Current smokers	28	1.86	1.13–3.05	62	0.68	0.51–0.90

[1]RR, relative risk adjusted for age and, among current smokers, for amount of tobacco smoking. Reference category: never users.

TABLE I – RR OF SELECTED CANCERS FOR USE OF SMOKELESS TOBACCO (SNUS)

	NU Cases	Ever users (PY = 61,335)			Former users (PY = 23,452)			Current users (PY = 37,883)		
		Cases	RR[3]	95% CI	Cases	RR[3]	95% CI	Cases	RR[3]	95% CI
Oral/pharyngeal cancer	25	9	1.10	0.50–2.41	3	1.04	0.31–3.50	6	1.13	0.45–2.83
Esophageal cancer	18	9	1.40	0.61–3.24	5	1.90	0.69–5.27	4	1.06	0.35–3.23
Stomach cancer	143	74	1.11	0.83–1.48	32	1.29	0.87–1.91	42	1.00	0.71–1.42
Pancreatic cancer	60	45	1.67	1.12–2.50	18	1.80	1.04–3.09	27	1.60	1.00–2.55
Lung cancer (all types)	271	72	0.80	0.61–1.05	28	0.80	0.54–1.19	44	0.80	0.58–1.11
Lung adenocarcinoma	39	11	0.83	0.42–1.65	4	0.86	0.30–2.43	7	0.81	0.36–1.85
Kidney cancer	66	22	0.72	0.44–1.18	13	1.17	0.63–2.16	9	0.47	0.23–0.94
Bladder cancer	169	69	0.83	0.62–1.11	30	0.98	0.66–1.47	40	0.72	0.52–1.06

[1]NU, never users (reference category, 158,672 person years).–[2]PY, person-years of observation (analysis of pancreatic cancer risk).–[3]RR, relative risk adjusted for age and smoking of cigarettes, cigars and pipe.

be explained by methodological aspects such as adequacy of control for tobacco smoking and statistical power; in any case, our results are consistent with previous evidence in supporting the conclusion that it is unlikely that the use of smokeless tobacco products in Europe and United States entails a substantial increase in the risk of oral and pharyngeal cancer. The reasons for the difference in carcinogenic risk entailed by smokeless tobacco products used in Europe, as compared to those used in developing countries, are not fully understood, but they might be related to tobacco species, fermentation and ageing.[38]

No effect of snus use on esophageal[36,39,40] and stomach cancer[41] was detected in previous studies, and our results might be attributed to chance. Previous studies of cancers of the bladder[42,43] and kidney[44,45] do not suggest an association with use of smokeless tobacco products, which is in agreement with our findings.

There is controversy on whether the use of smokeless tobacco products that are common in Northern Europe should be encouraged as an alternative to tobacco smoking, due to the apparent lack of a strong carcinogenic effect on organs such as the lung and the oral cavity.[3,46] Although the risk of cancer of the lung and some other organs in this population was lower among snus users than among non-users, the decrease was of small magnitude and not statistically significant, and there was no clear evidence of a beneficial effect among non-smokers. Our study does not offer arguments in favor of the use of smokeless tobacco products to reduce the burden of tobacco-related cancer incidence or mortality. Furthermore, it provides evidence of a carcinogenic effect on the pancreas, which should be taken into account in the assessment of the health effects of this group of products.

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Annexe 52

Cancer Epidemiology, Biomarkers & Prevention

Smokeless and Other Noncigarette Tobacco Use and Pancreatic Cancer : A Case-Control Study Based on Direct Interviews

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Smokeless and Other Noncigarette Tobacco Use and Pancreatic Cancer: A Case-Control Study Based on Direct Interviews

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Abstract

Cigarette smoking is an important and well-established cause of pancreatic cancer. In contrast, little is known about the effects of smoking cigars, pipes, and use of smokeless tobacco on pancreatic cancer risk. The objective of the present study was to examine the association between noncigarette tobacco use (*i.e.*, cigars, pipes, smokeless tobacco) and pancreatic cancer risk among nonsmokers of cigarettes. A population-based case-control study of pancreatic cancer was conducted during 1986–1989 among residents of Atlanta, Georgia, Detroit, Michigan,, and 10 counties in New Jersey. Direct interviews were successfully completed with 526 newly diagnosed pancreatic cancer patients and 2153 controls ages 30–79 years. This analysis was restricted to lifelong nonsmokers of cigarettes and based on interviews with 154 cases newly diagnosed with carcinoma of the exocrine pancreas and 844 population controls who reported no history of cigarette smoking. We observed a consistent pattern of increased risk associated with cigar smoking, although these elevations were not statistically significant. Participants who smoked cigars regularly (*i.e.*, at least one cigar/week for ≥6 months) experienced a 70% increased risk [95% confidence interval (CI): 0.9–3.3], and those who never used other form of tobacco had a 90% increased risk (95% CI: 0.8–4.3). Risk was elevated among those who smoked more than one cigar/day [odds ratio (OR) = 1.8; 95% CI: 0.8–4.2) and among those who smoked cigars > 20 years (OR = 1.9; 95% CI: 0.9–3.9). Trends in risk with increasing amount and duration smoked were consistent but not statistically significant ($P = 0.17$ and $P = 0.16$, respectively). Subjects who used smokeless tobacco regularly had a 40% increased risk of pancreatic cancer (95% CI: 0.5–3.6) compared with nonusers of tobacco. We observed a marginally significant increasing risk with increased use of smokeless tobacco ($P = 0.04$); participants who used >2.5 oz of smokeless tobacco a week had an OR of 3.5 (95% CI: 1.1–11). Long-term use of smokeless tobacco (*i.e.*, >20 years) was also associated with a nonsignificant increased risk (OR = 1.5; 95% CI: 0.6–4.0). In contrast, pipe smokers experienced no increased risk (OR = 0.6; 95% CI: 0.1–2.8). Our results suggest that heavy use of smokeless tobacco, and to a lesser extent, cigar smoking may increase the risk of pancreatic cancer among nonsmokers of cigarettes.

Introduction

Noncigarette tobacco use has been increasing in the United States since the early 1990s (1, 2), heightening awareness of the health effects of use of noncigarette tobacco. Recent results from the American Cancer Society Prospective Cancer Prevention Study suggest that men who smoked cigars, but not cigarettes or pipes, are at increased risk of several sites of cancer known to be associated to cigarette consumption, including lung, esophagus, larynx, oral cavity, and possibly pancreas (3). Cigarette smoking is an important and well-established cause of pancreatic cancer. In contrast, little is known about the effect of noncigarette tobacco use on pancreatic cancer risk. Studies of the noncigarette tobacco use pancreatic cancer association have been hampered by the relatively few nonsmokers of cigarettes who used other forms of tobacco. Exclusion of cigarette smokers from such studies is important to estimate the independent effect of noncigarette tobacco use. Additional limitations of most case-control studies of pancreatic cancer include misclassification of disease and low response rates because of the rapid fatality from this disease (4–6). Patterns of risk by type of tobacco use coupled with information about differences in the putative carcinogens present in these types of tobacco may help to identify the human pancreatic carcinogens present in tobacco. The purpose of our study was to estimate the risk of pancreatic cancer associated with smoking cigars, pipes, and use of smokeless tobacco.

Materials and Methods

Detailed methods have been described previously (5). Briefly, this population-based case-control study was initiated simultaneously with case-control studies of three other malignancies (*i.e.*, esophagus, prostate, and multiple myeloma). The case series included all cases of carcinoma of the exocrine pancreas (International Classification of Diseases for Oncology code = 157) newly diagnosed from August 1986 through April 1989 among 30–79-year-old residents of geographic areas covered by population-based cancer registries located in Atlanta, Georgia (DeKalb and Fulton counties); Detroit, Michigan (Macomb, Oakland, and Wayne counties); and the state of New Jersey (10 counties). Despite a relatively short median time from diagnosis to interview (7 weeks), 471 of the 1153 patients initially iden-

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Table 1 Risk of pancreatic cancer by tobacco type among nonsmokers of cigarettes

Type of tobacco	No. of cases	No. of controls	Adjusted odds ratio[a]	(95% confidence interval)
Nonusers of tobacco	123	682	1.0	
Cigars				
Ever cigars	16	85	1.7	(0.9–3.3)
Only cigars	9	37	1.9	(0.8–4.3)
Pipes				
Ever pipes	9	62	0.6	(0.1–2.8)
Only pipes	1	24	0.3	(0.04–2.4)
Smokeless tobacco				
Ever used smokeless tobacco	7	44	1.4	(0.5–3.6)
Only used smokeless tobacco	5	28	1.1	(0.4–3.1)

[a] Cigarette smokers excluded. Adjusted by race, gender, geographic site, cigar smoking, smokeless tobacco, and age.

tified for study died before the interview could be conducted. Of the 682 surviving patients identified for study, 526 (77%) case patients were interviewed.

The control series was drawn from the general population of the study areas, frequency-matching controls to the expected age-race-gender distribution of cases of all four types of cancer combined in each study area. Controls 30–64 years old were selected by random-digit dialing. Of the 17,746 households telephoned, 86% provided a household census that served as the sampling frame for selection of controls under age 65 years. Of the 1568 controls chosen from these households, we interviewed 1227 (78%). Controls ages 65–79 years consisted of a stratified random sample drawn from The Centers for Medicare and Medicaid Services (formerly Health Care Financing Administration) rosters of the population age ≥ 65 years in each study area. Of the 1232 older controls selected, we interviewed 926 (75%).

We excluded from analysis 32 cases who were unlikely to have adenocarcinoma of the exocrine pancreas and 13 cases and 54 controls with unsatisfactory interviews. All cigarette smokers (327 cases and 1255 controls) were also excluded from this analysis. Thus, the analysis was based on first person interviews with 154 cases with a diagnosis of carcinoma of the exocrine pancreas and 844 population controls who were lifelong nonsmokers of cigarettes. The study was reviewed and approved by the institutional review board of the National Cancer Institute.

Cigar smokers were defined as subjects who reported smoking at least one cigar/week for at least 6 months. The same 6-month requirement (one pipe/week, chewed one pouch or plug/week, or ever used snuff) was used to define regular users of pipes, chewing tobacco, and snuff, respectively. Because of the small number of users of chewing tobacco and snuff and the high correlation between them, we combined use of chewing tobacco and/or snuff into one smokeless tobacco use variable. The amount of chewing tobacco and snuff was combined onto ounces of smokeless tobacco with each can of snuff contributing 1.2 oz of tobacco and each unit of chewing tobacco contributing 3 oz (pouches) or 2.33 oz (plugs) of tobacco. We defined nonusers of tobacco as subjects who reported not using any type of tobacco product.

Odds ratio (OR) and 95% confidence intervals (CIs) were estimated by unconditional logistic regression analysis (7). Statistical models included terms for exposure (*i.e.*, cigar smoking, pipe smoking, and smokeless tobacco), matching factors (*i.e.*, age at diagnosis/interview, race, gender, and study area), as well as potential confounding factors (*i.e.*, ever smoked cigars and ever used smokeless tobacco). Additional potential confounders [*i.e.*, diabetes mellitus (diagnosed at least 5 years before the diagnosis of cancer), alcohol, gallbladder disease, income, obesity, marital status, total calories, and pipe smoking] did not substantially modify any of the risk estimates and were not included in the final models. To test for linear trend, we computed the Wald statistic. The exposure variable was treated as continuous in the model by entering the median value for each level of the categorical variable among the controls.

Results

Table 1 shows risk estimates for use of each type of tobacco (*i.e.*, cigars, pipes, and smokeless tobacco). Cigar smokers had an OR of 1.7 (95% CI: 0.9–3.3), and cigar smokers who never used other form of tobacco had an OR of 1.9 (95% CI: 0.8–4.3). Consistent positive trends in risk with both amount and duration smoked cigars were apparent, although these trends were not statistically significant ($P = 0.17$ and $P = 0.16$, respectively; Table 2). Risk was elevated among those who smoked more than one cigar/day (OR = 1.8; 95% CI: 0.8–4.2) and among those who smoked cigars > 20 years (OR = 1.9; 95% CI: 0.9–3.9).

Use of cigars and pipes was highly correlated. Most pipe smokers also smoked cigars. Those who ever smoked cigars but never smoked pipes had a higher risk (OR = 1.5; 95% CI: 0.7–3.5) than those who ever smoked pipes and never smoked cigars (OR = 0.7; 95% CI: 0.2–3.0). Risk estimates for cigar smokers were affected little by adjustment for pipe smoking (OR = 1.7; 95% CI: 0.8–3.5), but those for pipe smoking were close to the unity after cigar smoking was taken into account. After adjustment for cigar smoking and smokeless tobacco use, ORs were as follows: ever smoked pipes regularly 0.6 (95% CI: 0.1–2.8); smoked pipes > 20 years 0.8 (95% CI: 0.2–3.7); and smoked more than two pipe fills/day 0.7 (95% CI: 0.1–3.5).

Subjects who ever used smokeless tobacco and never smoked cigarettes had a 40% increased risk of pancreatic cancer (95% CI: 0.5–3.6) compared with nonusers of any tobacco product (Table 1). We observed a marginally significant increasing risk with increased use of smokeless tobacco ($P = 0.04$); subjects who used >2.5 oz of smokeless tobacco a week had an OR of 3.5 (95% CI: 1.1–11; Table 2). Long-term users of smokeless tobacco had an OR of 1.5 (95% CI: 0.6–4.0), but the trend in risk with duration of use was not significant ($P = 0.42$). Although use of chewing tobacco and snuff were highly correlated, chewing tobacco use seemed to contribute more than snuff use to the observed increased risk of pancreatic cancer among users of smokeless tobacco. When we included both types of smokeless tobacco in the same model adjusting for cigar smoking, the resulting ORs were 1.7 (95% CI: 0.6–

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Table 2 Numbers of cases and controls and odds ratios by amount and years smoked cigars and smokeless tobacco among nonsmokers of cigarettes

Type of tobacco	No. of cases	No. of controls	Adjusted (odds ratio)[a]	(95% CI)	*P* for trend
Nonusers of tobacco	123	682		1.0	
Cigars					
Cigars smoked/day					
≤1	7	41	1.6	(0.7–4.1)	
>1	9	41	1.8	(0.8–4.2)	0.17
No. of years smoked					
≤20	3	24	1.2	(0.3–4.3)	
>20	13	61	1.9	(0.9–3.9)	0.16
Smokeless tobacco					
Ounces/wk					
≤2.5	1	22	0.3	(0.04–2.5)	
>2.5	6	22	3.5	(1.1–10.6)	0.04
No. of years used					
≤20	1	10	1.1	(0.1–11.0)	
>20	6	33	1.5	(0.6–4.0)	0.42

[a] Cigarette smokers were excluded. Adjusted by race, gender, geographic site, and cigar smoking, smokeless tobacco, and age.

4.5) and 1.1 (95% CI: 0.4–3.5) for chewing tobacco and for snuff use, respectively. Subjects who chewed tobacco used more ounces of smokeless tobacco/week (mean of 7.2 oz) than those who dipped snuff (2.4 oz) and experienced a marginally significant increasing risk of pancreatic cancer with increased use of chewing tobacco ($P = 0.04$).

Additional analyses including cigarette smokers indicated patterns of risk similar to those observed for nonsmokers of cigarettes.

Discussion

Our results suggest that heavy use of smokeless tobacco and, to a lesser extent, cigar smoking may increase the risk of pancreatic cancer among nonsmokers of cigarettes.

Results of studies of the relation between cigar smoking and pancreatic cancer have been equivocal. Increased pancreatic cancer risk has been reported for cigar smokers in some prospective (2, 3, 8, 9) and retrospective studies (10–12) but not all (13, 14). Most studies with positive findings presented risks for smoking only cigars, whereas most negative studies included cigarette smokers in their analyses or did not report the effects of smoking only cigars.

Our study is the first positive report of the effect of smokeless tobacco on pancreatic cancer risk among noncigarette smokers. Increased risk for users of smokeless tobacco was previously reported in one case-control study (10) and two cohort studies (15, 16), but these studies included cigarette smokers. No association was reported in a third case-control study based on small numbers of subjects (17). Our results are similar to the only previous report of risk by type of smokeless tobacco, which suggested a positive association for chewing tobacco, but not for snuff (10).

Support for an association between pipe smoking and pancreatic cancer is weaker than that for cigar smoking and smokeless tobacco. Most studies have failed to find an association between pipe smoking and pancreatic cancer (12–14, 16, 18, 19), with only two studies reporting positive findings (10, 20).

Our estimates of pancreatic cancer risk associated with cigar smoking and use of smokeless tobacco were similar to those previously reported for cigarette smoking (5). The chemistry of cigar smoke is qualitatively similar to that of cigarettes, however, many quantitative differences do exist (2). Tobacco-specific *N*-nitrosamines (TSNA) are present in cigar smoke at significantly higher levels than in cigarette smoke. In particular, cigar smoke is richer than cigarette smoke in the highly carcinogenic TSNA N′-nitrosonorcotinine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The most important carcinogenic agents present in smokeless tobacco are TSNA, whereas the levels of polycyclic aromatic hydrocarbons in smokeless tobacco appear to be too low to make a significant contribution to smokeless tobacco carcinogenicity (2). Cigarette filters reduce the concentration of inhaled particulate containing the carcinogenic polycyclic aromatic hydrocarbons but do not significantly reduce the TSNA level. Switching from nonfilter cigarettes to filter cigarettes does not appear to lower the risk of pancreatic cancer (5, 10), suggesting that TSNA might play a more important role than polycyclic aromatic hydrocarbons in tobacco-induced pancreatic cancer. In addition, a recent study found measurable amounts of NNK and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human pancreatic juice with significantly higher levels among smokers than nonsmokers (21). Although it is unclear to what extent nitrosamines might be activated in the human pancreas (22, 23), NNK and NNAL are metabolically activated in the liver (24) and excreted into the bile. NNK metabolites have been detected and measured in the bile of rats after *intra peritoneum* administration of NNK (25) and are known to induce pancreatic tumors in experimental studies (26).

Our study has a number of strengths, including analyses based solely on nonsmokers of cigarettes, its population-based study design, availability of information obtained from direct interviews with patients, and a review of diagnostic material for all pancreatic cancer cases. Some possible limitations are also apparent. First, most point estimates are not statistically significant. We believe, however, that the consistency of the patterns of risk (*e.g.*, higher risks among heavily exposed subjects), coupled with similar results from previous studies, suggests that the observed associations between heavy use of smokeless tobacco/cigar use and pancreatic cancer are unlikely to be due to chance. Second, because 40% of patients initially identified for study died before the interview could be conducted, survival

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bias cannot be ruled out. A methodological substudy indicated that cigarette smoking habits of cases who survived enough to be interviewed were similar to those of cases who died before interview (5), suggesting that survival was not related to tobacco use and is unlikely to explain our findings.

In summary, our results suggest that heavy use of smokeless tobacco and possibly cigar smoking may increase the risk of pancreatic cancer among nonsmokers of cigarettes. Because of the recent rise of noncigarette tobacco use in the United States, coupled with the misconception that noncigarette tobacco is a safe product (2), additional research is needed to better understand whether smoking cigars and smokeless tobacco cause pancreatic cancer.

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Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study

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Summary

Background Although classified as carcinogenic, snuff is used increasingly in several populations. Scandinavian moist snuff (snus) has been proposed as a less harmful alternative to smoking, but precise data on the independent associations of snus use with site-specific cancers are sparse. We aimed to assess the risks for cancer of the oral cavity, lung, and pancreas.

Methods Detailed information about tobacco smoking and snus use was obtained from 279 897 male Swedish construction workers in 1978–92. Complete follow-up until end of 2004 was accomplished through links with population and health registers. To distinguish possible effects of snus from those of smoking, we focused on 125 576 workers who were reported to be never-smokers at entry. Adjusted relative risks were derived from Cox proportional hazards regression models.

Findings 60 cases of oral, 154 of lung, and 83 of pancreatic cancer were recorded in never-smokers. Snus use was independently associated with increased risk of pancreatic cancer (relative risk for ever-users of snus 2·0; 95% CI 1·2–3·3, compared with never-users of any tobacco), but was unrelated to incidence of oral (0·8, 95% CI 0·4–1·7) and lung cancer (0·8, 0·5–1·3).

Interpretation Use of Swedish snus should be added to the list of tentative risk factors for pancreatic cancer. We were unable to confirm any excess of oral or lung cancer in snus users.

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Introduction

Use of snuff has become increasingly popular in several countries, but Sweden has the highest consumption, predominantly in the form of moist snuff (snus). The habit is especially gaining popularity in adolescents and women.[1] At present, however, the majority of users are men; at least 23% of Swedish men used snus in 2002.[2]

About 30 carcinogens have been identified in smokeless tobacco, and the tobacco-specific nitrosamines, formed from nicotine and related tobacco alkaloids, are thought to be particularly important.[3] The tobacco-specific nitrosamines with the greatest proportions in snuff (4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone [NNK] and N′-nitrosonornicotine [NNN]), have been implicated in the cause of tobacco-related cancers.[4–6] Comparative studies have generally shown lower concentrations of tobacco-specific nitrosamines in Swedish snus than in American snuff,[7] leading to a perception that the use of Swedish snus is a suitable alternative to smoking. Indeed, with a few exceptions,[8–10] studies of Scandinavian snus have shown no risk associated with use of this form of tobacco.[7] The Scandinavian experience differs from that in South Asia[11] and elsewhere,[12,13] where smokeless tobacco is an established risk factor for oral cancer. This inconsistency might be attributable to methodological aspects, such as inadequate control for confounding by cigarette smoking and alcohol use, which are strong risk factors for oral cancer.

Because of NNK's specificity for the lung in rodent cancer models,[14,15] lung cancer should be another concern in relation to smokeless tobacco. However, few studies have addressed this risk in human beings. The only study of Scandinavian snus and lung cancer showed a non-significantly decreased risk in snus users,[10] raising questions about residual confounding due to smoking. Epidemiological evidence[10,16–18] suggests that the use of smokeless tobacco, including Scandinavian snus,[10] might increase the risk of pancreatic cancer, but published data are based on few snus-exposed cases.

With a growing awareness of the health hazards associated with smoking, snus could become increasingly popular,[19,20] and the habit might spread to people who would otherwise refrain from tobacco use. Therefore, valid and precise epidemiological data on health risks associated with use of snus are urgently needed. We consequently did a prospective study in Swedish construction workers, with a high prevalence of exposure to snus, to address the association of snus use with oral, lung, and pancreatic cancer.

Methods

Setting and participants

The background of the Swedish construction worker cohort has been described previously.[21] Briefly, from 1969 through 1992, preventive health check-ups were offered to all workers in the Swedish building industry, and from 1971, the collected data were compiled in a computerised central

register. Each record also contained the participant's National Registration Number, a unique personal identifier assigned to every Swedish resident at birth or immigration. This identifier includes the date of birth.

Because of ambiguities in the coding of smoking status in the questionnaires used during 1971–75 (Zendehdel K, et al, unpublished), we restricted our analysis to workers with at least one visit in the 1978–92 period, when information on smoking and snus use was obtained through personal interviews by nurses. Because the group contained few women, we limited our analyses to men. Links with nationwide registers of the total population, emigration, and death enabled us to exclude records with incorrect National Registration Numbers (which could not be found in any of these registers), and men with a death or emigration date before entry. Links with the Swedish Cancer Register led to exclusion of men with cancer before entry. We also excluded men with incomplete tobacco exposure data.

Procedures

We only used exposure information obtained at the first visit, which defined entry into the cohort: snus user status (never, previous, or current), grams of snus per day (<10 g or ≥10 g), smoking status (never, previous, or current), grams of smoking tobacco per day (continuous), and body-mass index (BMI; <25, 25–29, or ≥30). The quality of exposure data has been reviewed previously and was deemed satisfactory.[21]

Follow-up was done through linking of records to the nationwide, and essentially complete, population and health registers previously mentioned. For correct censoring, dates of death were obtained from the Causes of Death register, and dates of emigration came from the Register of Domestic and International Relocations. The Cancer Register, established in 1958, codes malignant neoplasms according to the International Classification of Diseases, 7th edition, and includes information on more than 98% of all diagnosed cases in Sweden.[22,23] We used codes 140, 141, 143, and 144 for incident cases of oral cancer (not including cancers of the salivary glands, pharynx, or larynx), code 162 for lung cancer, and code 157 for pancreatic cancer. Each cohort member contributed person-time from the date of entry until the date of any first cancer diagnosis, migration, death, or December 31, 2004, whichever occurred first.

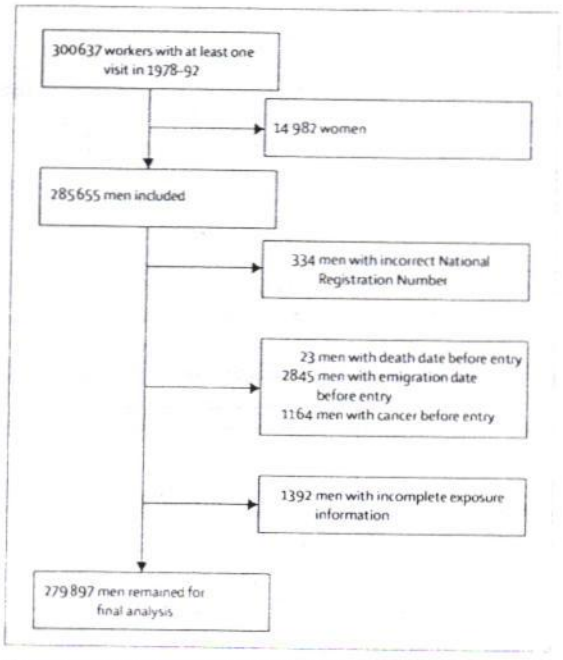

Figure: Summary of inclusion and exclusion criteria and final cohort used for analysis

Statistical analysis

All three cancers are highly age dependent. Therefore, we investigated age distributions in each exposure category. The associations between exposure variables and risk of cancer were expressed as relative risks (RRs) derived from Cox proportional hazards regression models, with attained age (continuous) as time scale. Initially, we fitted models in which the relative risks associated with smoking were adjusted for snus use, and in which relative risks linked to snus use were adjusted for smoking. To better control the strong confounding effect of smoking in our analyses of snus, we fitted models restricted to never-smokers. We adjusted for BMI in all our models. However, since BMI could conceivably be in the causal pathway, we also did analyses unadjusted for this factor. Tests for linear trend were done by creating a continuous variable from the median of the categories.

The assumption of proportional hazards was tested on the basis of the cumulative sums of Martingale residuals with the Kolmogorov-type supremum test,[24] in which 1000 realisations were used. Results indicated that the proportional assumption was satisfied for all models.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication.

Results

The figure shows the numbers of eligible workers included in and excluded from the group for our analysis. Characteristics of the 279897 men in our cohort, including smoking and snus use, are shown in table 1. Average age at entry was 35 years (SD 13). These men were followed-up for an average of 20 years (SD 6). At time of entry, 31% of the cohort members used or had previously used snus. The proportion of ever-smokers was greater for men older than 30 years than in younger

	Number	Person-years accumulated	Users of snus		Users of snus only		Smokers	
			Ever	Current	Ever	Current	Ever	Current
<30 years	122 820 (44%)	2 410 637	45 710 (37%)	41 501 (34%)	28 689 (23%)	27 122 (22%)	47 209 (38%)	37 066 (30%)
30–39 years	69 216 (25%)	1 492 628	21 194 (31%)	16 139 (23%)	5 505 (8%)	4 648 (7%)	46 538 (67%)	30 719 (44%)
40–49 years	45 065 (16%)	927 998	10 530 (23%)	7 700 (17%)	2 021 (4%)	1 711 (4%)	30 879 (69%)	18 990 (42%)
50–59 years	32 455 (12%)	612 408	6 262 (19%)	4 569 (14%)	1 043 (3%)	911 (3%)	22 593 (70%)	12 913 (40%)
≥60 years	10 341 (4%)	167 405	2 177 (21%)	1 601 (15%)	497 (5%)	426 (4%)	7 102 (69%)	3 621 (35%)
Total	279 897 (100%)	5 611 075	85 873 (31%)	71 510 (26%)	37 755 (13%)	34 818 (12%)	154 321 (55%)	103 309 (37%)

Table 1: Baseline characteristics by age at entry

	Number	Person-years	Oral cancer			Lung cancer			Pancreatic cancer		
			Cases	IR	RR (95% CI)	Cases	IR	RR (95% CI)	Cases	IR	RR (95% CI)
Never-users of any tobacco	87 821	1 751 072	50	3·1	1·0 (ref)	136	8·6	1·0 (ref)	63	3·9	1·0 (ref)
Ever-smokers	154 321	3 153 168	198	5·3	2·0 (1·4–2·7)	2062	54·7	7·2 (6·0–8·5)	385	10·2	2·8 (2·1–3·7)
Ex-smokers	51 012	1 069 923	48	3·1	1·1 (0·8–1·7)	329	19·8	2·6 (2·2–3·2)	105	6·3	1·8 (1·3–2·4)
Current smokers	103 309	2 083 245	150	6·9	2·5 (1·7–3·5)	1733	82·3	10·7 (8·6–12·2)	280	13·0	3·5 (2·6–4·6)

Combined use of snus and smoking tobacco was allowed in these analyses, but 37 755 men who used snus only were excluded. IR=incidence rate per 100 000 person years, standardised to age distribution of person-years experienced by all workers using 5-year age categories. *RR estimates obtained in models adjusted for attained age as time scale, BMI, and snus use.

Table 2: Relative risks of oral, lung, and pancreatic cancer in relation to tobacco smoking status at entry

men, whereas snus use was more common in those younger than 30 years, reflecting the spreading habit in the Swedish male population.

258 incident cancers of the oral cavity, 2216 of the lung, and 468 of the pancreas were recorded during follow-up. Of these, 60 oral, 154 lung, and 83 pancreatic cancers occurred in the 125 576 never-smokers.

We confirmed that tobacco smoking was a strong risk factor for all the studied cancers (table 2). The Cox regression models, which also included men who used snus simultaneously, were adjusted for attained age, BMI, and snus use. Removal of BMI from the models had little effect on the results (data not shown).

In analyses that included all cohort members, irrespective of smoking and snus user status, the adjusted relative risks for cancer in ever-users of snus, compared with never-users, were 0·7 (95% CI 0·5–0·9) for oral, 0·7 (0·6–0·7) for lung, and 0·9 (0·7–1·2) for pancreatic cancer. In analyses restricted to men who were never-smokers, ever-use of snus was associated with a significant increase of the risk for pancreatic cancer, compared with the risk in never-users of any tobacco (table 3). We also noted a significant dose-risk trend for pancreatic cancer with increasing amount of snus use (p=0·01). However, the point estimates for the two dose categories above zero (1–9 g and ≥10 g snus per day) did not differ greatly from each other. We did not observe an increased risk of oral cancer or lung cancer in men who used snus but did not smoke. Repeated analyses without adjustments for BMI produced similar results (data not shown).

Discussion

The main finding of this large cohort study was an increased risk of pancreatic cancer in never-smoking snus users compared with never-users of any tobacco, with some evidence for a dose-risk association. We did not detect any excess risk for cancer of the oral cavity or lung.

Our finding is at odds with the perception that use of Swedish moist snus has no demonstrable carcinogenic risk.[3] If valid, it will have important public-health implications, since snus has been proposed as a way to reduce harm in nicotine addicts.[19,20] The increase in risk is, however, in line with that reported in a cohort study from Norway[10]—the only published Scandinavian study on the association between use of smokeless tobacco and risk of pancreatic cancer. In that study, a significant 70% excess incidence was noted in ever-users relative to never-users of smokeless tobacco, after adjustment for smoking and alcohol use.[10,25] Some of the tobacco consumption was in the form of local chewing tobacco (skrå). In our cohort, the participants reported specifically about snus use, and use of other smokeless tobacco products was probably negligible. Results of several American studies of smokeless tobacco support our findings[16–18] although some do not.[26,27]

The excess risk was noticeable only in an analysis restricted to the never-smoking stratum. This analysis was defined a priori to eliminate residual confounding by smoking dose. Previous evidence, reinforced by observed data in the present study (not shown), suggests that individuals who combine smoking with snus use smoke

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	Number	Person-years	Oral cancer			Lung cancer			Pancreatic cancer		
			Cases	IR	RR (95% CI)†	Cases	IR	RR (95% CI)	Cases	IR	RR (95% CI)
Tobacco use											
Never-users of any tobacco	87821	1751072	50	3·1	1 (ref)	136	8·6	1 (ref)	63	3·9	1 (ref)
Ever-users of snus	37755	698542	10	2·6	0·8 (0·4–1·7)	18	6·4	0·8 (0·5–1·3)	20	8·5	2·0 (1·2–3·3)
Ex-users	2937	50469	1	1·9	0·7 (0·1–5·0)	3	8·5	0·9 (0·3–3·0)	2	6·6	1·4 (0·4–5·9)
Current users	34818	648074	9	2·7	0·9 (0·4–1·8)	15	6·0	0·8 (0·4–1·3)	18	8·8	2·1 (1·2–3·6)
Snus consumed*											
1–9 g/day	6704	134390	2	1·9	0·7 (0·2–2·8)	7	8·6	1·0 (0·5–2·1)	6	7·6	1·9 (0·8–4·3)
≥10 g/day	30683	564152	8	3·1	0·9 (0·4–2·0)	10	4·8	0·7 (0·4–1·3)	13	8·5	2·1 (1·1–3·8)
p for trend					0·8			0·2			0·01

Exposure status was that noted at entry. RR estimates obtained in models adjusted for attained age as time scale and BMI. IR=incidence rate per 100 000 person-years, standardised to age distribution of person-years experienced by all workers using 5-year age categories. *Analysis excluded 368 snus users without dose information, therefore totals for number of cases in dose-specific categories do not match exactly with corresponding totals of cases in ever-users.

Table 3: Relative risks of oral, lung, and pancreatic cancer in relation to snus use in 125 576 never-smokers

less and might increase their overall chances of subsequent abstinence, compared with those who only smoke.[28] Indeed, although findings of a Swedish case-control study[8] showed no significant relation between use of snus and overall risk of head and neck cancer in multivariate-adjusted analyses, snus use among never-smokers was associated with an almost five-times increased risk. In the Norwegian cohort study mentioned previously[10] a 20% reduction in risk of lung cancer was noted in multivariate-adjusted analyses, again suggesting residual negative confounding. The shift from a similar inverse association with lung cancer in our multivariate-adjusted analysis to a null result in the analysis restricted to never-smokers is in good agreement with the Norwegian data and provides further support for the concern about confounding. Hence, we believe that the estimate for snus in never-smokers is less biased than an estimate obtained in an overall analysis that also includes smokers and in which control for confounding by smoking is attempted through multivariate modelling. The absence of association with lung cancer in this stratum, in effect, confirms the absence of important confounding by smoking.

Efficient adjustment for smoking dose in snus-using smokers is expected to nullify any positive consequences of snus use conferred through its purported anti-smoking effects. The significant risk reductions for all three studied cancers among snus users noted in our conventional models that included the entire group, despite our attempts to adjust for smoking dose, suggest that the net effect of snus use in the studied population might be a reduced risk of cancer.

The apparent specificity for the pancreas as the target organ is biologically plausible. First, the carcinogenicity of tobacco-specific nitrosamines is remarkably organ-specific in animal experiments.[6] Although the lung and upper respiratory tract dominate as target organs, rats develop pancreatic adenocarcinoma when exposed to NNK or its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in drinking water.[14] Second, measurable amounts of NNK and NNAL have been documented in human pancreatic juice, in the case of NNK at significantly higher concentrations in smokers than in non-smokers.[29] Third, it is well established that NNK metabolites bind to DNA and induce activating point mutations in the RAS gene—mutations that are observed in 50–90% of all pancreatic adenocarcinomas.[30] Fourth, NNK acts as an agonist on β-adrenergic receptors, which activate signal transduction pathways that induce the formation of arachidonic acid and its mitogenic metabolites.[30] Fifth, Swedish data suggest a causal link between snus use and risk of type 2 diabetes,[31] and increasing evidence implicates insulin resistance and abnormal glucose metabolism as risk factors for development of pancreatic cancer.[32]

The absence of an increased risk for oral cancer in snus users confirms the negative results of published work on this particular type of smokeless tobacco.[8,30,33,34] However, residual negative confounding from smoking dose cannot be confidently excluded in these studies, as discussed above. An International Agency for Research on Cancer working party recently concluded, mainly on the basis of American and Asian data, that sufficient evidence exists that smokeless tobacco causes oral cancer in human beings.[13] With only ten cases among ever-users of snus in the never-smoker stratum, oral cancer was the least common cancer of the three studied in our analysis, making the estimates liable to chance variations.

In accord with our findings, previous epidemiological evidence on smokeless tobacco and lung cancer in developed countries has been essentially negative,[10,26,35] with few exceptions,[36] despite the strong link between exposure to tobacco-specific nitrosamines and formation of lung tumours in rodents.[6] The reasons for the discrepancy between animal and human data remain to be clarified; in our study, confounding from smoking dose is an unlikely explanation.

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Our study has several strengths but also some limitations. An important strength is the cohort design, which essentially precludes the possibility that the cancer outcome could have affected the initial reports about, or the actual use of, the tobacco products of interest. One disadvantage of this design is that individuals' tobacco-use habits might have changed during follow-up. The repeat visits during follow-up varied in number and timing, and therefore were sensitive to self-selection bias. However, we used the smoking information recorded at these visits to investigate whether workers who were initially classified as never-smoking snus users might differ from those who were classified as never-users of any tobacco. We found that 2132 of 17634 (12%) of never-smoking snus users were later recorded at some point in time as former or current smokers. The corresponding proportion in never-users of any tobacco was 2824 of 39469 (7%). We used these data and the effect sizes derived from tables 2 and 3 in a sensitivity analysis according to Schneeweiss.[17] The suggested misclassification of smoking status affected our reported estimates no more than trivially (data not shown). In accord with a recent Swedish study that reported a high probability of continuing snus use once the habit has been initiated,[18] our data from the repeat visits suggested that dose of snus remained stable over time (data not shown).

Another strength is the completeness of follow-up. Furthermore, the large cohort size and the high prevalence of exposure to snus made it possible to obtain meaningful estimates in never-smokers. However, the statistical precision is still a weak point; the estimates for the three types of cancer in never-smoking ever-users of snus were based on few cases, with considerable risk for type 2 error in analyses for oral and lung cancer.

The scarcity of information about covariates in our database needs careful consideration. The restriction to male construction workers allays concerns about confounding by sex, socioeconomic status, and occupational exposures. Furthermore, it is hard to imagine any negative confounding that would have hidden a true association of snus with risk for oral and lung cancer. In the case of pancreatic cancer, we were unable to identify any established or suspected risk factor[19] other than smoking that might be linked to snus use, although confounding by dietary factors is a possibility. Another, more speculative, confounding factor could be passive smoking, but such an effect seems unlikely in view of the strength of the association and the absence of an increased risk for lung cancer.

At present, our results can be confidently generalised only to Swedish male construction workers. Although our relative risk estimates—if unbiased and unconfounded—might reflect a biological relation that can be generalised to other populations, measures that depend on the underlying baseline risk and exposure prevalence rates (eg, risk difference, numbers needed to harm, population attributable risk percentage, etc) could differ substantially between population groups. These measures are typically the ones that are most important for public-health consequences.

We conclude that our findings are probably internally valid. Although we have some reservations about statistical power, the oral use of snus does not seem to be linked to the risk for cancer of the oral cavity or lung, in agreement with some but contrary to other previous work on oral cancer. However, the habit seems, with slightly greater certainty, to be associated with an increased risk of pancreatic cancer. The overall consistency of combined available evidence suggests that the association with pancreatic cancer is real, but perhaps weaker than that noted for smoking. Therefore, oral use of snus should be added to the list of tentative risk factors for pancreatic cancer. The Swedish snus investigated in this cohort, despite its low concentrations of tobacco-specific nitrosamines in comparison with many other smokeless tobacco products, might not be an entirely safe product. Because of the special characteristics of the cohort, additional studies in populations with other patterns of use, not the least in women, are desirable—albeit difficult to accomplish, in view of the sample sizes needed—to put the implications for public health in perspective.

Contributors

JL participated in the conception and design of the study, analysis of the data, and drafting the manuscript. WY participated in the conception and design of the study and in the interpretation of results. KZ assisted with data analysis. JA coordinated the data collection. HOA and PB provided scientific suggestions. ON was the lead author in the overall conceptualisation and design of the study, and provided overall supervision for the article. Raw data were reviewed by JL, WY, and ON. All authors took part in reviewing and editing the entire manuscript, and approved the final version of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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REVIEW ARTICLE

Smokeless tobacco use and cancer of the upper respiratory tract

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The most recent epidemiologic review of the cancer risks associated with smokeless tobacco use appeared in 1986, when 10 studies were available. This review describes 21 published studies, 20 of which are of the case-control type. We characterize each study according to the specific anatomic sites and according to the type of smokeless tobacco products for which it provides relative risks of cancer. The use of moist snuff and chewing tobacco imposes minimal risks for cancers of the oral cavity and other upper respiratory sites, with relative risks ranging from 0.6 to 1.7. The use of dry snuff imposes higher risks, ranging from 4 to 13, and the risks from smokeless tobacco, unspecified as to type, are intermediate, from 1.5 to 2.8. The strengths and limitations of the studies and implications for future research are discussed. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93:511-5)**

Smokeless tobacco (SLT) is well recognized as a cause of cancer of the oral cavity.[1] The most recent review of the epidemiology of this issue appeared in 1986 and described 10 studies.[2] The present review uses data from the 21 studies now available to estimate the relative risks (RRs) of each major type of oral and upper respiratory tract cancer associated with use of several types of SLT products.[3-23]

We identified reports from the United States and western Europe that provided data potentially usable for estimating SLT-related RRs of cancer. We excluded studies from India and other eastern countries where processed tobacco is not comparable to that used in the West. Furthermore, in eastern countries, SLT is commonly used in combination with betel leaf, areca nut, and powdered slaked lime.[1]

Twenty of the 21 available studies are of the case-control type. These provide RR estimates (or data that allow RRs to be estimated) for cancers of several anatomic sites. The Mantel-Haenszel summary odds ratio[24] was used to estimate the pooled RR for cancer of each anatomic site related to each type of SLT. The 95% 2-sided confidence interval (CI) of each RR was estimated using the test-based interval estimator.[25] Two-tailed *P* values were obtained from the Mantel-Haenszel summary chi-square statistic.

SMOKELESS TOBACCO TYPES

Three types of SLT commonly are used in the oral cavity.[26] Chewing tobacco is air-cured tobacco that is shredded into flakes and treated with sweet flavoring solutions; moist snuff consists of fire- and air-cured dark tobaccos that are finely cut and fermented; dry snuff is a fire-cured tobacco that is pulverized into powder. Chewing tobacco and moist snuff are used primarily by men, whereas dry snuff is used by women, especially in the southern United States.[27,28] All products are placed in contact with the oral mucosa, usually in the cheek or between the cheek and gum. We also present data for a fourth exposure category, SLT unspecified with respect to type, because the type of SLT used could not be determined in several studies.

CANCER OF THE ORAL CAVITY AND OTHER SITES

Oral cavity cancer (OCC) designates cancer of the tongue (International Classification of Diseases, Ninth Edition [ICD-9] code 141), gum (143), floor of the mouth (144), or of other or unspecified parts of the

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Table I. Characteristics of epidemiologic studies of smokeless tobacco and several forms of head and neck cancer

Reference number	First author	Year	Cases/controls	Tobacco type
3	Wynder	1957A	27/115	ST
4	Wynder	1957B	412/207	ST
5	Peacock	1960	45/146	ST
6	Vogler	1962	324/693	CT, DS
7	Vincent	1963	89/100	ST
8	Martinez	1969	170/510	ST
9	Williams	1977	*	ST
10	Wynder	1977	978/2560	CT, MS
11	Browne	1977	46/92	CT
12	Winn	1981	132/274	DS
13	Stockwell	1986	*	ST
14	Blot	1988	1114/1268	CT, DS
15	Spitz	1988	131/131	MS, CT
16	Maden	1992	131/136	ST
17	Zahm	1992	*	ST
18	Mashberg	1993	359/2280	ST, CT, MS
19	Kabat	1994	1560/2948	CT, MS, DS
20	Muscat	1996	1009/923	MS, CT
21	Schildt	1998	354/354	MS, CT
22	Schwartz	1998	165/302	ST
23	Lewin	1998	423/550	MS

ST, Smokeless tobacco–unspecified; *CT*, chewing tobacco; *DS*, dry snuff; *MS*, moist snuff.
*These studies provided relative risk estimates, but no case-control enumerations.

mouth (145). Code 145 includes the cheek, vestibule, palate, uvula, and retromolar region. Cancer of the lip (140) was excluded from all but 5 studies[6,8,10,17,21] and cancer of the major salivary glands (142) from all but two studies.[10,17]

Cancer of the pharynx includes cancer of the oropharynx (146) and hypopharynx (148) but excludes cancer of the nasopharynx (147). However, in 3 studies,[8,10,17] data for cancer of the nasopharynx could not be separated from that for other pharynx sites. Some studies provided data specific for cancer of the larynx (161), whereas others did not separate it from cancer of the oral cavity and pharynx.

FINDINGS BY TYPE OF SLT

For each study reviewed, Table I lists the first author, year of publication, number of cases and controls, and the types of SLT for which data are provided. Eight studies appeared in the 1990s, twice as many as appeared in any other decade.

Eighteen case-control studies supplied data that were used in at least 1 of the summary RRs. The remaining 3 studies provided an RR estimate but no primary data; they are described separately. Summary RRs for the 4 categories of SLT and several forms of cancer are given in Table II.

Chewing tobacco

Eight studies contributed to summary RRs for use of chewing tobacco. For OCC, the summary RR of 0.6 (95% CI = 0.3-1.3) was derived from 2 studies. For cancer of the oral cavity/pharynx, the summary RR was 1.1 (0.8-1.6). The RR was 1.3 (0.9-1.8) for cancer of the larynx and 1.7 (1.2-2.4) for the combined disease entity oral cavity/pharynx/larynx. For all sites combined, the summary RR for chewing tobacco was 1.2 (1.0-1.4).

Moist snuff

Five studies specified RRs for various forms of cancer among moist-snuff users. The RRs ranged from 0.7 both for cancer of the pharynx (0.4-1.4) and for oral cavity/pharynx (0.4-1.2) to 1.2 (0.9-1.7) for cancer of the larynx. For all sites combined, the RR was 1.0 (0.8-1.2).

Dry snuff

Four studies provided RRs for cancer related to dry snuff use. Data from 3 yielded a summary RR of 4.0 (2.7-5.9) for cancer of the oral cavity and pharynx combined. The fourth study reported an RR of 13 (8.0-21) for cancer of the oral cavity, pharynx and larynx combined. The overall RR for all sites combined was 5.9 (1.7-20).

One OCC subsite, gingiva and buccal mucosa (not included in Table II), is of special interest because it is the location where SLT products are held. One study[12] reported a RR of 26 (7.6-92) for cancer of the gingival and buccal mucosa among dry-snuff users.

SLT–unspecified

Seven studies contributed to the summary RRs for use of SLT unspecified as to type. OCC was evaluated in 4

Table II. Relative risk of several forms of cancer according to type of smokeless tobacco product used

Form of cancer	*CT*	*MS*	*DS*	*SLT–unspecified*
Oral cavity				
No. of studies	2	2	—	4
Cases/controls	283/296	482/995	—	581/798
Relative risk	0.6	1.1	—	2.8
95% Confidence interval	0.3-1.3	0.8-1.6	—	1.9-4.1
References	11,21	21,23	—	4,5,7,8
Pharynx				
No. of studies	—	1	—	3
Cases/controls	—	138/641	—	169/472
Relative risk	—	0.7	—	2.3
Confidence interval	—	0.4-1.4	—	1.2-4.4
References	—	23	—	4,7,8
Oral/pharynx				
No. of studies	4	3	3	3
Cases/controls	2113/4454	1682/3931	298/947	655/2718
Relative risk	1.1	0.7	4.0	1.5
Confidence interval	0.8-1.6	0.4-1.2	2.7-5.9	1.1-2.0
References	10,14,19,20	10,19,20	12,14,19	16,18,22
Larynx				
No. of studies	1	2	—	1
Cases/controls	387/2560	544/3201	—	23/100
Relative risk	1.3	1.2	—	1.8
Confidence interval	0.9-1.8	0.9-1.7	—	0.3-9.3
References	10	10,23	—	7
Oral/pharynx/larynx				
No. of studies	2	—	1	—
Cases/controls	362/457	—	93/393	—
Relative risk	1.7	—	13	—
Confidence interval	1.2-2.4	—	8.0-20	—
References	6,15	—	6	—
All sites				
No. of studies	8	5	4	7
Cases/controls	3145/5245	2846/4926	391/1340	1428/3681
Relative risk	1.2	1.0	5.9	1.9
Confidence interval	1.0-1.4	0.8-1.2	1.7-20	1.5-2.3

CT, chewing tobacco; *MS*, moist snuff; *DS*, dry snuff; *SLT*, smokeless tobacco.

studies, yielding a statistically significant RR of 2.8 (1.9-4.1). RRs for cancer of the pharynx (2.3) and of the oral cavity and pharynx combined (1.5) were lower than that for OCC, but both were statistically significant. A single study reported elevated RRs for cancer of the larynx (1.8, 0.3-9.3). For all cancers combined, the 7 studies yielded a summary RR of 1.9 (1.5-2.3).

Two studies[3,4] reported a combined RR of 2.3 (1.3-4.1) for cancer of the gingival and buccal mucosa in users of SLT–unspecified.

OTHER FINDINGS

Three studies that reported relevant RRs did not provide primary data, so they could not be included in the summary RRs. Williams and Horm[9] reported RRs for users of SLT–unspecified for OCC (RR = approximately 5, CI not available), pharynx (0.7), and larynx (2.0). Stockwell and Lyman[13] reported RRs for users of SLT–unspecified: oral cavity (11.2, 4.1-31), pharynx (4.1, 0.9-18), and larynx (7.3, 2.9-18). Data from the one retrospective follow-up study[17] could not be combined with those from the case-control studies. This study reported a standardized mortality ratio of 3.0 (2.0-4.5) for OCC and 8.7 (4.1-18) for cancer of the pharynx among users of SLT–unspecified.

Two studies contributed data to some summary RRs and also reported other findings that could not be included. Spitz et al[15] reported a RR of 3.4 (1.0-11) for cancers of the oral cavity, pharynx, and larynx combined among moist-snuff users. Mashberg et al[18]

reported on cancer of the oral cavity and pharynx among users of moist snuff (0.8, 0.4-1.9) and chewing tobacco (1.0, 0.7-1.4).

DISCUSSION

This review indicates that the increased risks of cancers of the upper respiratory tract associated with the use of SLT generally are modest and differ depending on the type of product used. The lowest RRs are found among users of chewing tobacco (0.6-1.7) and among users of moist snuff (0.7-1.2). Users of dry snuff have higher risks, with RRs from about 4 to 15. Risks are intermediate for SLT–unspecified, possibly reflecting use of either the lower- or higher-risk products among different individuals.

The distinctive risk profiles of moist snuff and chewing tobacco on the one hand, and dry snuff on the other, have gone largely unnoticed. One article[29] did suggest that the use of chewing tobacco may be associated with a lower risk of oral cancer than is the use of snuff. No distinction in risks has been made previously between dry snuff and moist snuff, even though these products differ considerably. For this review, however, we separated dry snuff as a distinct exposure because it is essentially the only SLT product used by women, especially in the southern United States.[27,28]

A strength of the data available now is that because most of the summary RRs presented are based on rather large numbers of cases and controls, they are reasonably precise. However, most of the studies do have limitations. The majority of them did not control confounding by 2 strong determinants of oral cancer, cigarette smoking and alcohol use. Seven studies partially controlled for smoking.[8,9,12,14,19,21,23] Confounding by smoking would occur if SLT users smoke more than do nonusers. On the other hand, negative confounding is plausible and would occur if smoking rates are lower among SLT users than among nonusers. Three studies[12,21,23] controlled for alcohol use, where only positive confounding is likely. Control for alcohol consumption probably would have reduced somewhat many of the RRs presented.

Another limitation of these studies, and this area of research, is the lack of clarity with regard to the anatomic sites studied. Although the major site of interest in epidemiologic studies of SLT is the oral cavity, in many studies RRs were reported only for cancers of the oral cavity and pharynx combined, or even for the oral cavity, pharynx, and larynx combined. Nomenclature was not particularly consistent, even for such a seemingly well-defined entity as OCC. For example, although most studies used the same subsites to comprise OCC, 5 included the lips, major salivary glands, or both.[6,8,10,17,21] Furthermore, 4 studies[12,16,20,22] specify oral cancer in their titles but in fact report on cancer of the oral cavity and pharynx combined. Future studies should provide data for specified subsites in addition to designating SLT product types. However, even with these limitations, there is reasonable consistency among the results of these studies that span 45 years.

Twenty-nine reviews or broadly based articles published since 1985 have discussed oral cancer and SLT use. Surprisingly, all of these cited 6 or fewer of the relevant epidemiologic studies, and few presented actual risk estimates. Rather, they focused on issues such as the initiation and prevalence of SLT use. Although these are genuine public health concerns, the abundance of data now available indicates that commonly used SLT products increase the risk of oral and upper respiratory tract cancers only minimally.

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Annexe 28

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Smokeless tobacco and increased risk of hypopharyngeal and laryngeal cancers: A multicentric case–control study from India

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Hypopharyngeal and laryngeal cancers are among the most common cancers in India. In addition to smoking, tobacco chewing may be a major risk factor for some of these cancers in India. Using data from a multicentric case–control study conducted in India that included 513 hypopharyngeal cancer cases, 511 laryngeal cancer cases and 718 controls, we investigated smoking and chewing tobacco products as risk factors for these cancers. Bidi smoking was a stronger risk factor compared to cigarette smoking for cancer of the hypopharynx (OR_{bidi} 6.80 *vs.* OR_{cig} 3.82) and supraglottis (OR_{bidi} 7.53 *vs.* OR_{cig} 2.14), while the effect of the 2 products was similar for cancer of the glottis (OR_{bidi} 5.32 *vs.* OR_{cig} 5.74). Among never-smokers, tobacco chewing was a risk factor for hypopharyngeal cancer, but not for laryngeal cancer. In particular, the risk of hypopharyngeal cancer increased with the use of Khaini (OR 2.02, CI 0.81–5.05), Mawa (OR 3.17, CI 1.06–9.53), Pan (OR 3.34, CI 1.68–6.61), Zarda (OR 3.58, CI 1.20–10.68) and Gutkha (OR 4.59, CI 1.21–17.49). A strong dose-response relationship was observed between chewing frequency and the risk of hypopharyngeal cancer ($p_{trend} < 0.001$). An effect of alcohol on cancer of the hypopharynx and supraglottis was observed only among daily drinkers (OR 2.22, CI 1.11–4.45 and OR 3.76, CI 1.25–11.30, respectively). In summary, this study shows that chewing tobacco products commercially available in India are risk factors for hypopharyngeal cancer, and that the potency of Bidi smoking may be higher than that of cigarette smoking for hypopharyngeal and laryngeal cancers.
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Key words: smokeless tobacco; chewing tobacco; hypopharyngeal cancer; laryngeal cancer; India; betel quid; pan; khaini; mawa; zarda; gutkha; snuff

An increasing trend in mortality from head and neck cancers has been observed in Europe and Asia. In India alone, over 75,000 people are diagnosed with pharyngeal and laryngeal cancers each year.[1] Despite advancements in treatment protocols, the 5-year survival rate still remains around 50%.[2] The major risk factors for pharyngeal and laryngeal cancers are tobacco smoking,[3–6] alcohol drinking[7–12] and tobacco chewing.[5,6,13–15]

Tobacco chewing is a common habit in India, which has been growing consistently over the past few decades owing to successful marketing and packaging that allows for easier use.[16] More alarmingly, its popularity continues to grow, especially among the most vulnerable populations, such as children, teenagers and pregnant women.[16] There are various forms of chewing tobacco that are used in India,[5,16,17] of which Pan is one of the most common. Pan is a mixture of areca nut, catechu (areca catechu), slaked lime, tobacco and additional spices, wrapped in a betel leaf.[5,16,17] Although Pan can also be made without tobacco, most habitual chewers in India tend to include tobacco.[17] Other chewing tobacco products commonly used in India include Khaini (a mixture of tobacco and slaked lime), Mawa (tobacco, areca nut and slaked lime), Gutkha (tobacco, catechu, areca nut and slaked lime) and Zarda (tobacco and slaked lime).[5] Although not as common as chewing, snuffing of tobacco products represents an additional method of consuming smokeless tobacco products in India. This includes oral snuffing as well as nasal snuffing. The most common snuffing product in this region, called Naswar, is a mixture of tobacco and slaked lime.[5]

Recently, betel quid with and without tobacco, along with areca nut, has been classified as a known human carcinogen by the International Agency for Research on Cancer,[5] with increased risk observed for cancers of the pharynx and esophagus. However, limited data exist on other chewing products commercially available in India. Similarly, the role of snuffing products in hypopharyngeal and laryngeal cancer is not clear. Using data from a multicentric case–control study conducted in Ahmedabad, Bhopal, Chennai and Kolkata, we report the risks of hypopharyngeal and laryngeal cancers associated with smoking, snuffing and chewing different tobacco products used in India.

Methods

A multicentric case–control study was conducted in India between 2001 and 2004. The 4 participating centers were the Gujarat Cancer and Research Institute in Ahmedabad, the Gandhi Medical College in Bhopal, the Chittaranjan National Cancer Institute in Kolkata and the Cancer Institute (WIA) in Chennai. Altogether, 1,062 head and neck cancer cases, and 718 controls matched on age (±5 years), sex and geographical area of residency were recruited. Overall, 19% of the controls were hospital-based (patients with disease not related to alcohol or tobacco consumption) and 81% were visitors to patients at the hospital. A standardized questionnaire was administered to all study participants by trained staff members, who collected data on demographic and socioeconomic status, clinical history, family history of cancer, tobacco and alcohol consumption habits, dietary factors, occupation, residential history and usage of different chewing products available locally.

Of the 1,062 head and neck cancer cases, 38 (3.6%) were excluded from the analysis because the histological subtype was missing, the cancer was an *in situ* carcinoma, or they were cancers other than that of hypopharyx or larynx. Of the 1,024 eligible cases, 513 were hypopharyngeal cancer cases (ICDO-2 codes C12 and C13) and 511 were laryngeal cancer cases (ICDO-2 codes: C32.0 (glottis = 178), C32.1 (supraglottis = 120) and C32.2–C32.9 (other larynx = 213)). Of the 213 other laryngeal cancer

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TABLE I – DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

	Controls		Hypopharynx		Glottis		Supraglottis		Larynx_other	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Total	718		513		178		120		213	
Centre										
Ahemdabad	203	28.3	222	43.3	58	32.6	86	71.7	69	32.4
Bhopal	73	10.2	21	4.1	5	2.8	2	1.7	40	18.8
Calcutta	110	15.3	117	22.8	47	26.4	2	1.7	70	32.9
Chenni	332	46.2	153	29.8	68	38.2	30	25.0	34	16.0
Sex										
Male	607	84.5	430	83.8	170	95.5	111	92.5	197	92.5
Female	111	15.5	83	16.2	8	4.5	9	7.5	16	7.5
Age										
≤34	76	10.6	20	3.9	13	7.3	2	1.7	9	4.2
35–44	156	21.7	54	10.5	12	6.7	10	8.3	10	4.7
45–54	230	32.0	158	30.8	46	25.8	29	24.2	59	27.7
55–64	182	25.3	163	31.8	66	37.1	51	42.5	70	32.9
65–74	68	9.5	91	17.7	30	16.9	23	19.2	53	24.9
≥75	6	0.8	27	5.3	11	6.2	5	4.2	12	5.6
SES category										
Low	60	8.4	128	25.3	28	16.3	33	28.0	36	16.9
Low medium	195	27.2	232	45.9	77	44.8	56	47.5	76	35.7
High medium	216	30.1	107	21.2	35	20.3	25	21.2	71	33.3
High	247	34.4	38	7.5	32	18.6	4	3.4	22	10.3
Religion										
Hindu	634	88.3	427	84.6	155	90.1	108	91.5	184	86.4
Christian	25	3.5	16	3.2	5	2.9	1	0.8	3	1.4
Muslim	47	6.5	66	13.1	18	10.5	10	8.5	25	11.7
Other	12	1.7	4	0.8	0	0.0	1	0.8	1	0.5

cases, the majority (84%) had a cancer in an unspecified part of the larynx (ICDO-2 code 32.9) and the remaining 16% were characterized by a combination of overlapping regions of the larynx and subglottis (ICDO-2 codes C32.8, C32.2 and C32.3). Separate analyses were conducted for different sites within the larynx (glottis, supraglottis and other larynx) whenever possible, except in instances where the numbers were too small. In such instances, an overall analysis was conducted for laryngeal cancer that combined the aforementioned 3 subcategories. Altogether, 90% of the 1,024 cases were squamous cell carcinomas.

Ever-smokers were defined as individuals who smoked at least 50 cigarettes over a 6-month period, while ever-chewers and ever-drinkers were defined as those who chewed tobacco products or drank alcohol at least once a week for a minimum of 6 months. Cumulative tobacco consumption was calculated after assigning a cigarette-equivalent value of 0.5, 1 and 2 to 1 Bidi, cigarette and cigar/cheroot, respectively,[3,6,18] and multiplying the number of cigarette-equivalents by the years of smoking. To create a composite socioeconomic status (SES) variable, we assigned a score of 1–5 for level of education; monthly family income and crowdedness at home (number of people per room). A composite SES variable was created by summing up the score and dividing it into distinct categories. For the product specific analysis of chewing tobacco, individuals were assigned to the product they reported using for the longest duration, if they used more than 1 chewing products.

Statistical analysis

Statistical analyses were performed using STATA, version 8 (Stata, College Station, TX). Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for each risk factor under consideration were estimated using unconditional logistic regression models after adjusting for age (continuous), sex, participating center, SES (categorical) and cumulative tobacco consumption (pack years, continuous). Tests for linear trends were performed by treating the categorical variables as continuous predictors in the logistic regression models.

Results

The majority of participants in the study were men as shown in Table I. The proportion of female cases ranged from 4.5% for cancer of the glottis to 16.2% for hypopharyngeal cancer, compared to 15.5% among controls. In general, controls were of slightly higher SES status compared to cases, while the majority of both cases and controls were Hindus.

Ever smoking was associated with increased risks of all types of cancer considered (Table II), with odds ratios ranging from 5.35 (glottis) to 8.28 (other larynx). Analyses based on types of tobacco product smoked showed that Bidi smokers may have a higher risk of hypopharyngeal cancer (OR 6.80, CI 4.64–9.97) compared to cigarette smokers (OR 3.82, CI 2.32–6.29). Similar results were observed for cancer of the supraglottis (OR_{bidi} 7.53, CI 3.84–14.74, $OR_{cigarette}$ 2.14, CI 0.63–7.30). In contrast, comparable risk estimates were observed among cigarette smokers and Bidi smokers for cancer of the glottis (OR_{bidi} 5.32, CI 3.18–8.90, $OR_{cigarette}$ 5.74, CI 3.20–10.31). A strong dose response relationship was observed, based on duration as well as frequency of Bidi smoking for all types of cancer considered ($p_{trend} < 0.001$). Similar dose response relationships were also observed with cigarette smoking for cancer of the hypopharynx and glottis.

An increased risk of hypopharyngeal cancer (Table III) was observed among tobacco snuffers (OR 2.25, CI 0.99–5.13). When the analysis was restricted to never smokers, the risk was still evident (OR 2.85, CI 1.15–7.08). In contrast, there was no increased risk of laryngeal cancers associated with tobacco snuffing. A moderate increase in the risk of hypopharyngeal cancer was observed among chewers of both nontobacco (OR 1.95, CI 0.96–3.97) and tobacco (OR 1.51, CI 1.08–2.11) products. When the analysis was restricted to never-smokers, the risk associated with chewing nontobacco product was not apparent (OR 1.21, CI 0.39–3.78), while that associated with chewing tobacco products increased in magnitude (OR 3.18, CI 1.92–5.27). In contrast, no association was observed between tobacco chewing and the risk of laryngeal cancer (OR 0.75, CI 0.52–1.70 for all individuals, OR 0.95, CI 0.52–1.73 for never smokers).

A more detailed analysis was conducted to evaluate hypopharyngeal and laryngeal cancer risk associated with various chewing products commonly used in India (Table IV). An increased risk of hypopharyngeal cancer was observed among those who reported chewing Zarda (OR 2.23, CI 1.11–4.50). In general, no increased risk of laryngeal cancer was observed for the individual chewing

TABLE II – SMOKING HABITS AND PRODUCTS AND THE RISK OF HYPOPHARYNGEAL AND LARYNGEAL CANCERS

	CTRL	Hypopharynx			Glottis			Supraglottis			Larynx_other		
		CS	OR	CI	CS	OR	CI	CS	OR	CI	CS	OR	CI
Ever smoke													
No	457	149	1.00		37	1.00		21	1.00		39	1.00	
Yes	261	364	5.66	(3.99–8.02)	141	5.35	(3.40–8.42)	99	6.69	(3.50–12.77)	174	8.28	(5.02–13.67)
Smoking product													
Never	457	149	1.00		37	1.00		21	1.00		39	1.00	
Cigerette	104	48	3.82	(2.32–6.29)	37	5.74	(3.20–10.31)	4	2.14	(0.63–7.30)	20	5.06	(2.50–10.26)
Bidi	113	278	6.80	(4.64–9.97)	87	5.32	(3.18–8.90)	83	7.53	(3.84–14.74)	129	9.61	(5.65–16.35)
Cigerette and bidi	33	23	4.74	(2.42–9.29)	11	5.42	(2.37–12.39)	9	15.92	(5.46–46.45)	17	9.52	(4.15–21.85)
Other	11	13	4.21	(1.69–10.47)	6	3.47	(1.14–10.60)	3	4.24	(0.81–22.20)	7	5.85	(1.85–18.50)
Frequency of cigarette smoking													
0	457	151	1.00		37	1.00		21	1.00		40	1.00	
1–10 per day	79	24	2.47	(1.34–4.54)	24	3.74	(1.96–7.13)	2	1.33	(0.27–6.65)	8	2.57	(1.05–6.32)
>10–20 per day	19	15	5.24	(2.19–12.53)	12	6.63	(2.60–16.92)	1	4.28	(0.45–40.72)	10	10.95	(3.94–30.40)
>20 per day	6	9	9.75	(2.95–32.22)	1	1.94	(0.20–18.58)	1	6.55	(0.46–92.57)	2	7.05	(1.12–44.46)
p_{trend}			<0.001			<0.001			0.09			<0.001	
Duration of cigarette smoking													
0 years	457	151	1.00		37	1.00		21	1.00		40	1.00	
1–15 years	44	4	1.15	(0.36–3.64)	9	3.35	(1.36–8.23)	0	–		2	1.50	(0.32–7.06)
>15–30 years	35	21	4.77	(2.41–9.48)	9	3.25	(1.36–7.79)	2	3.77	(0.73–19.54)	7	4.51	(1.61–12.61)
>30 years	25	23	4.26	(2.05–8.87)	19	5.71	(2.55–12.81)	2	2.16	(0.39–11.85)	11	6.64	(2.65–16.64)
p_{trend}			<0.001			<0.001			0.17			<0.001	
Frequency of bidi smoking													
0	457	151	1.00		37	1.00		21	1.00		40	1.00	
1–10 per day	62	55	2.83	(1.73–4.63)	15	2.01	(0.96–4.20)	14	3.07	(1.29–7.33)	20	2.82	(1.40–5.67)
>10–20 per day	25	73	9.45	(5.32–16.78)	18	5.31	(2.42–11.63)	16	7.25	(2.77–18.94)	38	11.94	(5.74–24.84)
>20 per day	26	150	17.13	(9.97–29.44)	54	14.59	(7.47–28.50)	53	20.31	(9.10–45.31)	71	24.71	(12.56–48.61)
p_{trend}			<0.001			<0.001			<0.001			<0.001	
Duration of bidi smoking													
0 years	457	151	1.00		37	1.00		21	1.00		40	1.00	
1–15 years	16	26	6.35	(3.02–13.33)	6	3.37	(1.15–9.90)	5	5.09	(1.43–18.16)	2	1.54	(0.32–7.53)
>15–30 years	43	70	5.51	(3.31–9.16)	19	3.96	(1.91–8.19)	19	6.04	(2.54–14.35)	32	7.16	(3.60–14.23)
>30 years	54	182	9.22	(5.78–14.73)	62	7.76	(4.16–14.47)	59	11.04	(5.10–23.91)	95	12.99	(7.14–23.61)
p_{trend}			<0.001			<0.001			<0.001			<0.001	

Adjusted for center, age, sex, SES, alcohol consumption, tobacco snuffing and tobacco chewing.

TABLE III – SNUFFING AND CHEWING HABITS AND THE RISK OF HYPOPHARYNGEAL AND LARYNGEAL CANCERS

Snuffing	Chew nontobacco prd.	Chew tobacco prd.	CTRI	Hypopharynx			Larynx		
				Case	OR	95% CI	Case	OR	95% CI
All Individuals[a,b]									
–	–	–	547	331	1.00		386	1.00	
+	–	–	12	25	2.25	(0.99–5.13)	9	1.26	(0.46–3.42)
–	+	–	24	23	1.95	(0.96–3.97)	13	0.82	(0.36–1.91)
–	–	+	133	130	1.51	(1.08–2.11)	93	0.75	(0.52–1.70)
Never Smokers[a,c]									
–	–	–	346	71	1		67	1	
+	–	–	11	17	2.85	(1.15–7.08)	7	1.73	(0.59–5.05)
–	+	–	17	5	1.21	(0.39–3.78)	1	0.31	(0.04–2.46)
–	–	+	82	55	3.18	(1.92–5.27)	20	0.95	(0.52–1.73)

[a]Catagories are mutually exclusive.–[b]Adjustd for center, age, sex, SES, alcohol consumption and tobacco pack years.–[c]Adjustd for center, age, sex, SES and alcohol consumption.

TABLE IV – CHEWING TOBACCO PRODUCTS AND RISK HYPOPHARYNGEAL AND LARYNGEAL CANCERS

	CTRI	Hypopharynx			Larynx		
	CS	OR	CI		CS	OR	CI
All individuals[a,b]							
Chewing tobacco products							
Never[c]	585	380	1.00		413	1.00	
Khaini	37	21	0.74	(0.39–1.42)	29	0.79	(0.43–1.44)
Zarda	16	32	2.23	(1.11–4.50)	19	0.81	(0.36–1.78)
Mawa	20	22	1.33	(0.61–2.89)	13	0.59	(0.25–1.45)
Pan	42	35	1.65	(0.96–2.85)	20	0.82	(0.43–1.55)
Gutkha	15	16	1.35	(0.56–3.27)	15	1.11	(0.45–2.74)
No. of tob prod. chewed/day							
0[c]	585	379	1		150	1	
1–3	48	48	1.35	(0.83–2.19)	36	0.78	(0.45–1.34)
>3	85	86	1.58	(1.06–2.35)	60	0.80	(0.52–1.22)
p_{trend}			0.017			0.22	
Never smokers only[b,d]							
Chewing tobacco products							
Never[c]	375	93	1.00		75	1.00	
Khaini	23	10	2.02	(0.81–5.03)	6	1.06	(0.39–2.90)
Zarda	9	8	3.58	(1.20–10.68)	1	0.36	(0.04–3.07)
Mawa	13	6	3.17	(1.06–9.53)	3	0.98	(0.26–3.75)
Pan	28	26	3.34	(1.68–6.61)	7	1.06	(0.43–2.62)
Gutkha	6	5	4.59	(1.21–17.49)	4	2.55	(0.62–10.44)
No. of tob prod. chewed/day							
0[c]	375	93	1		75	1	
1–3	25	17	2.58	(1.24–5.37)	5	0.72	(0.25–2.02)
>3	57	39	3.48	(1.96–6.20)	16	1.19	(0.62–2.29)
p_{trend}			<0.001			0.72	

[b]Adjusted for center, age, sex, SES, alcohol consumption tobacco snuffing and tobacco pack years.–[c]Product catagories are mutually exclusive.–[c]Reference category.–[d]Adjusted for center, age, sex, SES, alcohol consumption and tobacco snuffing.

products. When the analysis was restricted to never-smokers, an increased risk of hypopharyngeal cancer was observed for all individual tobacco products considered. The product specific ORs were: 2.02 (CI 0.81–5.05) for Khaini, 3.17 (CI 1.06–9.53) for Mawa, 3.34 (CI 1.68–6.61) for Pan, 3.58 (CI 1.20–10.68) for Zarda and 4.59 (CI 1.21–17.49) for Gutkha, respectively. In contrast, no product specific risks were observed for laryngeal cancers among never smokers (Table IV). Analysis based on frequency of tobacco chewing showed that increasing frequency of chewing was associated with increasing risk of hypopharyngeal cancer (p_{trend} = 0.017), with a stronger dose response observed among never-smokers (p_{trend} < 0.001). However, such a relationship was absent for laryngeal cancers.

In this study population, increased risk of hypopharyngeal and laryngeal cancers were not observed among ever drinkers of alcoholic beverages (Table V). When frequency of alcohol consumption was considered, an increased risk of the cancers of supraglottis (OR 3.76, CI 1.25–11.30) and hypopharynx (OR 2.22, CI 1.11–4.45) were observed among those who reported consuming alcohol daily, with a clear dose response for cancer of the supraglottis (p_{trend} = 0.02). However, duration of alcohol consumption was not associated with increased risk, except for other laryngeal cancers, where long duration (≥20 years) of consumption was associated with a moderate increase in risk (OR1.63, CI 1.00–2.69).

Discussion

The growing use of chewing tobacco products in India is alarming and represents a major public health concern. Every year, over 160,000 people are diagnosed with UADT cancers in India,[1] and these numbers will continue to grow in the foreseeable future. Therefore, understanding the risks associated with alcohol drinking as well as chewing and snuffing of tobacco products, in addition to smoking, is important and dissipating such knowledge to general public to avoid future burden of these disease is even more critical

In this study population, the strength of association for cigarette smoking varied by cancer site, with ORs ranging from 2.14 for

TABLE V – ALCOHOL CONSUMPTION AND RISK OF HYPOPHARYNGEAL AND LARYNGEAL CANCERS

	Control	Hypopharynx			Glottis			Supraglottis			Larynx_other		
	(All)	CS	OR	95% CI	CS	OR	95% CI	CS	OR	95% CI	CS	OR	95% CI
Alcohol consumption													
Never	580	393	1.00		135	1.00		88	1.00		148	1.00	
Ever	138	119	0.90	(0.63–1.30)	42	0.91	(0.57–1.45)	32	1.57	(0.84–2.92)	65	1.31	(0.83–2.05)
Frequency													
Never	580	393	1.00		135	1.00		88	1.00		148	1.00	
<Once a week	60	23	0.47	(0.26–0.87)	18	1.02	(0.53–1.95)	7	0.91	(0.33–2.54)	13	0.81	(0.38–1.70)
<Daily	51	49	0.97	(0.59–1.59)	13	0.66	(0.32–1.35)	12	1.63	(0.71–3.74)	32	1.36	(0.74–2.42)
Daily	17	42	2.22	(1.11–4.45)	10	1.46	(0.56–3.82)	11	3.76	(1.25–11.30)	15	2.20	(0.84–5.61)
p_{trend}				0.24			0.84			0.02			0.11
Duration													
Never	581	393	1.00		135	1.00		89	1.00		148	1.00	
<20 years	70	26	0.65	(0.37–1.16)	12	0.82	(0.39–1.72)	6	1.22	(0.43–3.52)	10	0.74	(0.32–1.70)
≥20 years	67	94	1.10	(0.72–1.69)	31	0.97	(0.56–1.68)	25	1.76	(0.88–3.53)	55	1.63	(1.00–2.69)
p_{trend}				0.92			0.83			0.11			0.08

Adjusted for center, age, sex, SES, tobacco snuffing, tobacco chewing and tobacco pack years.

supraglottis to 5.74 for glottis. Similarly, odds ratios for Bidi smoking ranged from 5.32 for cancer of glottis to 9.61 for other laryngeal cancer. The highest differences in ORs between cigarette and Bidi smoking was observed for cancer of the supraglottis ($OR_{cigarette}$ 2.14 *vs.* OR_{bidi} 7.56).

Tobacco snuffing was an independent risk factor for hypopharyngeal cancer, with higher magnitude of risk observed among never-smokers (Table III). There was no clear association between tobacco snuffing and risk of laryngeal cancer, even among the never-smokers. While chewing nontobacco products appeared to be a risk factor for hypopharyngeal cancer, the apparent lack of risk observed in never-smokers indicates that the observed risk in the overall population may be due to residual confounding from smoking. In contrast, chewing tobacco product was an independent risk factor for hypopharyngeal cancer, as evidenced by the increased risk observed among overall study population as well as among never-smokers, with a clear dose response relationship.

However, there was no increased risk of laryngeal cancer associated with tobacco chewing for all individuals as well as among never smokers. Based on the analysis conducted among never-smokers, all types of chewing products containing tobacco were risk factors for hypopharyngeal cancer in this study population (Table IV). The magnitude of risk was comparable across the various chewing products, with the odds ratios ranging from 2.02 for Khaini to 4.61 for Gutkha. The risk associated with chewing various tobacco products was further substantiated by the dose response relationship observed for frequency of tobacco chewing and the risk of hypopharyngeal cancer, among never-smokers. There was no apparent increase in risk of laryngeal cancer associated with the individual chewing products in this study. This was true even when the analysis was restricted among never smokers.

In this study population, we observed a consistent risk of hypopharyngeal cancer associated with tobacco chewing and tobacco snuffing. Equally consistent was the lack of risk of laryngeal cancer associated with these 2 habits. The lack of risk of laryngeal cancer observed in this study, is consistent with what has been reported previously.[19,20] However, additional mechanistic studies are needed to understand why chewing tobacco product is such a strong risk factor for hypopharyngeal but not for laryngeal cancers, considering the close proximity of the 2 sites. However, given the consistent results, a plausible hypothesis is that a direct and prolonged contact is necessary for the effect of chewing tobacco to manifest.

Alcohol consumption has been linked to increased risk of laryngeal and pharyngeal cancer in India previously.[20,21] In this study, an increased risk of hypopharyngeal cancer and cancer of supraglottis were observed only among those who drank daily, after adjusting for smoking and tobacco chewing. However, the lack of association observed among individuals who drink less than daily as well as the duration of drinking is not clear.

There are several strengths of this study including the large sample size and multicentric study design. This study was conducted in areas with a high prevalence of the main exposures of interest (tobacco chewing), as well as the outcomes of interest (hypopharyngeal and laryngeal cancer), and provides product specific risk estimates for the first time. In addition, very few studies have explored the relationship between snuffing habits and the risk of hypopharyngeal and laryngeal cancer in India. A potential limitation of this study is the exposure misclassification between various chewing tobacco products. Individuals may not always recall the different type of tobacco products they consumed over their lifetime accurately, unless their consumption pattern has not changed considerably. But the misclassification between different chewing tobacco products is likely to be nondifferential, thus attenuating the odds ratios. Another potential concern includes residual confounding by smoking, which we tried to address by restricting the analysis to never-smokers, whenever possible. Additionally, the proportion of female study participants is rather low (~12%) in this study, which excluded the possibility of restricting the analyses to women only, to evaluate gender differences in risks associated with the habit of tobacco chewing.

Results from this study suggest that tobacco chewing is an independent risk factor for hypopharyngeal cancer, in the absence of smoking and drinking. Similarly, tobacco snuffing is also a risk factor for hypopharyngeal cancer. Although chewing tobacco is a common habit in India and many South Asian countries, it is also prevalent in the other countries with migrant communities arising from these areas. The popularity of the smokeless tobacco product is growing in the North American youths as well, owing to the public usage of such products by social models such as professional athletes.[22,23] The increasing usage of smokeless tobacco products combined with the ill-perceived notion that it is a relatively safe product compared to cigarettes, may pose a substantial threat to public health in the coming years. These data in conjunction with other evidence show that tobacco is dangerous in any form.[24] Public health practitioners throughout the world need to recognize this and implement proper regulatory approaches before the usage of such tobacco products parallels that of south Asia.

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Annexure 64

Tobacco and alcohol as risk factors in cancer of the larynx in Kerala, India.

Sankaranarayanan R, Duffy SW, Nair MK, Padmakumary G, Day NE.

Int J Cancer. 1990 May 15;45(5):879-82.

Abstract

A case-control study of cancer of the larynx was carried out in Kerala, Southern India, on 191 male cancer cases and 549 male hospital-based controls. Risk factors investigated were pan(betel)-tobacco chewing, bidi and cigarette smoking, drinking alcohol and inhaling snuff. Significant positive associations with risk were observed for bidi smoking (p less than 0.001), bidi and cigarette smoking (p less than 0.001) and drinking alcohol (p less than 0.001). A predisposing effect of smoking cigarettes alone approached significance (0.1 less than p less than 0.05). What appeared to be an almost significant protective effect of pan-tobacco chewing (0.1 less than p less than 0.05) was found to be an artefact of confounding with smoking, and indeed a significant predisposing effect was observed of occasional chewing (p less than 0.001). After a stepwise logistic regression to eliminate those factors which were not significant when adjusted for other factors, significant effects remained of durations of bidi smoking and cigarette smoking, daily frequency of bidi and cigarette smoking and duration of alcohol drinking. Relative risks of 7.12, 5.18 and 2.58 were observed for durations of more than 20 years of bidi smoking, cigarette smoking and drinking alcohol respectively, and a relative risk of 12.68 was observed for those smoking more than 20 bidis/cigarettes per day, in each case relative to a baseline of those negative for the relevant habit.

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Publication Types, MeSH Terms

Publication Types:

- Research Support, Non-U.S. Gov't

MeSH Terms:

- Adult
- Age Factors
- Aged
- Alcohol Drinking*
- Carcinoma, Squamous Cell/epidemiology
- Carcinoma, Squamous Cell/etiology*
- Case-Control Studies
- Humans
- India
- Laryngeal Neoplasms/epidemiology
- Laryngeal Neoplasms/etiology*
- Male
- Middle Aged
- Plants, Toxic*
- Religion
- Risk Factors
- Smoking/adverse effects*
- Tobacco*
- Tobacco, Smokeless*

LinkOut - more resources

Medical:

- Smoking - MedlinePlus Health Information
- Smokeless Tobacco - MedlinePlus Health Information
- Alcohol - MedlinePlus Health Information

1.

Cohort study of all-cause mortality among tobacco users in Mumbai, India

Prakash C. Gupta[1] & Hemali C. Mehta[1]

Introduction Overall mortality rates are higher among cigarette smokers than non-smokers. However, very little is known about the health effects of other forms of tobacco use widely prevalent in India, such as bidi smoking and various forms of smokeless tobacco (e.g. chewing betel-quid). We therefore carried out a cohort study in the city of Mumbai, India, to estimate the relative risks for all-cause mortality among various kinds of tobacco users.

Methods A baseline survey of all individuals aged ≥ 35 years using voters' lists as a selection frame was conducted using a house-to-house approach and face-to-face interviews.

Results Active follow-up of 52 568 individuals in the cohort was undertaken 5–6 years after the baseline study, and 97.6% were traced. A total of 4358 deaths were recorded among these individuals. The annual age-adjusted mortality rates were 18.4 per 1000 for men and 12.4 per 1000 for women. For men the mortality rates for smokers were higher than those of non-users of tobacco across all age groups, with the difference being greater for lower age groups (35–54 years). The relative risk was 1.39 for cigarette smokers and 1.78 for bidi smokers, with an apparent dose–response relationship for frequency of smoking. Women were basically smokeless tobacco users, with the relative risk among such users being 1.35 and a suggestion of a dose–response relationship.

Discussion These findings establish bidi smoking as no less hazardous than cigarette smoking and indicate that smokeless tobacco use may also cause higher mortality. Further studies should be carried out to obtain cause-specific mortality rates and relative risks.

Keywords: cause of death; cohort studies; India; smoking, mortality; tobacco, adverse effects; tobacco, smokeless, adverse effects.

Voir page 882 le résumé en français. En la página 883 figura un resumen en español.

Introduction

Tobacco use is widely regarded as the most preventable cause of death and disease among adults today in the world. WHO has estimated that the excess premature mortality attributable to tobacco use (almost all of it in the form of cigarette smoking) amounts to 4 million deaths per year. Specific estimates are available for industrialized countries; for example, Peto et al. estimated that in developed countries in 1995 there were 2 million smoking-attributable deaths and that the excess mortality rate (per 100 000) among smokers aged 35–69 years was 701 for males and 312 for females (*1*). In China, the current tobacco-attributable mortality has been estimated to be 12% of adult male deaths, which corresponds to 700 000 deaths from tobacco use in the year 2000 (*2*).

India is the second most populous country in the world, and the third largest producer and consumer of tobacco. The country has a long history of tobacco use and a variety of ways of smokeless tobacco use and smoking, of which cigarettes form only a minor part (*3*). It has been clearly established that almost all forms of tobacco use carry serious health consequences (*4*). However, if the death and disease burdens from tobacco use in India are estimated only from cigarette smoking, the results may be a gross underestimation (*5*).

Previous estimates of tobacco-attributable mortality in India were based on the results of cohort studies in rural areas of Ernakulam District, Kerala (*6*), and in Srikakulam District, Andhra Pradesh (*7*). In these studies, cohorts of over 10 000 villagers aged ≥ 15 years were followed up over a period of 10 years using a house-to-house approach. Thus accurate estimates of all-cause mortality were obtained, enabling estimates to be made of the relative risks for different kinds of tobacco use. Using conservative figures and employing 1986 mortality data for the whole of India, tobacco-attributable mortality in the country was estimated to amount to 630 000 deaths per year (*8*). Since data on the causes of death were not available, cause-specific mortalities were not calculated.

With a view to obtaining cause-specific tobacco-attributable mortality in India we carried out cohort study in Mumbai (*9*). In this article we report preliminary results on all-cause mortality and the relative risks for various types of tobacco use.

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Ref. No. **99-0169**

Methods

Mumbai is a large (population in 1991: 9 925 891), densely populated city (16 461 inhabitants per km^2). It is divided into three sectors: the main city, the suburbs, and extended suburbs. The study was confined to the main city (population: 3 418 089) which is the most densely populated area (48 830 inhabitants per km^2). Since the objective was to estimate adult tobacco-attributable mortality, this cohort study was restricted to individuals aged ⩾ 35 years.

Baseline survey

The sampling frame used was the electoral rolls, which provided the name, age, sex, and address of all individuals aged ⩾ 18 years. The rolls were fairly complete since almost everyone aged ⩾ 18 years is entitled to vote and they are updated before every major election through house-to-house visits.

The electoral rolls were organized by geographical areas. The smallest unit was a polling station, generally having about 1000 but sometimes up to 1500 names of individuals aged ⩾ 18 years. Polling stations covering areas that largely contained apartment complexes housing upper-middle and rich classes were not selected for the study because the residents did not perceive any material gain from participating and because their security precautions caused access difficulties for the interviewers. These problems became apparent during the pilot phase of the study.

After selecting a polling station, all individuals aged ⩾ 35 years on the appropriate electoral list were approached by investigators for an interview. About 50% of individuals estimated to be thus eligible were available for the interview. The commonest reasons for nonavailability were that they had changed their address or the interviewers were refused access by security personnel in the building (high socio-economic group). Sometimes individuals not listed on the voters' list were also interviewed and included in the sample when they insisted that they were permanent residents at the address. Such individuals formed about 5% of the sample. Their residence status was confirmed by examining the ration card that is issued by the Mumbai Municipal Corporation. Every household keeps such a card because apart from entitling the holder to certain food items at subsidized prices, it serves as a residence card for access to all city and state government services.

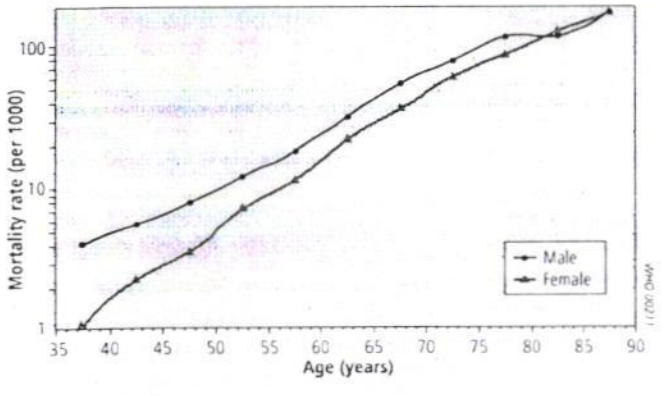
The interviews were conducted between February 1991 and May 1994 by trained investigators using handheld computers (electronic diaries). Details of the survey procedures and baseline characteristics of the cohort have been described elsewhere (*9*).

Table 1. **House-to-house follow-up results in the cohort study, Mumbai, India**

	No. of persons
Attempted contacts	52 568 (100)[a]
Address not located	1096 (2.1)
House demolished	1029 (2.0)
Incomplete address	67 (0.1)
Not identified	71 (0.1)
Invalid information about	122 (0.2)
Death	52 (0.1)
Migration	70 (0.1)
Denominator	51 279 (97.6)
Not contacted (due to migration)	5531 (10.5)
Date of migration not known	136 (0.3)
Contacted	45 748 (87.0)
Reported dead	4358 (8.3)
Date of death not available	237 (0.5)
Reinterviewed	38 836 (73.9)
Not available	2554 (4.9)

[a] Figures in parentheses are percentages

Fig. 1. **Annual mortality rates, by 5-year age intervals, among cohort study men and women, Mumbai**



Follow-up

Active follow-up of the cohort was begun 5–6 years after the initial survey. The field investigators were provided with lists of names and addresses of cohort members and were asked to revisit each person. If the person was alive and available, a face-to-face reinterview was conducted. If the person was reported dead, the date of death was recorded as accurately as feasible. Permanently moving out of the city of Mumbai was considered to be withdrawal from the study, and the date of moving out was noted.

Statistical analysis

Mortality rates were calculated using the person-years method. For this purpose, the person-months of follow-up were calculated first. Exact dates were rounded off to month and year, then the date of the baseline interview was subtracted from the date of withdrawal, i.e. the date of follow-up interview or the date of ascertainment that the person was alive for noninterviewed individuals. For those reported dead, the date of withdrawal was the date of death, and for those reported migrated, the date of migration. In cases where the exact date was not available, an appropriate midpoint was used. The information on age, gender, and details of tobacco use was abstracted

from the baseline data. Finally, the person-months were divided by 12 to obtain person-years.

The numerator for the mortality rate was the number of deaths. For calculating the age-specific mortality rate, the age at death was determined using baseline data. The age-specific mortality rates were plotted on a semi-log scale. The age-adjusted rates were obtained by direct adjustment, weighting by overall age-specific person-years; thus they are meant only for internal comparisons. Relative risks were calculated only from age-adjusted mortality rates.

The tobacco use analysis was restricted to three categories of individuals: those who did not report using tobacco in any smokeless or smoking form; those who reported using smokeless tobacco only; and those who reported smoking (some of whom could be smokeless tobacco users as well). The proportion of past users of tobacco was small, 2.2% among women (almost all smokeless tobacco users) and 4.5% among men (2.8% smokers and 1.7% smokeless tobacco users) (*9*); in the analysis they were combined with current users. In analysing the type of smokeless (or smoking) tobacco use, different categories were kept mutually exclusive. In the analysis of data by frequency of daily use of tobacco, individuals reporting multiple habits were excluded.

Tobacco use

In addition to cigarette smoking, a large variety of tobacco habits are prevalent in Mumbai, with use of bidis being the commonest. These are cheap smoking sticks (4–7.5 cm in length), handmade by rolling a dried, rectangular piece of *temburni* leaf (*Diospyros melanoxylon*) with 0.15–0.25 g of sundried, flaked tobacco into a conical shape and securing it with a thread.

In Mumbai the commonest form of smokeless tobacco is *mishri*, a black powder obtained by roasting and powdering tobacco. It is applied to the gums using a finger and the habit is generally begun by using *mishri* as a dentifrice.

Another common form of smokeless tobacco use that is prevalent in Mumbai, and also throughout India, is the chewing of betel-quid, a combination of betel leaf, areca nut, slaked lime, tobacco, and condiments, according to individual preferences. Other smoking and smokeless tobacco habits common in Mumbai that are also prevalent in many other parts of India have been described elsewhere (*3*).

Results

Table 1 shows the follow-up results for 52 568 individuals up to January 1999. A total of 1096 addresses could not be located, corresponding to 1029 individuals whose residential buildings were demolished and 67 whose address was not complete or specific enough for tracing. Mumbai has many old buildings that are demolished when either they become too dangerous to live in or to pave the way for development. Additionally, 71 individuals could not be identified. The follow-up information was invalid for 122 persons. Of these, 52 were reported dead and 70 had migrated, but their dates of death or of migration turned out to be earlier than the date of the interview in the baseline survey. These 1289 (2.4%) persons were excluded from both the numerator and the denominator of the mortality rates. Of the remaining 51 279 persons who

Table 2. **Person-years of follow-up and number of deaths in the cohort study, Mumbai**

	Men	Women	Total
No. of persons	20 322	30 957	51 279
No. of person-years	113 463	179 905	293 368
No. of deaths	2278	2080	4358
Crude mortality rate (per 1000 per year)	20.1	11.6	14.9
Age-adjusted mortality rate (per 1000 per year)	18.4	12.4	14.9

Table 3. **Person-years, annual mortality rates, and relative risks, by tobacco use, among cohort study women and men, Mumbai**

	No tobacco use	Smokeless tobacco[a]	Smoking
Women			
No. of person-years	64 414	114 980	511
No. of deaths	492	1575	13
Annual mortality rate (per 1000)	7.6	13.7	25.4
Crude	9.9	13.4	12.7
Age-adjusted			
Relative risk	1.0	1.35	1.28
Men			
No of person-years	27 236	57 890	28 338
No. of deaths	438	1096	744
Annual mortality rate (per 1000)	16.1	18.9	26.3
Crude	14.6	17.8	23.8
Age-adjusted			
Relative risk	1.0	1.22	1.63

[a] Non-smokers only.

Fig. 2. **Age-specific mortality rates among male smokers and non-users of tobacco, cohort study, Mumbai**

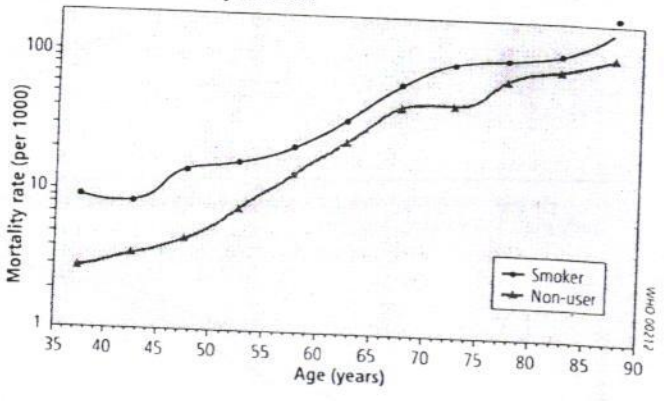


Fig. 3. **Age-specific mortality rates among a) male and b) female smokeless tobacco users and non-users of tobacco**

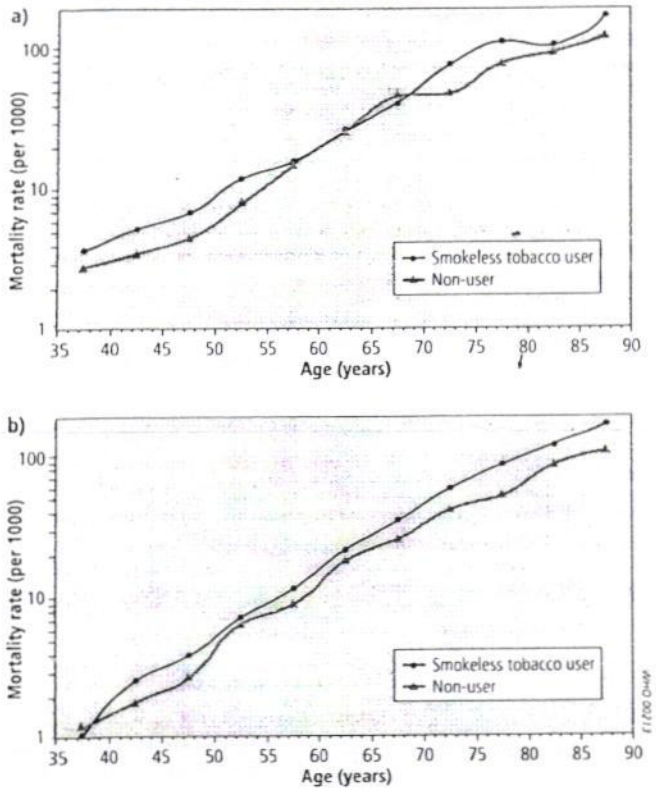


Table 4. **Mortality rates and age-adjusted relative risks by type and frequency of smoking habit among cohort study men, Mumbai**

	Person-years	Mortality rate[a]	Age-adjusted mortality rate[a]	Age-adjusted relative risk
Bidis	13 545	32.4	26.0	1.78
Cigarettes	13 329	19.2	20.3	1.39
Bidis + cigarettes	1163	33.5	32.5	2.23
Other	281	35.8	31.1	2.13
Bidi frequency (per day)				
1–5 times	2578	28.7	23.7	1.62
⩾6 times	10 967	33.3	27.1	1.86
Cigarette frequency (per day)				
1–5 times	6056	15.7	19.1	1.31
⩾6 times	7275	22.1	21.7	1.49
No tobacco use	27 236	16.1	14.6	1.00

[a] Per 1000 per annum.

contributed to the denominator, 5531 could not be contacted since they had migrated, mostly outside the study area. Attempts were made to determine the dates of migration (since this corresponded to the date of withdrawal from the study). The dates of migration of 136 individuals could not be determined, and for these, the midpoint date was used.

Of the 45 748 study persons, 4358 were reported to be dead; the dates of death for 237 of these individuals could not be ascertained and for these the midpoint was used. During follow-up 38 836 persons were reinterviewed, the remaining 2554 being unavailable despite multiple visits.

Table 2 shows the number of person-years and mortality rates by sex. A total of 293 368 person-years were observed. As in the original cohort, the male:female ratio, both in terms of the number of individuals as well as person-years, was about 2:3. More deaths were noted among men than women (2278 vs. 2080), and the crude mortality rate for men was nearly twice that for women (20.1 vs. 11.6 per 1000 per annum). After adjusting for age, the mortality rate among men was about 50% higher than that for women (18.4 vs. 12.4 per 1000 per annum).

Fig. 1 shows age-specific mortality rates for men and women. The rates for males were higher for all age groups, but the difference decreased with age.

Table 3 shows the mortality rates, by tobacco use, for men and women. The prevalence of smoking among women was very low, and only a few person-years (511) and deaths (13) were observed among women smokers. Among men smokers, the age-adjusted mortality rate (based on 744 deaths) was 23.8 per 1000 per annum, whereas the rate among non-users of tobacco (438 deaths) was 14.6 per 1000 per annum, giving a highly significant relative risk of 1.63. Smokeless tobacco use was very high among men and women, the age-adjusted relative risk for men (1096 deaths) being 1.22 and for women (1575 deaths) 1.35.

Fig. 2 shows the age-specific mortality rates among male smokers and non-users of tobacco. The rates among smokers were higher at all ages, but surprisingly the difference was higher for lower-age groups (35–54 years).

Fig. 3a and Fig. 3b show for men and women, respectively, the age-specific mortality rates among smokeless tobacco users compared with non-users of tobacco. For women the mortality rates among smokeless tobacco users were higher in all age groups except the lowest (35–39 years). Among men, except in the age range 55–65 years, mortality rates were higher among smokeless tobacco users.

Table 4 shows the mortality rates among men for the two major types of smoking habits prevalent in Mumbai: cigarettes and bidis. The age-adjusted relative risk was 1.39 for cigarettes and 1.78 for bidis. The daily frequency of smoking was divided into two classes: 1–5 times and ⩾6 times. A clear dose–response relationship was apparent for bidis as well as cigarettes.

Table 5 shows the mortality rates by the type of smokeless tobacco use among women and men. For women the most popular types were *mishri* and *mishri* + others, which had relative risks of 1.24 and 1.49, respectively. For men, the most popular type was *mishri* + others, which had a relative risk of 1.29.

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Table 6 shows the mortality rates by frequency of use of the two major types of smokeless tobacco use (*mishri* and betel-quid) by men and women. The daily frequency of use was not very high (1–5 times and ⩾ 6 times, except for male *mishri* users, for whom they were 1–2 times and ⩾ 3 times). Despite this low frequency of use, a dose–response relationship was discernible.

Discussion

A high relative risk of overall mortality for cigarette smokers compared with non-smokers has been reported from every cohort study from all parts of the world. The present study, which shows a relative risk of mortality of 1.39 for cigarette smokers, demonstrates that Indians are no different in this respect. The excess mortality among male smokers in the 35–69-year age group in the present study was 880 per 100 000. For developed countries the excess mortality among males has been estimated to be 701 per 100 000 (*1*). Although the daily frequency of cigarette smoking in our cohort was low (median, 5 cigarettes (*9*)) and the two frequency classes were 1–5 times and ⩾ 6 times, a dose–response relationship was quite apparent, the two relative risks being 1.31 and 1.49.

The predominant form of tobacco use practised in India is bidi smoking. Because Mumbai is a large city, in our cohort use of bidis and cigarettes was equally common, but in the country as a whole, bidis are 8–10 times more commonly smoked than cigarettes. Bidi smoking is also practised in neighbouring countries, and there are recent reports of its availability and popularity also in the USA, especially among youth. The results on bidi smoking are therefore more relevant for India, but interesting also for many other countries.

Bidi smoking exhibited a high relative risk (1.78) that was not entirely unexpected. In a previous cohort study in Ernakulam District, Kerala State, male smokers (90% of them bidi smokers) had an age-adjusted relative risk of overall mortality of 1.5 (*6*). In another cohort study from Pune District, Maharashtra, the relative risk of overall mortality for bidi smokers compared with tobacco chewers was 1.6 (*10*). Although a bidi contains a much smaller amount of tobacco (0.2 g) than a cigarette (1 g), it produces a comparable or higher amount of tar and nicotine (*4*).

A more disturbing finding is the higher difference in age-specific mortality rates among smokers in the lower age groups. Thus, the relative risk for the age group 35–54 years was 2.4. Although the daily frequency of smoking was slightly higher among this age group (⩾ 6 times reported by 82% of 35–54-year-olds vs. 78% of ⩾ 55-year-olds), this did not account for the difference. Another disturbing finding is the high relative risk (1.62) even at a low level of exposure among bidi smokers (1–5 bidis per day).

The findings for smokeless tobacco use are slightly more difficult to interpret, but are less equivocal for women. Except for the lowest age group (35–39 years), the age-specific mortality rates for women were always higher among smokeless tobacco users than

Table 5. **Mortality rates and age-adjusted relative risks, by type of smokeless tobacco habit, among cohort study women and men, Mumbai**

	Person-years	Mortality rate[a]	Age-adjusted mortality rate[a]	Age-adjusted relative risk
Women				
Mishri	56 515	8.6	12.3	1.24
Mishri + others	42 192	20.1	14.8	1.49
Betel quid	10 805	14.3	11.8	1.19
Other tobacco	1821	20.9	16.0	1.62
Areca nut	2343	15.8	12.6	1.27
No tobacco use	64 414	7.6	9.9	1.00
Men				
Mishri	9965	15.1	15.5	1.06
Mishri + others	24 425	20.5	18.9	1.29
Betel quid	12 681	18.8	16.2	1.11
Other tobacco	7911	17.9	18.4	1.26
Areca nut	709	12.7	14.8	1.01
No tobacco use	27 236	16.1	14.6	1.00

[a] Per 1000 per annum.

Table 6. **Mortality rates and age-adjusted relative risks, by daily frequency of smokeless tobacco use, among cohort study women and men, Mumbai**

	Person-years	Mortality rate[a]	Age-adjusted mortality rate[a]	Age-adjusted relative risk
Women				
Mishri use (per day)				
1–5 times	54 223	8.7	12.3	1.24
⩾ 6 times	2786	7.2	14.8	1.49
Betel-quid use (per day)				
1–5 times	8609	13.4	10.9	1.10
⩾ 6 times	2887	15.6	14.8	1.49
No tobacco use	64 414	7.6	9.9	1.00
Men				
Mishri use (per day)				
1–2 times	9118	14.9	15.7	1.08
3–4 times	907	16.5	16.5	1.13
Betel-quid use (per day)				
1–5 times	8893	18.1	15.4	1.05
⩾ 6 times	3882	20.1	16.9	1.16
No tobacco use	27 236	16.1	14.6	1.00

[a] Per 1000 per annum.

non-users, with the difference being greater among older age groups (≥ 65 years). Among men, the age-specific mortality rate for was same for smokeless tobacco users and non-users for the age group 60–64 years, slightly lower for the 65–69-year age group who used smokeless tobacco, with, as for cigarette smoking, the difference being greater for younger age groups (35–54 years). In the earlier study in Kerala (*6*), the relative risk for male smokeless users was 1.2 (not significant), and among women smokeless tobacco users it was 1.3 (significant). For both men and women, certain categories of smokeless tobacco use exhibited quite high relative risks, increasing with the frequency of use. Excess mortality among female smokeless tobacco users aged 35–69 years in the present study was 260 per 100 000 compared with 312 per 100 000 among women smokers in developed countries (*1*). It is therefore highly likely that smokeless tobacco use may also cause a higher overall mortality.

Our results have important public health implications. To date tobacco-attributable mortality has been calculated as that generally attributable to cigarette smoking. However, our findings demonstrate that the health effects of bidi smoking are at least as important as those of cigarette smoking. In India, where 8–10 times more bidis are smoked than cigarettes, a gross underestimation of the tobacco problem would therefore occur by ignoring bidis. In terms of tobacco control policies, appropriate warning labels on bidi packets and advertisements, and higher taxation on bidis, similar to that on cigarettes, seem highly desirable.

The main objective of this cohort study was to estimate tobacco-attributable mortality, and for that the next step is to determine the relative risks specific to the causes of death. We are currently ascertaining causes of death among the study cohort by examining the death information forms at Mumbai municipal corporation and are in the process of creating a computer database. We are matching cohort records with corporation death records using names and addresses and, to some extent, date of death. There are no standard spellings, however, and names and addresses may be entered in two record sets with different spellings and in a different order. Nevertheless, we are hopeful of achieving an adequate degree of matching that will enable us to calculate cause-specific mortality. ■

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Résumé

Etude de cohorte sur la mortalité générale des consommateurs de tabac à Mumbai (Inde)

Le taux de mortalité générale est plus élevé chez les fumeurs de cigarettes que chez les non-fumeurs. Néanmoins, les effets des autres habitudes tabagiques sur la santé restent méconnus, que ce soit pour les *bidis* (cigarettes locales roulées par le consommateur), ou pour les divers produits sans fumée. C'est pourquoi nous avons entrepris une étude de cohorte dans la ville de Mumbai afin d'estimer les risques relatifs de mortalité générale pour les différents groupes de consommateurs de tabac. Une enquête de référence portant sur toutes les personnes âgées d'au moins 35 ans, choisies dans les listes électorales, a été réalisée de porte en porte et au moyen d'entretiens. Nous avons entrepris le suivi actif de 52 568 personnes de la cohorte 5 à 6 ans après l'enquête en utilisant les mêmes méthodes ; 97,6 % des personnes ont ainsi pu être retrouvées. Nous avons perdu la trace des sujets manquants le plus souvent parce qu'ils avaient quitté leur domicile, devenu trop vétustes ou dangereux et, moins fréquemment, à cause du développement. Nous avons couvert au total 293 368 personnes-année et enregistré 4 358 décès. Les taux annuels de mortalité ajustés selon l'âge étaient de 18,4 ‰ pour les hommes (113 463 personnes-année) et de 12,4 ‰ pour les femmes (179 905 personnes-année). Nous avons pris pour référence les taux annuels de mortalité ajustés selon l'âge chez les personnes ne consommant pas de tabac : 14,6 ‰ pour les hommes (27 236 personnes-année) et 9,9 ‰ pour les femmes (64 414 personnes-année). Il en ressort que pour les hommes, le risque relatif (RR) général du tabagisme est de 1,63 (28 338 personnes-année). Les taux de mortalité, toutes classes d'âge confondues, sont plus élevés chez les fumeurs que chez ceux qui s'abstiennent de consommer du tabac, avec une différence plus grande (RR = 2,4) dans les classes moins âgées (35 à 54 ans). Les produits les plus consommés sont les cigarettes et les *bidis* avec des risques relatifs ajustés selon l'âge de 1,39 (13 545 personnes-année) et de 1,78 (13 545 personnes-année) respectivement. Une relation dose-effet est apparue avec la fréquence des cigarettes fumées chaque jour (1 à 5 fois et ≥ 6 fois) (RR = 1,31 et RR = 1,49 respectivement), de même que pour les *bidis* (RR = 1,62 et RR = 1,86, respectivement).

Très peu de femmes fumaient (511 personnes-année) : elles consomment essentiellement du tabac sans fumée avec un risque relatif de 1,35 (114 980 personnes-année), les deux principales catégories de produits sans fumée étant le *mishri* seul (sorte de pâte orale, RR = 1,24) ou le *mishri* et d'autres produits (RR = 1,49). Les hommes adeptes du tabac sans fumée consomment surtout le *mishri* et d'autres produits (RR = 1,29). Pour les hommes comme pour les femmes, on a évoqué la possibilité d'une relation dose-effet pour les deux principaux produits sans

fumée, le *mishri* et le bétel. Les résultats établissent que la consommation de *bidis* n'est pas moins dangereuse que celle des cigarettes et indiquent que le tabagisme sans fumée pourrait également entraîner une augmentation de la mortalité générale. La prochaine étape consistera à obtenir les taux de mortalité et les risques relatifs en fonction des causes.

Resumen

Estudio por cohortes de la mortalidad por todas las causas entre los consumidores de tabaco en Mumbai (India)

Las tasas globales de mortalidad son mayores entre los fumadores de cigarrillos que entre los no fumadores. Sin embargo, es muy poco lo que se sabe acerca de los efectos en la salud de otras formas de consumo de tabaco muy extendidas en la India, como son los *bidis* y diversas modalidades de tabaco sin humo. En consecuencia, iniciamos un estudio por cohortes en la ciudad de Mumbai, en la India, para estimar los riesgos relativos de mortalidad por todas las causas entre diversos tipos de consumidores de tabaco. Mediante visitas domiciliarias y entrevistas personales, se llevó a cabo una encuesta de referencia entre todos los individuos ⩾35 años identificados a partir de las listas de votantes. Al cabo de 5-6 años de esa encuesta, se emprendió un seguimiento activo de 52 568 individuos de la cohorte empleando los mismos métodos, localizándose al 97,6% de las personas. La razón más común de pérdida de individuos para el seguimiento fue la demolición de su vivienda, por vetustez o peligrosidad, o, con menor frecuencia, el desarrollo. Se abarcó a un total de 293 368 personas-año, y se registraron 4358 defunciones. Las tasas de mortalidad anual ajustadas por la edad fueron de 18,4 por 1000 para los hombres (113 463 personas-año) y 12,4 por 1000 para las mujeres (179 905 personas-año). Se adoptaron como categoría de referencia las tasas de mortalidad ajustadas por la edad observadas en los no fumadores, que fueron de 14,6 por 1000 al año (cifra basada en 27 236 personas-año) entre los hombres y de 9,9 por 1000 al año (cifra basada en 64 414 personas-año) entre las mujeres. En los hombres, el riesgo relativo (RR) global atribuible al tabaco fue de 1,63 (28 338 personas-año). Las tasas de mortalidad entre los fumadores fueron superiores a las correspondientes a los no fumadores en todos los grupos de edad, y la diferencia fue mayor (RR = 2,4) para los grupos de menor edad (35-54 años). El tabaco se consumía principalmente como cigarrillos y como *bidis*, y los riesgos relativos ajustados por la edad para esas dos modalidades de consumo fueron respectivamente de 1,39 (13 545 personas-año) y 1,78 (13 545 personas-año). Se observó una relación dosis-respuesta al tener en cuenta el número de cigarrillos consumidos al día (1-5 veces y ⩾ 6 veces) (RR = 1,31 y RR = 1,49, respectivamente), así como para esas mismas frecuencias de consumo de *bidis* (RR = 1,62 y RR = 1,86, respectivamente).

Fumaban muy pocas mujeres (511 personas-año). Las que lo hacían consumían fundamentalmente tabaco sin humo, y el riesgo relativo entre ellas (basado en 114 980 personas-año) fue de 1,35. Las dos principales categorías de tabaco sin humo consideradas fueron *mishri* (RR = 1,24) y *mishri* + otros (RR = 1,49). Entre los hombres, la principal categoría de consumo de tabaco sin humo fue *mishri* + otros (RR = 1,29). Parecía insinuarse una relación dosis-respuesta para dos formas importantes de consumo de tabaco sin humo consideradas separadamente: mascada de betel y *mishri*, tanto entre los hombres como entre las mujeres. Los resultados indican que fumar *bidis* no es menos peligroso que fumar cigarrillos, y que el consumo de tabaco sin humo también puede dar lugar a una alta mortalidad por todas las causas. El próximo paso del trabajo consistirá en determinar las tasas de mortalidad y los riesgos relativos por causas específicas.

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Chronic Disease Mortality in a Cohort of Smokeless Tobacco Users

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The purpose of this study was to characterize the relation between smokeless tobacco use and the risk of all-cause and disease-specific mortality. Using data from the First National Health and Nutrition Examination Survey Epidemiologic Followup Study, the authors assessed the 20-year mortality experience of smokeless tobacco users. Subjects aged 45 years or more at baseline (1971–1975) were categorized as either smokeless tobacco users ($n = 1,068$) or non-smokeless tobacco users ($n = 5,737$). Subjects were further stratified by smoking status and gender. Proportional hazard ratios were used to assess associations. After adjustment for confounders, no association between smokeless tobacco use and all-cause (hazard ratio = 1.1, 95% confidence interval (CI): 0.9, 1.3), all cancer (hazard ratio = 1.1, 95% CI: 0.6, 1.9), or all cardiovascular (hazard ratio = 1.1, 95% CI: 0.8, 1.5) mortality was found. There was an increase in all cancer mortality of borderline significance among female smokeless tobacco users (hazard ratio = 1.7, 95% CI: 1.0, 2.8). The lung cancer mortality rate among combined users (smokeless tobacco and cigarettes), based on the rates for exclusive smokeless tobacco users and exclusive smokers, was higher than expected, possibly because of heavier smoking among these subjects. The mortality experience of smokeless tobacco users was not significantly greater than that of non-tobacco users and was appreciably less than that of cigarette smokers. Furthermore, combined use of smokeless tobacco and cigarettes did not increase overall mortality beyond that expected from use of the individual products.

cardiovascular diseases; mortality; neoplasms; tobacco, smokeless

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; NHANES I, First National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiologic Followup Study.

Smokeless tobacco use may be associated with an increase in oral cancer incidence (1) and with elevated rates of other cancers and cardiovascular disease (2–4). However, little research has been done on the relation between smokeless tobacco use and mortality from chronic diseases. We investigated the relation between smokeless tobacco use and mortality from both broad classifications of chronic disease and several specific disease outcomes. Because information on smoking status was available, we also compared the effects of smokeless tobacco use with that of cigarette smoking and investigated the mortality associated with the combined use of these two tobacco products.

There is growing interest in the possible adverse health effects of smokeless tobacco because of the increasing prevalence of smokeless tobacco use among young adult White males (5, 6) and the role of smokeless tobacco as a nicotine replacement for cigarette smoking (7). The prevalence of smokeless tobacco use among adolescents (students in grades 9–12) increased from 2.2 percent in 1970 to 9.3 percent in 1997, with White males having the highest prevalence (20.6 percent) (8, 9). According to the 1989 Teenage Attitudes and Practices Survey, each day more than 2,200 adolescents (ages 12–18 years) first try smokeless tobacco and about 830 (38 percent) become regular users (10).

Smokeless tobacco may be used by some smokers as a method to quit smoking and by others as a substitute for cigarettes in locations where cigarette smoking is not allowed. A recent Swedish study found that smokeless tobacco use can lead to higher smoking quit rates (11). A 1986 US tobacco survey found that approximately 7 percent

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of adults who formerly smoked reported substituting other tobacco products (including snuff and chewing tobacco) for cigarettes in an effort to stop smoking (7). One national survey found that, among current smokeless tobacco users, one third were former smokers (12), suggesting that smokeless tobacco is occasionally used as a substitute for cigarettes. Recently, some researchers have proposed smokeless tobacco as nicotine replacement therapy for inveterate cigarette smokers (13). The use of smokeless tobacco as a safe alternative to cigarette smoking requires a complete understanding of the risks associated with smokeless tobacco use.

Our aims are to assess the potential increased mortality risks associated with ever smokeless tobacco use in a representative sample of the US population and to evaluate the effects of the combined use of smokeless tobacco and cigarette smoking on mortality from chronic diseases.

MATERIALS AND METHODS

Data sources for determination of mortality risk associated with smokeless tobacco use

We used data from the First National Health and Nutrition Examination Survey (NHANES I) and the NHANES I Epidemiologic Followup Study (NHEFS) to determine whether any increased mortality risks were associated with smokeless tobacco use. The prospective nature of the data collection provided a unique opportunity to examine multiple mortality outcomes over an approximate 20-year follow-up period. The wide range of available information on a variety of risk factors allowed us to control for many potential confounders.

The survey design and data collection methods of NHANES I and NHEFS have been described elsewhere (14–19). Briefly, NHANES I was a national probability sample of the noninstitutionalized US population conducted from 1971 to 1975, with oversampling of the elderly, the poor, and women of childbearing age. NHANES I used a multistage sampling design leading to unequal probabilities for selection of sample subjects. The initial survey included in-person interviews covering a wide array of health behaviors, as well as a physical examination. The NHEFS surveys were conducted in 1982–1984, 1986 (limited to subjects ≥55 years of age at baseline), 1987, and 1992 to provide approximately 10, 15, and 20 years of follow-up information.

NHANES I included 14,407 adults ranging from 25 to 74 years of age who underwent a physical examination in 1971–1975. Of these subjects, 13,861 (96 percent) were successfully traced in at least one follow-up survey. By 1992, 4,604 (32 percent) subjects were identified as deceased, with death certificates available for 98 percent of the decedents.

Exposure variable

Only a random sample (n = 3,847) of all subjects in NHANES I were asked about smokeless tobacco use at baseline, but all subjects successfully interviewed during the 1982–1984 NHEFS were asked questions regarding smokeless tobacco use. Data from the 1982–1984 NHEFS were used to infer smokeless tobacco status at baseline when necessary. Subjects reporting current smokeless tobacco use in NHANES I or ever use in the 1982–1984 NHEFS were considered ever smokeless tobacco users (n =1,503) in this study. Subjects reporting neither current use nor ever use in either survey were considered never smokeless tobacco users (n = 10,948). Of the 1,503 ever smokeless tobacco users, there were 505 (33.6 percent) who had never smoked ("exclusive" smokeless tobacco users), 952 (63.3 percent) who had ever smoked ("combined" users), and 46 (3.1 percent) with unknown smoking status.

Confounding variables

The demographic variables considered in this analysis include age at examination, race, sex, region of residence (Northeast, Midwest, South, West), and poverty index ratio. A poverty index ratio equal to 1.0 designates the poverty level, with ratios less than 1.0 below and ratios greater than 1.0 above poverty level. A poverty index ratio was calculated for only a sample of subjects in NHANES I (n = 11,348). Definitions of these variables are provided in the *Plan and Operation of the Health and Nutrition Examination Survey, United States—1971–1973* (14).

Cigarette smoking information was gathered on only a sample of subjects in NHANES I. Pack-years of smoking were calculated by multiplying the reported average number of cigarettes smoked daily by the duration smoked divided by 20 (1 pack = 20 cigarettes). For subjects whose smoking information was not obtained in NHANES I, smoking status and pack-years at baseline were inferred from responses to the 1982–1984 NHEFS, whenever possible. Other tobacco habits such as pipe or cigar use were not considered in the formation of tobacco exposure categories (i.e., a subject who did not use smokeless tobacco or smoke cigarettes but did smoke a pipe would be considered a non-tobacco user).

Nutritional information was obtained via a 24-hour recall dietary questionnaire and was asked of only a sample of the NHANES I subjects at baseline (n = 11,348). Standard food-composition data were used to calculate nutrient intake (20). Other potential confounders for which information was available from either the baseline interview or the physical examination include alcohol consumption, recreational physical activity, body mass index, blood pressure, serum cholesterol, and family history (parents, siblings, or children) of cancer.

Outcome variables

Both underlying and multiple cause-of-death codes, using *International Classification of Diseases*, Ninth Revision (ICD-9), codes obtained from the death certificate, were used to categorize deaths. The underlying cause of death was used to calculate hazard ratios for the broad classifications of disease, whereas multiple cause-of-death codes were used to calculate hazard ratios for specific causes of death. Decedents identified only through proxy interview (n = 107) were not included in this analysis because no ICD-9 code was available from the data set.

TABLE 1. Distribution of subjects according to tobacco use categories for selected baseline characteristics, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, 1971–1992

	No tobacco		Exclusive smokeless tobacco use		Exclusive smoking		Both smokeless tobacco use and smoking	
	No.	%	No.	%	No.	%	No.	%
Subjects	5,192		505		5,523		952	
Age (years) at examination (mean)	47.8		54.0		44.9		47.9	
Subjects ≥45 years of age	2,986*		414*		2,751*		654*	
Males	722	24.2	225	56.0	1,591	55.7	592	92.7
Whites	2,629	92.0	248	66.6	2,448	93.0	551	90.7
Poverty index ratio (mean)	2.4		1.8		2.5		2.0	
Region of residence								
Northeast	678	26.8	42	11.5	660	25.2	91	13.8
Midwest	758	26.7	60	17.7	658	24.6	136	23.4
South	756	21.7	239	50.9	672	23.0	265	38.6
West	794	24.8	73	19.9	761	27.2	162	24.2
Smoking status								
Current					1,682	62.9	329	53.6
Former					1,069	37.1	325	46.4
Pack-years (mean)					35.1		42.3	
Alcohol†								
None	1,451	41.5	218	42.2	616	19.1	193	25.9
Less than 12 times/year	693	25.4	54	18.3	569	20.1	113	16.4
About 13–48 times/year	430	16.3	72	19.5	638	23.5	132	20.2
At least 104–156 times/year	407	16.9	68	20.0	922	37.4	212	37.4
Fruit and vegetable intake								
None or <1 serving/day	201	5.8	88	28.2	240	8.4	83	15.5
1 or 1.5 servings/day	583	24.6	123	28.2	567	27.8	193	35.8
2 or 2.5 servings/day	913	38.9	98	31.3	734	41.5	156	32.2
≥3 servings/day	636	30.7	30	12.4	378	22.4	63	16.6
Recreational physical activity								
Little	1,472	46.7	235	49.5	1,227	43.7	280	41.6
Moderate	1,089	37.7	127	33.6	1,053	38.7	237	39.0
Much	424	15.6	51	16.9	470	17.6	136	19.4
Blood cholesterol (mg/dl) (mean)	237.8		228.7		235.1		226.9	
Systolic blood pressure (mmHg) (mean)	142.3		147.8		136.6		139.2	
Body mass index (kg/m^2) (mean)	26.8		27.5		25.5		25.7	
Vitamin A intake (IU) (mean)	5,699.9		5,203.5		5,620.2		4,376.3	
Vitamin C intake (mg) (mean)	94.4		76.1		88.5		77.3	
Dietary fat intake (g) (mean)	62.4		72.1		77.6		84.6	

* Individual variable totals may not add up to column total because of missing responses.
† In 12 months prior to baseline.

This analysis was limited to White subjects and Black subjects, because of the small number of subjects in the "other" race category (n = 172). Because of the differences in age between exclusive smokeless tobacco users and non-tobacco users (table 1) and the low prevalence of smokeless tobacco use among subjects less than 45 years of age, the mortality analyses were restricted to those subjects 45–75 years of age at baseline (n = 6,805).

Statistical analysis

The distribution of potential confounding variables was calculated for the four tobacco categories (non-tobacco users, exclusive smokeless tobacco users, exclusive smokers, and combined smokeless tobacco users and smokers). The Cox proportional hazards model was used to calculate both the crude and the adjusted hazard ratios. Most

TABLE 2. Hazard ratios for selected causes of death for exclusive smokeless tobacco users relative to non-tobacco users, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, 1971–1992

Disease classification (ICD-9* code)	Males				Females			
	Crude HR*	95% CI*	Adjusted HR†	95% CI	Crude HR	95% CI	Adjusted HR†	95% CI
All causes	1.5	1.1, 1.9	1.0	0.8, 1.3	1.7	1.2, 2.4	1.3	0.9, 1.7
Malignant neoplasms (140–209)	1.1	0.5, 2.4	0.9	0.3, 2.3	1.6	1.0, 2.6	1.7	1.0, 2.8
Endocrine, nutritional, and metabolic diseases and immunity disorders (240–279)	2.7	0.7, 10.9	2.4	0.7, 8.8	2.9	0.6, 13.4	1.4	0.1, 13.5
Diseases of the nervous system and sense organs (320–389)	1.6	0.2, 10.2	1.1	0.2, 5.2	0.3	0.1, 1.3	0.6	0.1, 2.6
Diseases of the circulatory system (390–459)	1.5	1.1, 2.0	1.0	0.7, 1.5	1.8	1.0, 3.1	1.2	0.7, 1.9
Diseases of the respiratory system (460–519)	2.1	0.7, 5.8	0.9	0.3, 2.5	0.7	0.2, 2.5	0.6	0.1, 2.3
Diseases of the digestive system (520–579)	3.1	0.7, 12.7	1.9	0.4, 9.8	0.0‡		0.0§	

* ICD-9, *International Classification of Diseases*, Ninth Revision; HR, hazard ratio; CI, confidence interval.
† Adjusted for age, race, and poverty index ratio.
‡ Crude hazard ratio derived from 0/29, where the numerator represents the number of cases among exclusive smokeless tobacco users, and the denominator represents the number of cases among non-tobacco users.
§ Adjusted hazard ratio derived from 0/24, where the numerator represents the number of cases among exclusive smokeless tobacco users, and the denominator represents the number of cases among non-tobacco users.

analyses were stratified by gender. Follow-up time was calculated from the date of examination to the time the subject died, the time the subject was last known alive, or the endpoint of the study. Subjects lost to follow-up (i.e., not traced in any of the four studies of the NHEFS) were excluded from the analyses ($n = 100$). Subjects with a preexisting condition at baseline were excluded for analyses of that particular condition (e.g., subjects reporting stroke history at baseline were excluded from all analyses of stroke outcomes). To account for the complex survey design and the oversampling of certain populations, SUDAAN software was used to conduct the majority of the analyses. SUDAAN software (Research Triangle Institute, Research Triangle Park, North Carolina) is a software package specifically designed to analyze data from complex surveys that incorporate multistage sampling designs and unequally weighted designs (21).

Standardized mortality ratios were calculated as the measure of effect for oral cancer. Expected numbers were based on mortality rates from the National Center for Health Statistics for 1982, the approximate midpoint of the follow-up period.

RESULTS

There were 1,068 smokeless tobacco users in this cohort 45 years of age or older, 414 (39 percent) of whom were never smokers. Exclusive smokeless tobacco users were older (mean age = 64.9 years), poorer (mean poverty index ratio = 1.8), and more likely to reside in the South than other subjects (table 1). Crude differences between smokeless tobacco users and other subjects also were found in the frequency of alcohol intake (they drink less often than smokers), fruit and vegetable intake (less than smokers and non-tobacco users), and recreational physical exercise (less than smokers and non-tobacco users). Crude blood pressure and body mass index levels were higher among exclusive smokeless tobacco users than for other tobacco categories. Intakes of vitamin A, vitamin C, and dietary fat also differed across the four tobacco use categories.

After adjustment for age, race, gender, and poverty status, exclusive smokeless tobacco users did not experience statistically significant increased mortality from all causes (hazard ratio = 1.1, 95 percent confidence interval (CI): 0.9, 1.3), all cancer (hazard ratio = 1.1, 95 percent CI: 0.6, 1.9), or all cardiovascular outcomes (hazard ratio = 1.1, 95 percent CI: 0.8, 1.5) compared with non-tobacco users. Table 2 describes the relation between exclusive smokeless tobacco use and the causes of death for which there were at least 30 deaths, stratified by gender. Male smokeless tobacco users experienced statistically nonsignificant increases in mortality from endocrine, nutritional, and metabolic diseases and immunity disorders (hazard ratio = 2.4, 95 percent CI: 0.7, 8.8) and from diseases of the digestive system (hazard ratio = 1.9, 95 percent CI: 0.4, 9.8). Female smokeless tobacco users experienced an increase in mortality from all cancers (hazard ratio = 1.7, 95 percent CI: 1.0, 2.8) of borderline significance.

Table 3 presents hazard ratios from several specific chronic diseases. Male exclusive smokeless tobacco users did not experience significant increases in mortality for any type of cancer considered. The increased mortality from lung cancer among female smokeless tobacco users (never or ever smokers), although statistically significant, was based on only three deaths and four deaths, respectively. Smokeless tobacco use was not associated with significant increases in mortality for ischemic heart disease or stroke in either gender.

TABLE 3. Hazard ratios according to smokeless tobacco use relative to non-tobacco use for specific causes of death, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, 1971–1992

Cause of death (ICD-9* code)	Ever smokeless tobacco users: males								Ever smokeless tobacco users: females							
	Never smokers				Ever smokers				Never smokers				Ever smokers			
	Crude HR*	95% CI*	Adjusted HR	95% CI	Crude HR	95% CI	Adjusted HR	95% CI	Crude HR	95% CI	Adjusted HR	95% CI	Crude HR	95% CI	Adjusted HR	95% CI
Lung cancer (162)	0.0†		0.0‡,§		0.5	0.1, 3.8	22.6‡	6.4, 80.3	7.0	1.6, 30.9	9.1‡	1.1, 75.4	8.7	3.3, 22.4	1.2‡	0.2, 8.9
Digestive cancers (150–159)	1.2	0.5, 3.1	0.9¶	0.3, 2.3	0.3	0.1, 1.0	0.7¶	0.3, 1.8	0.8	0.3, 2.4	0.8¶	0.3, 2.7	0.7	0.3, 1.7	0.2¶	0.1, 1.1
IHD* (410–414)	1.4	0.9, 2.1	0.6#	0.3, 1.2	1.1	0.8, 1.6	1.0#	0.6, 1.7	1.7	1.1, 2.8	1.4#	0.8, 2.2	1.1	0.4, 2.7	1.1#	0.4, 3.2
Stroke (430–438)	1.2	0.5, 2.7	0.7**	0.2, 2.0	0.7	0.3, 1.3	0.7**	0.3, 1.5	2.2	1.2, 4.0	1.0**	0.3, 2.9	1.7	0.5, 6.4	1.7**	0.4, 7.0

* ICD-9, *International Classification of Diseases*, Ninth Revision; HR, hazard ratio; CI, confidence interval; IHD, ischemic heart disease.

† Crude hazard ratio derived from 0/9, where the numerator represents the number of cases among exclusive smokeless tobacco users, and the denominator represents the number of cases among non-tobacco users.

‡ Adjusted for age, race, poverty index ratio, region of residence, alcohol, recreational physical exercise, and fruit/vegetable intake.

§ Adjusted hazard ratio derived from 0/6, where the numerator represents the number of cases among exclusive smokeless tobacco users, and the denominator represents the number of cases among non-tobacco users.

¶ Adjusted for age, race, poverty index ratio, alcohol, and dietary fat intake.

Adjusted for age, race, poverty index ratio, alcohol, recreational physical exercise, fruit/vegetable intake, systolic blood pressure, serum cholesterol, and body mass index.

** Adjusted for age, race, poverty index ratio, alcohol, recreational physical exercise, fruit/vegetable intake, and systolic blood pressure.

The analyses investigating the combined effects of smokeless tobacco use and smoking on specific outcomes were restricted to male subjects because of the low prevalence of combined use among females ($n = 62$). As shown in table 4, the lung cancer mortality among combined users was nearly twice that of exclusive smokers (hazard ratios = 22.6 and 13.2, respectively). Combined users did not experience increased mortality for ischemic heart disease, although exclusive smokers had a statistically significant increase in mortality (hazard ratio = 1.6, 95 percent CI: 1.3, 1.9).

There were no oral cancer deaths among exclusive smokeless tobacco users (table 5). In a cohort of this size followed for approximately 20 years, only one death would have been expected. Among ever smokeless tobacco users, two deaths from oral cancer were observed and two deaths were expected. Both oral cancer decedents among smokeless tobacco users were White males. Once again, this is

TABLE 4. Adjusted hazard ratios according to smokeless tobacco use and smoking status relative to non-tobacco users: males, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, 1971–1992

	IHD*		Lung cancer		All cancer	
	HR*,†	95% CI*	HR‡	95% CI	HR§	95% CI
Non-tobacco users	1.0		1.0		1.0	
Exclusive smokeless tobacco users	0.6	0.3, 1.2	0.0¶		1.0	0.3, 2.5
Exclusive smokers	1.5	1.1, 2.1	13.2	4.5, 38.2	1.3	0.8, 2.1
Current	2.0	1.4, 2.8	24.7	8.3, 73.5	1.8	1.1, 3.1
Former	1.2	0.8, 2.0	7.0	2.1, 23.2	1.0	0.5, 1.8
Smokeless tobacco users and smokers	1.0	0.6, 1.7	22.6	6.4, 80.3	1.6	0.9, 2.7
Smokeless tobacco and current	0.8	0.5, 1.5	33.9	8.0, 143.7	2.2	1.2, 3.7
Smokeless tobacco and former	1.1	0.6, 2.1	9.0	2.0, 40.8	0.9	0.4, 1.8

* IHD, ischemic heart disease; HR, hazard ratio; CI, confidence interval.

† Adjusted for age, race, poverty index ratio, alcohol, recreational physical exercise, fruit/vegetable intake, systolic blood pressure, serum cholesterol, and body mass index.

‡ Adjusted for age, race, poverty index ratio, region of residence, alcohol frequency, recreational physical exercise, and fruit/vegetable intake.

§ Adjusted for age, race, poverty index ratio, alcohol, recreational physical exercise, fruit/vegetable intake, dietary fat intake, and family history of cancer.

¶ Adjusted hazard ratio derived from 0/6, where the numerator represents the number of cases among exclusive smokeless tobacco users, and the denominator represents the number of cases among non-tobacco users.

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TABLE 5. Observed and expected deaths according to tobacco status: oral cancer, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, 1971–1992

	Observed deaths	Expected deaths*	SMR†,‡	95% CI†
Overall	19	12.2	156	93, 231
Ever smokeless tobacco user	2	1.9	107	10, 308
Exclusive smokeless tobacco user	0	0.8	0	0, 580
Ever smoker	14	5.0	278	150, 439
Exclusive smoker	11	3.8	288	142, 480

* Based on 1982 mortality rates for US adults 45–75 years of age.
† SMR, standardized mortality ratio; CI, confidence interval.
‡ Indirectly adjusted only for age.

what would be expected in a cohort of this size (standardized mortality ratio among White males = 114, 95 percent CI: 11, 327). Comparatively, among all smokers, 14 oral cancer deaths were observed, whereas only five were expected (standardized mortality ratio = 278, 95 percent CI: 150, 439).

DISCUSSION

The crude hazard ratios show increased mortality among smokeless tobacco users, largely because smokeless tobacco users were older than non-tobacco users and smokers. After controlling for age, gender, race, and poverty status, we found that smokeless tobacco users did not experience higher mortality than did non-tobacco users in this cohort. After stratification by gender, no statistically significant increases in mortality were found for males. Among females, a borderline statistically significant increase was found for all cancer mortality.

Few studies have investigated mortality in relation to smokeless tobacco use. Results from the National Mortality Followback Survey showed that smokeless tobacco use was not associated with increased risk for all cancer, oral cancer, or cancer of the digestive organs (22). Zahm et al. (23) found a nonsignificant increase in soft tissue sarcoma among US veterans who had ever chewed tobacco or used snuff (relative risk = 1.4, 95 percent CI: 0.8, 2.6), with no soft tissue sarcoma originating in the head, neck, and face region among smokeless tobacco users. They found no soft tissue sarcoma deaths among those who used smokeless tobacco only. They did find an increase in mortality from buccal cancer among smokeless tobacco users (relative risk = 3.0, 95 percent CI: 2.0, 4.5) (23). In a recent ecologic study, no increased mortality rate for oral/pharyngeal cancer was found in West Virginia, the state with the highest prevalence of smokeless tobacco use, compared with the United States as a whole (24). Although few in number, these studies generally support the results of our analysis.

The scant body of epidemiologic evidence for smokeless tobacco use and cardiovascular disease mortality differs from our results. A study of Swedish construction workers found a small but statistically significant increased risk for all cardiovascular disease mortality (relative risk = 1.4, 95 percent CI: 1.2, 1.6), ischemic heart disease, and stroke (3). However, common risk factors for cardiovascular disease such as blood pressure, exercise, diet, and alcohol were not controlled and may explain the increased risk. Of note in the Swedish study was the absence of an increased risk for all cancer deaths (relative risk = 1.1, 95 percent CI: 0.9, 1.4), similar to our results. Another study from Sweden found a small but statistically nonsignificant increased risk from fatal myocardial infarction (including sudden death) among snuff dippers (odds ratio = 1.5, 95 percent CI: 0.5, 5.0) (4).

Although smokeless tobacco users in the present study experienced no increased risk in cardiovascular disease mortality, smokers experienced a small but statistically significant increased risk for ischemic heart disease. This disparity supports evidence that something other than nicotine is causing the increase in cardiovascular mortality (25).

Although oral cancer is the adverse effect most accepted as a consequence of smokeless tobacco use (1), we found no association between oral cancer mortality and ever smokeless tobacco use. Although the number of observed deaths among exclusive smokeless tobacco users was too small to calculate a hazard ratio, the number of expected deaths in this cohort was less than one. The reasons why smokeless tobacco leads to an increase in oral cancer incidence but not to an increase in oral cancer mortality may be due to advances in cancer detection and treatment or to insufficient follow-up time for deaths to occur among a small number of cases.

The validity of the data should not be a concern, as the hazard ratio for oral cancer mortality among cigarette smokers is similar to the findings of other studies (26). Similarly, the magnitude of association between cigarette smoking and lung cancer (hazard ratio = 13.2, 95 percent CI: 4.5, 38.2 among males) is consistent with that observed in other studies, as is the finding of greater lung cancer mortality among current smokers than former smokers (27).

The complex survey design and oversampling of certain populations required the use of SUDAAN software to analyze the data set. However, results reflecting a small number of outcomes have been found to strongly influence estimates (28). Although we found statistically nonsignificant associations between smokeless tobacco use by males and diseases of the endocrine and digestive systems and

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statistically significant increases in all cancer and lung cancer mortality among female smokeless tobacco users, these results could be due to outcomes experienced by a small number of subjects having large sample weights. The association for all cancer among female smokeless tobacco users was influenced by a small number of deaths at two sites (three lung cancer deaths and two uterine cancer deaths among smokeless tobacco users). Future studies, including both male and female subjects, should be conducted to determine whether these associations with smokeless tobacco use are causal.

Although the mortality rate among combined users was higher than that expected from the individual rates, this result is not likely due to a synergistic effect between smokeless tobacco and cigarettes. The combined users smoked more than exclusive smokers did (42.3 and 35.1 mean pack-years, respectively). The higher cigarette smoking dose, not the use of smokeless tobacco, is likely leading to the increased lung cancer mortality among combined users. A possible explanation is that combined users may be strongly addicted to nicotine and using smokeless tobacco in addition to cigarettes rather than as a substitute for them.

The apparent lack of an effect among combined users for ischemic heart disease mortality is counterintuitive. Combined users smoked more than exclusive smokers did, yet their ischemic heart disease mortality was less than that of exclusive smokers. Combined users were more likely to be former smokers than were exclusive smokers, possibly accounting for the decreased risk found here.

Of the two oral cancer deaths among ever smokeless tobacco users (both White males), one was a current smoker and the other was a former smoker. However, these two observed deaths were not more than expected in this cohort, even when limiting the analysis to White males. In this cohort, cigarette smoking was responsible for the increased oral cancer mortality.

One limitation of this analysis is that the exposure category is based only on ever use of smokeless tobacco. Therefore, potential increases in mortality associated with current versus former use could not be determined. Similarly, no dose-response analysis could be done. Because of the lack of information on lifetime use, subjects who used smokeless tobacco once were categorized the same as those who used smokeless tobacco many times.

Rouse (29) found that, among males who had ever tried smokeless tobacco, 60 percent used it in the past year; among females who had tried it, 42 percent used it in the past year. She also found that, among those who reported any lifetime use, 26 percent used it almost daily in the past year (29). Therefore, it may be a reasonable assumption that smokeless tobacco users in our study were not one-time users, with many having used smokeless tobacco regularly. Also, the restriction to subjects 45 years of age or more created a homogeneous exposure group with respect to duration of smokeless tobacco use. The majority of smokeless tobacco users initiate smokeless tobacco use prior to the age of 18 years (30).

Tobacco categories represent self-reported responses, and neither smokeless tobacco status nor smoking status was biologically confirmed. Confounding variables were also self-reported (e.g., alcohol intake, physical activity). However, as this information was collected prospectively, the potential for recall bias is much less than that found in case-control studies.

Although this analysis was restricted to subjects 45–75 years of age at baseline to create more similar comparison groups with respect to unknown and uncontrolled confounders, residual or uncontrolled confounding (e.g., other tobacco habits or factors relating to survival) may contribute to the results found in this study.

Because only a sample of individuals were asked about their tobacco habits in NHANES I, the results from 1971 to 1975 were supplemented by information collected in the 1982–1984 NHEFS. This approach may have resulted in some nondifferential misclassification of tobacco use, as data from 1982–1984 may not be as accurate as those collected in 1971–1975 (because of recall error or the use of proxies for subjects who died between the baseline interview and the initial follow-up). The expected effect would be a bias toward the null hypothesis of no association. However, as smokeless tobacco use is defined as only ever/never, this effect should be minimal.

This analysis represents one of the most comprehensive studies of the relation between smokeless tobacco use and mortality. The 20-year follow-up period allowed ample time to investigate common outcomes among smokeless tobacco users in a representative US population. Available data on a wide variety of risk factors allowed us to minimize the potential for confounding as an explanation for any results.

Overall, we found no increased mortality for subjects who reported ever smokeless tobacco use when compared with subjects who reported no tobacco use. The few increases in mortality that we discovered, although likely due to chance, should be investigated further. Evidence from this study shows that smokeless tobacco use is a safer alternative than continued cigarette smoking. Mortality for exclusive smokeless tobacco users is considerably less than mortality for exclusive smokers for all cancer (especially lung cancer) and for ischemic heart disease. Further studies are needed to determine whether regular smokeless tobacco use is appreciably more harmful than ever use and to determine whether there is increasing risk with increasing amount or duration of use of smokeless tobacco products.

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Annexure 12

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Tobacco use, body mass and cancer mortality in Mumbai Cohort Study.

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Abstract

BACKGROUND: Tobacco use and body mass are major risk factors for many cancers. Despite this, very little is known about their combined effect on cancer mortality. These relationships are virtually unexplored in populations having patterns of both tobacco use and body habitus atypical of those typically enrolled in epidemiologic studies.

METHODS: A prospective cohort study of 148,173 men and women aged > or =35 years was conducted in Mumbai, India. Subjects were recruited during 1991-1997, measured for a variety of risk factors, including tobacco use and anthropometry, and then followed for approximately 5-6 years.

RESULTS: During 774,129 person-years of follow up, a total of 796 cancer deaths were observed. Tobacco use, especially smoking in men, was associated with particularly high risk of death in extreme categories of body mass. At highest risk were underweight smoking males [hazard ratio (HR)=9.45, 5.87, and 5.75 for those smokers who were extremely thin (<16.0kg/m(2)), very thin (16.0 to <17.0kg/m(2)), or thin (17.0 to <18.5), respectively]. Significant effects of underweight among never and smokeless tobacco users disappeared with exclusion of individuals with < or =2 years of follow up. Extremely thin (<16.0kg/m(2)) women smokeless tobacco users had an elevation in risk, HR=2.95, that actually appeared to increase (to 3.21) with exclusion of individuals who were diagnosed within 2 years of follow up.

CONCLUSION: Tobacco use and undernutrition are known to be serious problems in developing countries. The current study underlines the strikingly elevated risk of cancer when they occur together.

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Cancer and mortality among users and nonusers of snus

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Scandinavian moist snuff (snus) is claimed to be a safer alternative to smoking. We aimed to quantify cancer incidence among male snus users and to shed light on the net health outcome by studying their overall mortality. A cohort, comprised of 9,976 men who participated in a population-based survey, was compiled in 1973–74. Follow-up until January 31, 2002, was accomplished through record-linkages with nation-wide and essentially complete registers of demographics, cancer and causes of deaths. Adjusted relative risks among exposed relative to unexposed men were estimated using Cox proportional hazards regression. The cohort members contributed more than 220,000 person-years at risk for cancer. A statistically significant increase in the incidence of the combined category of oral and pharyngeal cancer among daily users of snus (incidence rate ratio 3.1, 95% confidence interval 1.5–6.6) was found. Overall mortality was also slightly increased (hazard ratio 1.10, 95% confidence interval 1.01–1.21). Although the combined previous literature on snus and oral cancer weigh toward no association, this population-based prospective study provided suggestive evidence of snus-related risks that cannot be lightly ignored.
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Key words: epidemiology; cancer; mortality; smokeless tobacco

The carcinogenic potential of oral snuff, including the Scandinavian moist type (snus), has been evaluated and established by 2 working groups at the International Agency for Research on Cancer.[1] However, in view of the comparably low levels of tobacco-specific nitrosamines in snus and the idea of using snus as a way of reducing smoking dose among inveterate smokers,[2–4] possible health consequences of snus use is presently the topic of intense debate. Several Swedish case-control studies concluded that there was no significant association between use of snus and head and neck cancer,[5–7] while a significant excess risk of pancreatic cancer was reported from 2 recent cohort studies.[8,9] Moreover a moderately increased all-cause mortality was observed among snus-using male construction workers.[10]

We aimed to quantify cancer incidence among male snus users, and to shed light on the net health outcome by studying their overall and disease group-specific mortality.

Material and methods

The cohort

A cohort from Uppsala County, central Sweden, was established in 1973–74 as an emanation from a population-based survey investigation aimed at establishing the prevalence of oral lesions.[11] All residents of the municipalities of Enköping or Håbo aged 15 years or older during the year of examination (n = 30,118) were invited to participate. In the first round, a total of 18,659 (62% of all invited) individuals participated. Of those remaining, 2,292 were randomly selected for an intense recruitment effort, which resulted in another 1,674 (73%) examined participants. The total participation was 20,333 individuals constituting 68% of all invited (Fig. 1). All participants filled in a questionnaire about tobacco and alcohol consumption, and all underwent a clinical examination of the oral cavity, performed by one of the present authors (TA). For 121 individuals, the data from 1973 to 74 was lost. Since virtually no women were exposed to snus, we restricted our analysis to men (n = 9,976).

Follow-up

Follow-up for mortality and cancer incidence between 1973 and 2002 was accomplished through record-linkages with the nation-wide and essentially complete registers of cancer,[12,13] causes of deaths[14] and total population,[15] using the individually unique National Registration Numbers, assigned to all Swedish residents and included in all registers, as identifiers.

Cancer diagnoses

We grouped the cancer diagnoses into the following 3 nested categories: a combined category of oral and pharyngeal cancer (ICD7: 140–148); smoking-related cancers according to Levitz *et al.*[16] including oral and pharyngeal cancer (ICD7: 140–148), oesophageal and gastric cancer (ICD7:150–151) pancreatic cancer (ICD7:157), laryngeal and pulmonary cancer (ICD7:161–162), cancer of the kidney, bladder and other urinary organs (ICD7:180–181); and any cancer (ICD7: 140–209). The list proposed by Levitz *et al.*[16] differs somewhat from that published by the International Agency for Research on Cancer[17] in that it does not include cancers of the nasal cavities and sinuses, liver, and myeloid leukemia.

As we only counted first cancers, individuals with a history of any cancer diagnosis before entry into the cohort in 1973–74 were excluded (n = 116). The follow-up for cancer thus comprised 9,860 men.

Causes of death

We grouped causes of death into the following 4 categories: Cancer deaths (ICD8, ICD9: 140–209, ICD10: C00–D48); cardiovascular deaths (ICD8, ICD9: 390–458, ICD10: I00–I99); and respiratory deaths (ICD8, ICD9: 460–519, ICD10: J00–J99) and all-cause mortality. The follow-up for mortality comprised all 9,976 men.

Statistical methods

In addition to computing crude incidence and mortality rates (the number of events divided by corresponding person-time), we analyzed data with Cox proportional hazard regression using attained age as the underlying time-scale. We estimated hazard ratios (HR) for cancer incidence and mortality, with 95% confidence intervals (CI), as measures of relative risk of cancer and death, respectively.

In the follow-up for mortality, person-time was calculated from the date (age) of first examination (1973–74) until the date (age) of death, emigration or end of follow-up (January 31, 2002), whichever occurred first. In the follow-up for cancer additional censoring took place at date of first cancer (any site).

Exposure to snus was categorized as never or ever daily use at entry into the cohort in 1973–74. The models were adjusted for

Abbreviations: CI, confidence interval; HR, hazard ratios; ICD, International Classification of Diseases; IR, incidence rate; MR, mortality rate; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosonornicotine; TSNA, tobacco-specific nitrosamines.

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smoking (never versus ever daily use), alcohol consumption (less than once a week versus once a week or more), and area of residence (rural, small municipality or town). All covariate information emanated from 1973 to 74. We also adjusted for calendar period (attained) in 5-year-intervals (1973–1977, 1978–1982, 1983–1987, 1988–1992, 1993–1997, 1998–2002). Since all participants entered at approximately the same time in 1973–74, calendar time was equivalent to time-in-study.

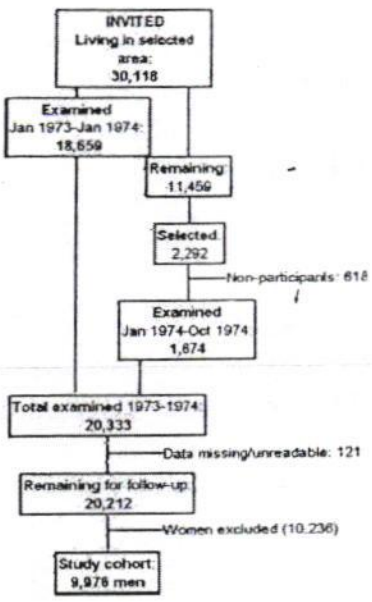

FIGURE 1 – Overview of the recruitment to the population-based cohort.

Nonproportionality of hazards (interaction between age [underlying time-scale] and covariates) was investigated using the Grambsch and Therneau test based on Schoenfeld residuals.[18] In cases of nonproportional hazards, separate covariate effects were fitted for 2 age strata, where the chosen cut-off age was 70 years for cancer analyses and 75 years for mortality analyses (since death occurs at higher ages than cancer). For respiratory deaths, the age cut-off was chosen as 80 years since virtually all these deaths occurred at advanced ages. The interaction between covariates and the dichotomized age-scale was further tested using likelihood ratio tests, and p-values are presented. Only participants with complete information on outcome and all covariates were included in the models. Stata version 9 was used for the statistical analyses.[19]

Results

At time of cohort accrual in 1973–74, 867 men (9%) were classified as ever daily users of snus (but never daily smokers), 5,309 (53%) as ever daily smokers (but never daily users of snus), and 692 (7%) as both ever daily smokers and ever daily users of snus. The cohort was followed for up to 29 years and the study participants contributed 223,528 and 231,542 person-years at risk for cancer and death, respectively (Table I). There were 237 ever-users of snus among the 1,575 individuals who were diagnosed with any first cancer. A total of 3,630 cohort members died and

TABLE I – NUMBER OF PARTICIPANTS, PERSON-YEARS, CRUDE INCIDENCE (IR) AND MORTALITY (MR) RATES BY SNUS USE, SMOKING AND SOME OTHER BACKGROUND FACTORS

	Any cancer[1]				All-cause mortality[2]	
	No of individuals (n)[3]	Person-years[4]	Cases (n)	CrudeIR[5]	Deaths (n)	Crude MR[6]
Snus use						
Never daily use	8,311	189,561	1,337	7.1	2,988	15.2
Ever daily use	1,548	33,944	237	7.0	641	18.3
Missing	1		1		1	
Smoking						
Never daily use	3,930	91,978	544	5.9	1,262	13.3
Ever daily use	5,930	131,550	1,031	7.8	2,368	17.4
Alcohol consumption						
No/low	1,447	29,895	228	7.6	703	22.6
Moderate/high	8,407	193,522	1,345	6.9	2,922	14.6
Missing	6		2		5	
Area of residence						
Rural	3,513	77,353	626	8.1	1,494	18.5
Small community	1,492	36,391	188	5.2	402	10.8
Town	4,855	109,784	761	6.9	1,734	15.3
Calender period (attained)						
1973–1977	9,860	42,127	175	4.2	457	10.7
1978–1982	9,298	44,676	260	5.8	632	13.8
1983–1987	8,559	40,999	241	5.9	641	15.2
1988–1992	7,872	37,447	299	8.0	674	17.3
1993–1997	7,115	33,658	323	9.6	656	18.5
1998–2002	6,353	24,622	277	11.3	570	21.6
Age (attained)						
14–24	1,625	8,656	2	0.2	7	0.8
25–34	3,832	26,891	8	0.3	22	0.8
35–44	5,374	44,964	25	0.6	56	1.2
45–54	6,449	48,433	100	2.1	163	3.3
55–64	6,192	42,499	288	6.8	358	8.2
65–74	4,675	31,700	555	18.0	849	24.8
75+	2,941	20,386	597	29.0	2,175	90.8

[1]Any cancer includes ICD7 codes 140–209.–[2]All cause mortality includes all ICD8, ICD9, and ICD10 codes.–[3]Number of cohort members in the cancer analysis (n = 9,860). Since we excluded 116 cohort members with prevalent cancer at time of entry in the cohort, the mortality analysis included a slightly larger number of individuals (n = 9,976). Their distributions across exposures categories were very similar to that exhibited here and are therefore not shown.–[4]The distribution of person-years across exposure categories differ marginally in the mortality analysis due to a slightly larger number of cohort members from start and absence if censoring at cancer incidence. The difference is so small that these data are not shown.–[5]Crude incidence rate of any cancer per 1,000 person-years.–[6]Crude mortality rate per 1,000 person-years.

TABLE II – INCIDENCE RATE RATIOS (IRR) FOR ANY CANCER, SMOKE-RELATED CANCER AND THE COMBINED CATEGORY OF ORAL AND PHARYNGEAL CANCER BY SNUS USE AND SMOKING, OBTAINED IN MODELS THAT INCLUDED ALL PARTICIPANTS AND IN MODELS RESTRICTED TO NEVER-SMOKERS

	Any cancer			Smoke-related cancer[1]			The combined category of oral and pharyngeal cancer[1]		
	Cases (*n*)	Crude IR[2]	HR[3] (95% CI)	Cases (*n*)	Crude IR[2]	HR (95% CI)	Cases (*n*)	Crude IR[2]	HR[4] (95% CI)
Snus use									
Never daily use	1,335	7.1	1.00 (ref)	422	2.2	1.0 (ref)	23	0.1	1.0 (ref)
Ever daily use	237	7.0	1.00 (0.87–1.15)	71	2.1	1.1 (0.8–1.4)	11	0.3	3.1 (1.5–6.6)
Smoking									
Never daily use	544	5.9	1.00 (ref)	112	1.2	1.0 (ref)			
Ever daily use	1,028	7.8	1.26 (1.13–1.40)	381	2.9	2.2 (1.8–2.7)			
Restricted to never smokers									
Snus use									
Never daily use	406	5.5	1.0 (ref)	73	1.0	1.0 (ref)			
Ever daily use	138	7.8	1.1 (0.9–1.4)	39	2.2	1.6 (1.1–2.5)			

Age <70 years			
Never	8	0.1	1.0 (ref)
Ever	5	0.05	0.5 (0.1–1.4)
Age ≥70 years			
Never	3	0.2	1.0 (ref)
Ever	18	0.9	5.6 (1.6–19.6)
	6	0.1	1.0 (ref)
	5	0.3	2.3 (0.7–8.3)

All models were adjusted for calendar period (attained), area of residence, alcohol consumption, and smoking or snus use; along with interaction terms where appropriate (see footnotes).

[1]For definitions, see text.–[2]Crude incidence rate per 1,000 person-years.–[3]Interaction term included in model: Age × calendar period (attained).–[4]Interaction term included in model: Age × smoking.

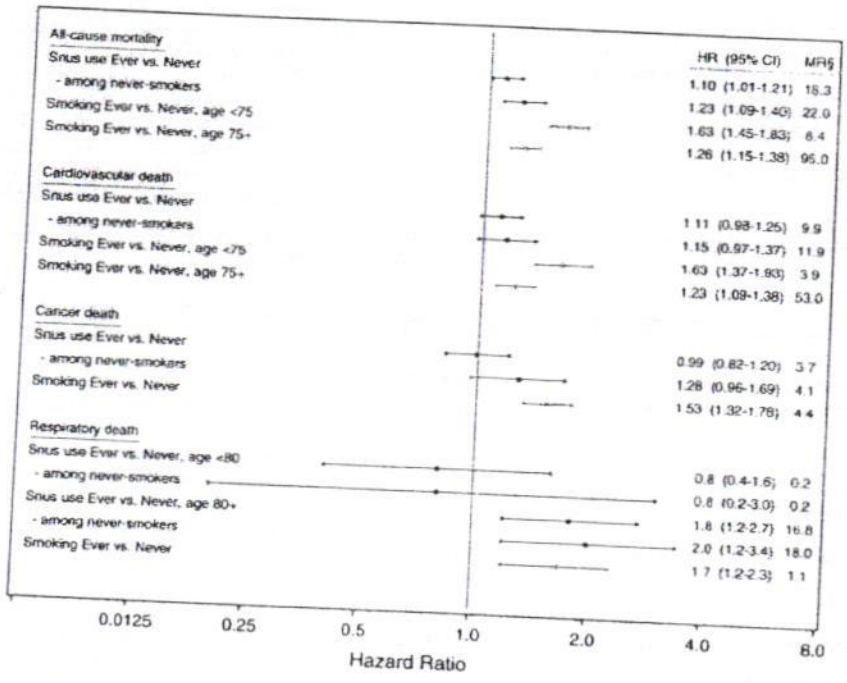

FIGURE 2 – Hazard ratios (HR) and mortality rates (MR) for all-cause mortality, cardiovascular deaths, cancer deaths, and respiratory deaths by snus use (blue) and smoking (yellow). Data are given for all participants and (in analyses of snus effects) for the substratum of never smokers. All models used attained age as the underlying time-scale and were adjusted for calendar period (attained), area of residence, alcohol consumption and smoking or snus use. Models for all-cause mortality (including model restricted to never-smokers) contained the following interaction terms: Age × smoking, age × area of residence, and age × alcohol consumption. Interaction terms in the models for cardiovascular deaths were: Age × calendar period, age × smoking and age × area of residence. In the models for cancer deaths the interaction terms were age × area of residence and age × alcohol consumption. Models for respiratory deaths had interaction terms for age × calendar period and age × snus use. § Crude Mortality rate per 1,000 person-years.

641 of them had reported snus use in 1973–74. Table I exhibits characteristics of the study cohort, including crude incidence rates of cancer and death by exposure categories.

Cancer incidence

While smokers exhibited a statistically significant 26% (95% CI 13–40%) excess incidence of cancer overall relative to never-smokers (Table II), no corresponding excess was observed among ever-users of snus relative to never-users (HR 1.00) in a model that included all cohort members and where mutual adjustments were made for smoking and snus use. A similar difference between smoking and snus use was evident in an analogous analysis where the outcome was smoking-related cancers; as expected, smokers had an increased risk (HR 2.2, 95% CI 1.8–2.7), whereas snus use, relative to nonuse of snus, was linked to a trivial and nonsignificant excess (HR 1.1, 95% CI 0.8–1.4). On the other hand, when the outcome was restricted to the combined category of oral and pharyngeal cancer a significant 3.1-fold (95% CI 1.5–6.6) risk elevation was revealed among ever-users of snus relative

to never-users, based on 11 exposed cases. In the analysis of the relationship between smoking and the combined category of oral and pharyngeal cancer, we observed a significant interaction ($p < 0.0015$) between smoking and attained age. We therefore proceeded with age-stratified analyses, which showed a substantial smoking-related excess (HR 5.6, 95% CI 1.6–19.6) confined to ever-smokers who had attained an age of 70 years or more, relative to never-smokers in the same age bracket.

We then restricted our analyses of snus effects to the never-smoker stratum in order to eliminate possible residual confounding from smoking dose. When total cancer incidence was the outcome, no excess incidence emerged among non-smoking ever-users of snus (HR 1.1, 95% CI 0.9–1.4) relative to individuals who had never smoked nor used snus, but a 60% excess of smoking-related cancers (HR 1.6, 95% CI 1.1–2.5) was significant (Table II). We were unable to statistically confirm a risk elevation for the combined category of oral and pharyngeal cancer, but the relative risk estimate was based on no more than 5 exposed cases (HR 2.3, 95% CI 0.7–8.3).

Mortality

We estimated relative risks for death of any cause, cancer death, cardiovascular death and respiratory death. In a model including all cohort members and where mutual adjustments were made for smoking and snus use, smoking was significantly linked to increased risks for all of the studied mortality outcomes (Fig. 2). Also snus use was associated with a statistically significant, albeit small, risk elevation for death of any cause (HR 1.10, 95% CI 1.01–1.21; Fig. 2). A trend toward a snus-associated excess of cardiovascular death of a similar magnitude did not attain statistical significance, while the risk of cancer death was close to that among never-users of snus. There was a significant ($p < 0.025$) interaction between snus use and attained age in the model with respiratory death as the outcome. Consequently, the risk for this outcome was analyzed separately in strata of age below versus equal to or above 80 years. A statistically significant excess risk among snus users, relative to never-users of snus, was noted in the older stratum (HR 1.8, 95% CI 1.2–2.7) but not in the younger.

Analyses of snus effects in strata of never-smokers generally produced relative risk estimates that were higher than those yielded in the models that included all cohort members. HR was statistically elevated 1.23 (95% CI 1.09–1.40) and 2.0 (95% CI 1.2–3.4) for death of any cause among all never-smoking users of snus and for respiratory death among such users who had attained an age of 80 years or more, respectively. Observed hazard ratios of 1.15 and 1.28 for cardiovascular death and cancer death, respectively, remained statistically nonsignificant.

We performed sensitivity analyses with restriction to men aged 25 years or above at entry into the cohort. It is unusual that people take up smoking above this age. The outcomes were (*i*) all cancer, (*ii*) the combined category of oral and pharyngeal cancer, and (*iii*) all-cause mortality, and the analyses were done in the total cohort as well as in the cohort of never smokers at entry. In all of these analyses, the results were essentially identical to those obtained in the exhibited main analyses without age restrictions (data not shown).

Discussion

The results of this population-based cohort study among Swedish men with essentially complete register-based follow-up and an accumulated person-time experience of more than 220,000 years suggest that snus use is not associated with an increased incidence of cancer overall but tentatively with an excess incidence of the combined category of oral and pharyngeal and of total smoking-related cancer. In analyses confined to never-smokers, where confounding from smoking dose is unlikely to occur, we observed relative risks of 2.3 (though based on 5 cases) and 1.6, respectively. In addition, statistically significant excesses were noted with regard to all-cause mortality and mortality due to respiratory diseases, the latter excess being limited to the very oldest.

The excess of the combined category of oral and pharyngeal cancer incidence is at odds with results from all of the more recent case-control[5–7,20] and cohort[8,9] studies of Scandinavian moist snus. However, since individuals who combine smoking with snus use may be exposed to a lower smoking dose and may increase their overall chances of subsequent abstinence compared to those who only smoke,[21] residual negative confounding from total cumulative smoking dose is an important concern. Indeed, while a Swedish case-control study found no significant relation between use of snus and overall risk of head and neck cancer, snus use among never-smokers (where this residual confounding is more likely to have been eliminated) was associated with an increased risk of 4.7 (95% CI 1.6–13.8).[5] In another study with prospective design and adjustment for smoking intensity through multivariate modeling[8] a 20% reduction in risk of lung cancer was noted, again suggesting residual negative confounding. Well in line with these indications are the consistently higher relative risk estimates in our analyses that were confined to the never-smoking stratum. We believe that the effect estimates for snus in these strata are less biased compared to the estimates obtained in analyses involving the total cohort of smokers and non-smokers and in which control for confounding by smoking is attempted through multivariate modeling. With only one exception,[5] previous studies did not have sufficient power to analyze snus effects in strata of never-smokers.

The presence of a range of carcinogens, among which the tobacco-specific nitrosamines (TSNAs) NNN and NNK appear to be the most important ones, is well established in smokeless tobacco.[22] Although TSNA levels in snus on the Swedish market have been greatly reduced since the 1980s,[23] the prerequisites for carcinogenicity are indisputably present. A recent report from the United States[24] provides evidence that users of smokeless tobacco may be exposed to NNK to a similar degree as are smokers. And others have shown that differences in current TSNA levels between American and Swedish moist snuff may not be substantial.[25] Therefore, while disagreeing with previous Scandinavian studies, our results may be biologically plausible but they have to be confirmed in further studies on Swedish moist snus.

Whether or not the observed increased overall mortality and the similarly sized, statistically nonsignificant excess of cardiovascular deaths can be attributed to snus use warrants further studies. Experimental data in both animals[26–28] and humans[29–31] have demonstrated that nicotine and smokeless tobacco, including Swedish moist snus[32,33] raise blood pressure and pulse rate, albeit the results are ambiguous as regards the risk of chronic hypertension. Two Swedish cohort studies indicated an approximately 40% excess risk of death[10] or incidence[34] from cardiovascular disease. Additional Swedish case-control data suggest that the excess of myocardial infarction might be confined to fatal cases,[35,36] in line with animal data showing an increased propensity for cardiac arrhythmias[37] and an increased size of experimentally induced myocardial infarctions after exposure to nicotine.[38,39] Previous epidemiological data on the risk of fatal cardiovascular disease, however, have been inconsistent, and the positive findings did not attain statistical significance.

Our observed excess risk of respiratory deaths, seemingly limited to the very oldest, is consistent with findings in the American Cancer Prevention Study.[40] The mechanisms, including the possibility of confounding, are yet to be established. The effect-modification by attained age might suggest that at least 60 years of exposure is required for the effect. An alternative possibility is that the very oldest were the ones who were most heavily exposed to snus from the distant past. If snus has become successively less detrimental to the general health it is conceivable that late effects might be seen only among octogenarians and older. The manufacturing processes for Swedish snus have changed over the decades and there are data to support that the levels of N-nitrosamines have diminished in the past 25 years.[23]

Strengths of our study include the prospective design with essentially complete follow-up, and the anchorage in the general population.

We restricted our analysis to first cancers only and excluded all potential cohort members who had a cancer documented in the nationwide cancer register, which goes as far back as 1958. A special feature of our study is that all cohort members were screened for oral cancer at time of entry into the cohort. Thus, there were no prevalent oral cancers at time of entry, and the possibility of reversed causation or selection bias vis-à-vis oral cancer is practically excluded.

An important caveat is the fact that the exposure information was collected in 1973–74, up to 29 years prior to the occurrence of studied outcomes. It is possible that the tobacco habits had changed after inclusion into the cohort. In a subcohort comprising 252 men tobacco habits were recorded both at entry (1973–74) and at reexamination in 1993–95.[41–43] Among the 22 who were never users of tobacco in 1973–74 nobody had taken up smoking, but 1 man had taken up daily snus use. Among 56 exclusively ever daily smokers in 1973–74 seven had become daily users of snus exclusively and 28 had stopped using tobacco. None of 60 exclusively snus users in 1973–74 had changed to smoking.

Since smoking is rarely taken up after age 25, the analyses that were restricted to never-smokers should not have been seriously affected by changes in smoking habits. Sensitivity analyses restricted to men who had attained the age of 25 before entry into the cohort, performed both among never-smokers at entry and in the entire cohort, confirmed that the results were practically identical to those obtained when younger men were also allowed in the cohort. If confounding by misclassified smoking due to changed habits during follow up would explain the observed excess risk among our snus users, it must be assumed that smoking exposure increased more among snus users than among nonusers of snus. This is highly unlikely.[44] A recent Swedish study reported a high probability of continuing snus use once the habit has been initiated.[45]

Of further concern is the unavailability of data on a range of conceivable confounding factors. Fortunately, relevant are only factors that are linked to the use of snus and which are not in the causal pathway between snus use and the studied outcomes. This probably rules out covert factors such as cholesterol levels, hypertension, but also even anthropometric measures, infections, and presence of diabetes. We were able to adjust for alcohol consumption. However, confounding by dietary pattern, physical activity and socioeconomic status could have shifted the relative risks in any direction. Although adjustments for area of residence could have reduced possible confounding by socioeconomic status somewhat, the absence of information on these potential confounding factors is an important limitation of our study.

Even though more than 220,000 person-years were under surveillance statistical precision is still a concern. The snus-related relative risks for the combined category of oral and pharyngeal cancer in the entire cohort and in the never-smoking substratum were based on no more than 11 and 5 exposed cases, respectively. This resulted in wide confidence intervals. Moreover, although the outcomes studied were strictly defined *a priori*, the analysis of multiple outcomes in multiple exposure strata may have produced some chance findings.

As 32% of the initially invited individuals chose not to participate, the external validity is somewhat uncertain. It is conceivable that a "healthy participant effect" was in operation so that the participants, on average, were healthier than the general Swedish population. Therefore, effect sizes might differ somewhat from what would have been observed if the entire population had participated. On the other hand, the "healthy participant effect" is likely to have slightly reduced the range of exposure to various lifestyle factors, thereby correspondingly limiting potential confounding from these factors.

In conclusion, our results are inconsistent with claims that the use of Scandinavian moist snus is without demonstrable risk. While relative risks of the studied outcomes are consistently lower than those associated with smoking, and the combined previous Scandinavian literature on snus and oral cancer has not shown any association, the possible snus-related risks are biologically plausible and warrant further exploration. Presently, they should not be categorically dismissed.

Acknowledgements

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Smokeless Tobacco Use and Increased Cardiovascular Mortality among Swedish Construction Workers

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ABSTRACT

Objectives. Little is known about the risks of cardiovascular disease associated with the use of smokeless tobacco, which produces blood nicotine levels similar to those caused by cigarette smoking.

Methods. Male Swedish construction industry employees (n = 135 036) who attended a health examination were followed by studying cause-specific mortality during a 12-year period. The study population comprised 6297 smokeless tobacco users, 14 983 smokers of fewer than 15 cigarettes per day, 13 518 smokers of 15 or more cigarettes per day, 17 437 ex-smokers, 50 255 "other" tobacco users, and 32 546 nonusers.

Results. The age-adjusted relative risk of dying from cardiovascular disease was 1.4 for smokeless tobacco users and 1.9 for smokers of 15 or more cigarettes per day, compared with nonusers. Among men aged 35 through 54 years at the start of follow-up, the relative risk was 2.1 for smokeless tobacco users and 3.2 for smokers. When data were adjusted for body mass index, blood pressure, and history of heart symptoms, the results were essentially unchanged. Cancer mortality was not raised in smokeless tobacco users.

Conclusions. Both smokeless tobacco users and smokers face a higher risk of dying from cardiovascular disease than nonusers. Although the risk is lower for smokeless tobacco users than for smokers, the excess risk gives cause for preventive actions. (*Am J Public Health.* 1994;84:399–404)

Introduction

Although there is well-established evidence for a causal link between cigarette smoking and cardiovascular damage and disease,[1] the reasons behind the development of atherosclerosis in smokers are not fully understood. The nicotine content of cigarette smoke is a suspected contributor to vascular damage, as nicotine has a variety of potentially relevant cardiovascular effects. Nicotine most likely promotes atherosclerotic disease by its actions on lipid metabolism and coagulation,[2–5] by hemodynamic effects,[1,4] and/or by causing endothelial injury.[6]

However, there have been no studies on long-term exposure to pure nicotine in humans, and only limited experience from animal studies.[7] Therefore, users of smokeless tobacco (snuff) present an excellent opportunity for studying the effects of exposure to nicotine without simultaneous exposure to carbon monoxide and other combustion products of tobacco smoke. It has been shown that the use of smokeless tobacco, during which nicotine is absorbed through the buccal mucosa, produces maximum blood levels of nicotine similar to those produced by cigarette smoking and results in a larger overall exposure to nicotine owing to prolonged absorption.[8,9]

In a recent cross-sectional study, it was observed that middle-aged and older smokeless tobacco users had a significantly higher prevalence of hypertension than either nonusers or smokers.[10] The smokeless tobacco users were also affected more than nonusers by cardiovascular symptoms. During a 4-year follow-up period, smokeless tobacco users had a higher risk than nonusers of disability retirement due to cardiovascular diseases. The excess risk was quite similar to the excess risk observed in smokers.

The aim of the present study was to investigate whether long-term exposure to smokeless tobacco is associated with an excess risk of dying from cardiovascular disease in users compared with nonusers and to compare this potential excess risk among smokeless tobacco users with the corresponding excess risk among cigarette smokers.

Materials and Methods

Subjects

The study population comprised 135 036 men who had received medical checkups under the auspices of the Swedish Construction Industry's Organization for Working Environment Safety and Health during the years 1971 through 1974. The cohort included construction workers, electricians, painters, sheet metal workers, and other construction industry employees in the whole of Sweden. The invitation to the voluntary medical examination was sent out by the construction site staff and about 75%

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TABLE 1—Distribution of the Study Population, by Age and Tobacco Habit

Age	Nonusers	Smokeless Tobacco Users	Smokers, <15 cig/d	Smokers, ≥15 cig/d	Ex-Smokers	Total
<35 y	13 120	2891	7 626	6 350	4 369	34 356
35–54 y	13 784	1672	5 225	5 785	8 222	34 688
55–65 y	5 642	1734	2 132	1 383	4 846	15 737
All	32 546	6297	14 983	13 518	17 437	84 781

Note. Those who had mixed tobacco use or who smoked pipes or cigars (50 255 subjects, or 37.2% of the total sample of 135 036) are excluded from table.

responded to it. In 1974 there were 183 865 registered workers in the Swedish construction industry; it is not known to what extent the nonattending workers (≈25%) were not reached by the invitation or were not willing to come. Women (< 0.5% of workers in the construction industry) were excluded from the study.

Procedures

A standardized program was followed for the medical examination. Body weight and height were determined. Blood pressure was measured after 5 minutes of rest in a supine position. A standard mercury manometer on the upper arm was used to record the systolic level when phase 1 (Korotkoff) sounds were heard and the diastolic level at phase 5 (disappearance of sounds). Blood pressure was recorded to the nearest 2 mm Hg. Heart rate was recorded as beats per minute, simultaneously with the blood pressure measurement.

Tobacco habits by kind of tobacco use (cigarettes, smokeless tobacco, pipe, cigar, or mixed use), amount of smoked tobacco, and duration of the tobacco consumption habit were recorded with the aid of a questionnaire that the subject filled out together with a nurse. The questionnaire also requested information about present or past history of symptoms and diseases as well as current medication.

The members of the study population identified between 1971 and 1974 and who were alive on January 1, 1974, were followed regarding cause-specific mortality during the period 1974 through 1985 with the aid of the National Cause of Death Register,[11] with certification of the underlying cause of death according to the *International Classification of Diseases,* 8th revision (ICD-8). The underlying cause of death is defined as the illness that started the chain of events that directly led to death. The diagnoses specifically studied were ischemic heart disease (ICD 410–414), cerebrovascular disorders (ICD 430–438), all cardiovascular diagnoses (ICD 390–458), and all malignant neoplasms (ICD 140–209).

Analyses

The classification of tobacco habits was aimed at isolating subjects in groups with a single type of exposure to tobacco. Tobacco users were divided into smokeless tobacco users, smokers, ex-smokers, and others. Nonusers were subjects who reported that they had never used tobacco. Smokers were divided into cigarette smokers who smoked fewer than 15 cigarettes per day and those who smoked 15 cigarettes per day or more, both groups being without any other kind of former or present tobacco use. Smokeless tobacco users were subjects who reported only present smokeless tobacco use and no former or present smoking. Ex-smokers were cigarette smokers who had never smoked a pipe, smoked cigars, or used smokeless tobacco and who had quit smoking; they were further divided into those who had not smoked for less than 5 years and those who had not smoked for 5 or more years. "Others" were all subjects with mixed tobacco use or subjects who smoked a pipe or cigars. The duration of the tobacco habit was divided into less than 15 years and 15 or more years. Because smokers of more than 15 cigarettes per day consume about the same amount of nicotine as daily smokeless tobacco users,[9,12] special emphasis should be placed on this group when interpreting the analysis.

In the analysis, blood pressure was divided into four categories: systolic blood pressure ≤ 140, 141–159, 160–179, and ≥180 mm Hg and diastolic blood pressure <85, 85–94, 95–104, and ≥105 mm Hg. Blood pressure and heart rate data were missing for 0.2% of the subjects. The body mass index was calculated as body weight in kilograms divided by height in meters squared. Body mass indexes were divided into four categories: ≤20.0, 20.1–25.0, 25.1–30.0, and >30.0.

Relative risks of death due to specific causes, together with 95% confidence intervals, were estimated for subjects with different tobacco habits in comparison with the nonusers. To adjust for potential confounding factors, the Mantel-Haenszel procedure was used[13] and 95% confidence intervals were estimated according to Greenland et al.[14] Potential confounding factors were considered to be age (5-year brackets), area of domicile, blood pressure, blood pressure medication, previous cardiac symptoms, diabetes, and body mass index.

Analyses of the relationship between different tobacco habits and mortality were performed for the entire cohort, for workers entering the study at ages 35 through 54 years, and for those entering the study at ages 55 through 65 years.

Results

The distribution of the study population by tobacco habit is shown in Table 1; 24.1% of the subjects were nonusers, 4.7% were smokeless tobacco users, 11.1% were smokers of fewer than 15 cigarettes per day, 10.0% were smokers of more than 15 cigarettes per day, and 12.9% were ex-smokers. The 37.2% of the population who smoked pipes or cigars or who had mixed tobacco use (n = 50 255) were excluded from all analyses.

During the follow-up period (1974 through 1985), there were a total of 8293 deaths in the whole study cohort. Fifty-seven pereent of the deaths occurred in the analyzed tobacco-use groups: nonusers, 1322; smokeless tobacco users, 440; smokers of fewer than 15 cigarettes per day, 900; smokers of 15 or more cigarettes per day, 923; and ex-smokers, 1126. Cardiovascular disease was the most common cause of death among the construction workers. Ischemic heart disease caused 38% of the deaths in the whole study population, implying a crude cumulative mortality of 2.3% during the 12-year follow-up period.

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TABLE 2—Observed Numbers of Deaths and Relative Risks (RRs)[a] for Causes of Death for Different Tobacco Habit Groups Compared with Nonusers

Cause of Death	Nonusers[b] (At-Risk n = 32 546)	Smokeless Tobacco Users (At-Risk n = 6297)		Smokers, <15 cig/d (At-Risk n = 14 983)		Smokers ≥15 cig/d (At-Risk n = 13 518)		Ex-Smokers, 1–5 y (At-Risk n = 6761)		Ex-Smokers, >5 y (At-Risk n = 9800)	
	No.	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
All cardiovascular disease	641	220	1.4 (1.2, 1.6)	450	1.8 (1.6, 2.0)	381	1.9 (1.7, 2.2)	169	1.4 (1.1, 1.6)	402	1.1 (0.9, 1.2)
All cancer	372	96	1.1 (0.9, 1.4)	216	1.5 (1.3, 1.8)	276	2.5 (2.2, 3.0)	119	1.6 (1.3, 2.0)	249	1.3 (1.1, 1.6)
All causes	1322	440	1.4 (1.3, 1.8)	900	1.7 (1.6, 1.9)	923	2.2 (2.0, 2.4)	350	1.3 (1.2, 1.5)	776	1.1 (1.0, 1.2)

Note. The deaths of 3582 men who were pipe or cigar smokers or had a mixed tobacco use habit are not presented in the table. For 876 ex-smokers (5%), length of time since quitting smoking was unknown; these ex-smokers were not included in this analysis. CI = confidence interval.
[a]Adjusted for age in 5-year intervals and for region of origin.
[b]Nonusers are the referent category (RR = 1.0).

Table 2 shows the age-adjusted relative risks of dying of cardiovascular disease, malignant tumors, and any cause for different tobacco-use groups compared with the nonusers. The excess risk of dying of cardiovascular disease was most pronounced for smokers, with a dose–response relation. In ex-smokers, the excess risk diminished with the time since smoking was stopped. Smokeless tobacco use was also found to be associated with an excess risk of dying of cardiovascular disease, whereas regarding death from cancer, no excess risk was observed. Although the present study did not analyze different cancer diagnoses in detail, it was obvious that smoking had a dose–response relationship to overall cancer risk and that the excess risk diminished gradually with the time since smoking was stopped.

Table 3 shows the results of the analysis of more specific causes of death in workers in two age groups. Higher relative risks were observed in the younger than in the older group for both smokeless tobacco users and smokers, compared with the nonusers. For smokeless tobacco users compared with nonusers, the relative risk of dying of cardiovascular disease was 2.1 (95% confidence interval [CI] = 1.5, 2.9) for those in the younger group and only 1.1 (95% CI = 1.0, 1.4) for those in the older group.

Death from stroke was less common than death from ischemic heart disease, but with regard to tobacco habits, the risk patterns for ischemic heart disease and stroke were the same. The relative risk of stroke among the younger smokeless tobacco users was close to 2, compared with the nonusers, but the number of cases was small and therefore the confidence interval was wide.

Lung cancer was studied specifically to evaluate whether hidden smokers could be found among the declared smokeless tobacco users. Three deaths from lung cancer were found in this group, whose relative risk compared with the nonusers was 0.9 (95% CI = 0.2, 3.0).

When potential confounding due to age, area of domicile, body mass index, blood pressure, diabetes, and history of heart symptoms or blood pressure medication at the time of entering the study was analyzed according to the Mantel-Haenszel procedure, the relative risks of death from cardiovascular diseases remained essentially unchanged. For cancer and overall mortality, no changes in the relative risk estimates were found when confounding factors were considered.

It was not considered meaningful to evaluate the duration of the tobacco habit in relation to cardiovascular mortality because very few subjects in age groups prone to various cardiovascular manifestations (i.e., those older than 45 years) exhibited a duration of tobacco use of less than 15 years, as most tobacco users start the habit at a young age. Eighty-seven percent of the cardiovascular deaths among smokeless tobacco users were associated with a tobacco habit duration of more than 15 years at the time the subjects entered the study. The corresponding figure for smokers of fewer than 15 cigarettes per day was 89%; for smokers of 15 or more cigarettes per day, the figure was 97%.

Figure 1 shows, for subjects who entered the study at ages 35 through 54 years, the relative risk of dying of ischemic heart disease for subjects in different tobacco-use categories compared with the nonusers. For smokeless tobacco users, the risk of death from ischemic heart disease was higher than that of nonusers and ex-smokers but lower than that of cigarette smokers.

Discussion

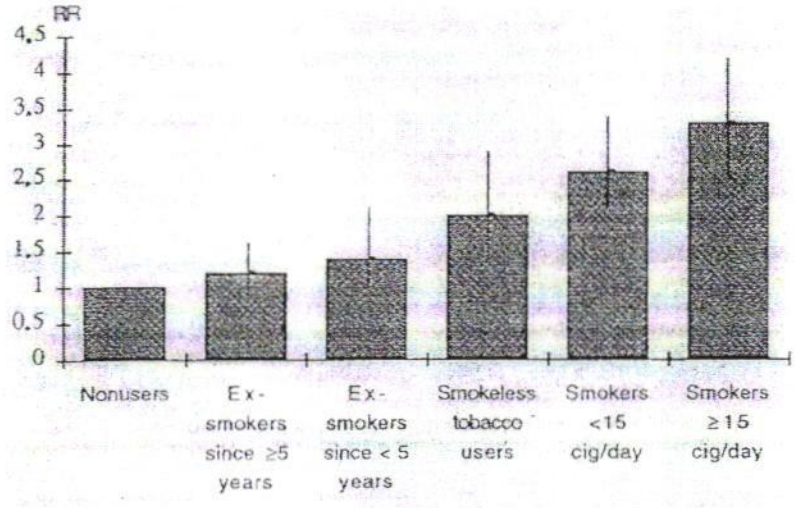
The present study of cardiovascular and cerebrovascular mortality in a cohort comprising more than 6000 smokeless tobacco users is the first observational epidemiological cohort study with the possibility of comparing a large group of smokeless tobacco users with both smokers and subjects not using any kind of tobacco. The results indicate an apparent excess risk of death from cardiovascular and cerebrovascular diseases of about 40% to 100% among smokeless tobacco users, compared with nonusers, when possible confounding factors are taken into account. Smokers face even higher risks of both cardiovascular and cerebrovascular causes of death.

In a recent case–control study from northern Sweden encompassing 35- through 64-year-old men with a first myocardial infarction and population-derived controls, smoking but not the use of smokeless tobacco was associated with an increased risk of myocardial infarction.[15] These results, which are contradictory to ours, could be due to differences in study design and composition of reference groups. Reasonably, the power to detect potential hazard effects from smokeless tobacco use is greater in an observational cohort study

TABLE 3—Cause-Specific Mortality among Swedish Construction Workers during 12-Year Follow-Up after 1971–1974 Health Examination

Cause of Death	Nonusers[a]	Smokeless Tobacco Users		Smokers, <15 cig/d		Smokers ≥15 cig/d		Ex-Smokers, 1–5 y		Ex-Smokers, >5 y	
	No.	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
Age 35–54 years at entry into study											
	(At-Risk n = 13 784)	(At-Risk n = 1672)		(At-Risk n = 5225)		(At-Risk n = 5785)		(At-Risk n = 2882)		(At-Risk n = 5005)	
Ischemic heart disease	123	35	2.0 (1.4, 2.9)	128	2.6 (2.1, 3.4)	162	3.3 (2.6, 4.2)	37	1.4 (1.0, 2.1)	67	1.2 (0.9, 1.6)
Stroke	16	4	1.9 (0.6, 5.7)	17	2.7 (1.4, 5.4)	19	3.0 (1.5, 5.7)	4	1.2 (0.4, 3.7)	5	0.7 (0.2, 1.9)
All cardiovascular disease	154	44	2.1 (1.5, 2.9)	164	2.7 (2.2, 3.4)	199	3.2 (2.6, 3.9)	46	1.4 (1.0, 2.0)	83	1.1 (0.9, 1.5)
All cancer	128	22	1.2 (0.8, 1.9)	62	1.2 (0.9, 1.7)	116	2.2 (1.8, 2.9)	42	1.6 (1.1, 2.2)	62	1.1 (0.8, 1.5)
Lung cancer	5	1	1.2 (0.2, 9.1)	16	8.1 (3.2, 20.4)	43	21.4 (8.5, 54.1)	7	6.7 (2.3, 19.7)	3	1.2 (0.3, 4.5)
All causes	440	105	1.9 (1.6, 2.4)	317	2.0 (1.7, 2.3)	437	2.6 (2.3, 3.0)	114	1.3 (1.1, 1.6)	189	1.0 (0.9, 1.2)
Age 55–65 years at entry into study											
	(At-Risk n = 5642)	(At-Risk n = 1734)		(At-Risk n = 2132)		(At-Risk n = 1383)		(At-Risk n = 1076)		(At-Risk n = 3660)	
Ischemic heart disease	359	137	1.2 (1.0, 1.5)	225	1.7 (1.4, 1.9)	122	1.4 (1.2, 1.8)	89	1.3 (1.1, 1.6)	248	1.1 (0.9, 1.2)
Stroke	70	26	1.2 (0.7, 1.8)	19	0.7 (0.4, 1.2)	25	1.6 (1.0, 2.5)	20	1.5 (0.9, 2.5)	35	0.8 (0.5, 1.2)
All cardiovascular disease	480	174	1.1 (1.0, 1.4)	272	1.5 (1.3, 1.7)	167	1.5 (1.3, 1.7)	120	1.3 (1.1, 1.6)	317	1.0 (0.9, 1.2)
All cancer	223	69	1.0 (0.8, 1.3)	145	1.7 (1.4, 2.1)	148	2.9 (2.3, 3.5)	69	1.6 (1.3, 2.1)	183	1.3 (1.1, 1.5)
Lung cancer	8	2	0.8 (0.1, 3.9)	36	11.9 (5.5, 25.6)	57	30.6 (14.6, 64.1)	14	9.4 (3.9, 22.3)	12	2.3 (1.0, 5.7)
All deaths	820	301	1.2 (1.0, 1.3)	496	1.6 (1.5, 1.8)	377	2.0 (1.8, 2.2)	212	1.4 (1.2, 1.6)	576	1.1 (1.0, 1.2)

Note. For some ex-smokers (335 [4.1%] of those aged 35–54 years at entry and 110 [2.3%] of those aged 55–65 years at entry), length of time since quitting smoking was unknown; these ex-smokers were not included in this analysis. No. = number of deaths in the group; RR = relative risk, adjusted for age (5-year intervals) and for region of origin, for tobacco users compared with nonusers; CI = confidence interval.
[a]Nonusers are the referent category (RR = 1.0).



Note. Only subjects who were 35–54 years of age at entry into the study are included.

FIGURE 1—Adjusted relative risk (RR), together with 95% confidence interval, of dying due to ischemic heart disease among subjects in different tobacco habit groups as compared with nonusers.

with 3159 deaths due to ischemic heart disease (of which 172 were smokeless tobacco users) than in a smaller case–control study with 585 incident cases of myocardial infarction (of which 59 were smokeless tobacco users). In addition, our nonusers had never used any tobacco, whereas the nonusers in the case–control study included both former smokers and former smokeless tobacco users. The use of such "nonusers" might have contributed to a dilution of a possible excess risk for myocardial infarction in smokeless tobacco users.

Possible bias due to misclassification of both exposure and disease should be considered in our study. Assuming that smokers have a higher risk of dying from cardiovascular disease than smokeless tobacco users, a misclassification of smokers in the smokeless tobacco users group would lead to an overestimation of the relative risk associated with smokeless tobacco (i.e., the observed relative risk would be too high). How-

ever, if the proportion of misclassified smokers in the group classified as using smokeless tobacco was considerable, an elevated risk of dying from lung cancer would have been expected. Only three deaths from lung cancer were found among those classified as smokeless tobacco users. The corresponding relative risk of dying from lung cancer, compared with nonusers, was 0.9 (95% CI = 0.2, 3.0). In addition, different kinds of smokers or smokeless tobacco users wrongly classified as nonusers would result in an underestimation of the correlation between smokeless tobacco use and mortality due to cardiovascular disease. On combining different sources of bias due to misclassification of exposure, one finds that an underestimation of the relative risk of death from cardiovascular disease associated with smokeless tobacco use is more likely than an overestimation.

No follow-up recording of subjects' tobacco habits after entry into the study has been made. The most common change in tobacco habits in adults is to quit using tobacco. If our subjects had quit using tobacco, the relative risk estimates might have been diluted compared with what would be expected if no change took place during the follow-up period. If smokeless tobacco users had a tendency to start smoking, the estimated relative risks for smokeless tobacco users would be exaggerated. Nearly all smokeless tobacco users had used smokeless tobacco for more than 15 years without smoking, so it is reasonable to assume that the possible influence of such changes has been small.

The completeness of the Swedish National Cause of Death Register is almost 100%, as all deaths are required to be registered.[16] The validity of the underlying causes of death stated in death certificates has been evaluated and found to be high regarding cardiovascular diseases, stroke, and cancer.[17] Possible misclassifications are not likely to be dependent on the type of tobacco habit and therefore should not affect the relative risk estimates.[18]

The relationship between smokeless tobacco use and mortality due to specific causes was scrutinized regarding potential confounding from age, area of domicile, body mass index, blood pressure, diabetes, and history of heart symptoms or blood pressure medication at the time of entering the study. Cardiovascular risk markers such as total cholesterol were not routinely measured at the time of the medical examinations of this cohort, and therefore it was not possible to adjust for hypercholesterolemia as a confounding factor in the analysis. Cholesterol and high-density lipoprotein cholesterol did not differ between smokeless tobacco users and nonusers in two studies of relatively young users of smokeless tobacco,[19,20] but significantly higher levels of plasma cholesterol were found in smokeless tobacco users in one study in which older users were also examined.[21] The body mass index of smokeless tobacco users is generally higher than that of nonusers and considerably higher than that of smokers,[10] possibly implying differences in lipoprotein levels. However, the body mass index regarded as a confounder in the analysis did not change the relative risk estimates for the association between smokeless tobacco use and mortality due to cardiovascular disease.

It was not possible to consider potential confounding due to alcohol use, as no information on alcohol use was included in the medical examination data for this cohort. There is a positive correlation between hypertension and alcohol consumption.[22] Other studies have shown that smokeless tobacco users consume more alcohol than nonusers.[19,20] Similarly, tobacco users tend to exhibit other risk behaviors more often than nonusers.[22] Considering the relative homogeneity of the study population—all of whom were construction industry employees—and the relative risk associated with smokeless tobacco use among subjects aged 35 through 54 years at entry into the study, as well as the relative risk associated with heavy alcohol consumption,[23] it is unlikely that differences in alcohol consumption (between smokeless tobacco users and nonusers) would explain the findings entirely. Moreover, the studies on the relationship between alcohol consumption and cardiovascular disease have been ambiguous.[24] There have been, however, no observations indicating a difference in alcohol consumption between smokeless tobacco users and cigarette smokers, and therefore the possible confounding effect of alcohol use can be suspected to be comparable for both kinds of tobacco use.

In a cross-sectional study of the health status of this cohort, systolic and diastolic blood pressure values were found to be significantly higher among smokeless tobacco users than among either nonusers or smokers.[10] This difference was not significant at younger ages but became obvious in subjects older than 45 years. Smokers had the lowest prevalence of hypertension, as has been found in many other epidemiological studies.[22,25,26] The significantly higher prevalence of hypertension found among smokeless tobacco users, compared with cigarette smokers, could reflect differences in the pharmacodynamic effects of nicotine in smokeless tobacco users and smokers. The use of smokeless tobacco yields high blood concentrations of nicotine and more prolonged and more perpetual levels than smoking. These high concentrations might be accompanied by longer periods of cutaneous vasoconstriction, systemic venoconstriction, and increased muscle blood flow in smokeless tobacco users,[27] and it could be speculated that such mechanisms are more operative for the development of hypertension in smokeless tobacco users than in smokers.

The construction industry demands a high level of physical performance. Persons with decreased capacity are not hired or leave the industry; therefore, construction workers are physically fitter than average citizens of the same age. Because the study sample was drawn from active workers and not from company lists, which might include retired workers, the healthy worker selection could be expected to be more obvious among the workers who belonged to the higher age group at entry into the study. This situation could explain the more pronounced excess risk of cardiovascular mortality found among the younger tobacco users than among the older tobacco users in relation to nonusers in the same age group.

Since smoking—and probably also the use of smokeless tobacco—affects the cardiovascular system in an unfavorable way and leads to poorer physical performance, the above-mentioned selection process may also be related to tobacco habit, probably resulting in an underestimation of the strength of the relationship between tobacco use and cardiovascular mortality.

The results of this study support the hypothesis that smokeless tobacco users face a higher risk than nonusers of dying of ischemic heart disease and cerebrovascular disorders. Smokers still seem to be at the highest risk, and quitting smoking

considerably reduces the risk of cardiovascular events. Even though nicotine is the main substance common to both smokers and smokeless tobacco users, it remains to be elucidated in clinical studies and by laboratory experiments whether the higher risk of cardiovascular disease in smokeless tobacco users is caused by nicotine or by some other exposure related to smokeless tobacco. Data on vasoconstriction, arrythmias, release of stress hormones, atherogenic effects, or hypertension caused by the exposure to nicotine in smokeless tobacco might elucidate this matter. The higher risk of dying of cardiovascular disease in smokers than in smokeless tobacco users supports the idea that there are substances in tobacco smoke other than nicotine that are hazardous. Although the risk of dying of cardiovascular disease is lower for smokeless tobacco users than for smokers, the excess risks are sufficiently impressive to call for action to be taken against the use of smokeless tobacco. □

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Effect of chewing a mixture of areca nut and tobacco on periodontal tissues and oral hygiene status

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Abstract: The present study was conducted to clarify the effects of chewing a quid containing areca nut and tobacco on periodontal tissue and oral hygiene status. A total of 365 subjects (168 chewers and 197 non-chewers with a mean age of 32.5 ± 0.7 and 30.4 ± 0.8 years, respectively) were enrolled. Clinical data on periodontal tissues, oral hygiene status, as well as information on bleeding from gums, ulcers in the oral cavity, or a burning sensation in the soft tissues, were collected as indicators of the possible presence and extent of periodontal lesions. The results indicated that a significantly higher number of quid-chewers suffered bleeding from the gums, halitosis, difficulty in opening the mouth and swallowing solid food, a burning sensation in the soft tissues, and ulcers in the oral cavity than non-chewers. There was no significant difference between quid-chewers and non-chewers with respect to oral hygiene measures adopted. However, clinical examination using the oral hygiene index score indicated that the oral hygiene status of quid-chewers was significantly deteriorated. The effect of quid-chewing on the periodontium, i.e. the occurrence of periodontal pockets, gingival lesions and gum recession, were significantly higher in quid-chewers than in non-chewers. Age, sex and smoking adjusted odds ratios for quid-chewers against non-chewers using logistic regression analysis indicated that, in general, chewers were at significantly higher risk for various oral complaints and periodontium status. The present data indicate that chewing quid comprising areca nut and tobacco has adverse effects on periodontal tissues, oral hygiene and incidence of oral lesions. (J. Oral Sci. 50, 57-62, 2008)

Keywords: periodontal; chewers; tobacco; areca nut; smokeless tobacco; gingival lesions; oral hygiene.

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Introduction

A number of diseases are associated with food habits, lifestyle and environmental factors. It is estimated that about 600 million people chew areca nut (1), among whom a large proportion use tobacco with it. Gupta and Warnakulasuriya reported that a substantial proportion of the world's population is engaged in chewing areca nut, and that the habit is endemic throughout the Indian subcontinent, large parts of south Asia and Melanesia. A large variety of ingredients, including tobacco, may be used along with areca nut constituting a betel quid (2). Furthermore it has been reported that use of betel quid and areca nut in any form is unsafe for oral health, and that commercial forms seems to pose an even higher risk (3). Both areca nut and tobacco are addictive. From the viewpoint of the various effects of areca nut-chewing on health, and its carcinogenic potential designated recently by the IARC (4), we consider that chewing areca nut with or without tobacco poses one of the greatest threats to global health today. The habit is widespread in Southeast Asia and the South Pacific and among people of Indian origin who have migrated elsewhere. There has been a sharp rise in this habit

especially amongst the young. In addition, the new habit of chewing panmasala [consisting of areca nut (*Areca catechu*), catechu (*Acacia catechu*), lime, cardamom (*Elettaria cardamomum*), and unspecified flavoring agents with tobacco (gutaka) or without tobacco (plain or meetha-sweetened)] is increasing rapidly, even among those who generally refrain from smoking and tobacco-chewing. Increasing use of tobacco and betel nut chewing, especially panmasala with or without tobacco, by vulnerable members of society, i.e. children and pregnant women, and available data on the role of different chewing habits and cancer, suggest that the hazardous effects of these habits need to be reassessed (5).

A wide variety of chewing and smoking habits are believed to be linked to oral and pharyngeal cancer. These habits also contribute to other diseases of the oral cavity and may also affect teeth and supporting periodontal tissues due to the excessive mastication load and exposure to various components of the chewing quid. Recently we have published a letter indicating that chewing quid composed of areca nut and tobacco affects the oral hard tissues, based on data suggesting that quid-chewers have a higher prevalence of dental attrition and sensitivity than non-chewers (6). In addition, chewing areca nut and tobacco might also affect other organ systems, as it has been reported that panmasala plain and panmasala with tobacco both induce a higher incidence of sperm head morphological abnormality in Swiss albino mice than in controls (7). Very little attention has been paid to the association of smokeless tobacco and areca nut-chewing and the health of gingival and periodontal tissues, although a few reports have addressed the chewing of betel or areca nut and its effects on the periodontium (8). Recently, in an *in vitro* study, Jeng et al. found that arecoline (one of the major areca nut alkaloids) and areca nut extract suppressed the growth of cultured gingival keratinocytes (9). Furthermore, Chang et al. have demonstrated that areca nut extracts suppress growth and protein synthesis in cultured human periodontal fibroblasts (10). These *in vitro* findings suggest a role of areca nut-chewing in the deterioration of gingival and periodontium tissues. The present study assessed the gingival, periodontium, and oral hygiene status of chewers of a mixture of areca nut and tobacco in comparison with non-chewers.

Materials and Methods

Participants

A cross-sectional study was conducted among apparently healthy patients attending the Outpatient Department (OPD) of the Government Dental College and Hospital, Ahmedabad, Gujarat, India, because of various dental diseases, as well as subjects attending the OPD of the Civil Hospital, Ahmedabad, Gujarat, India. Written consent was obtained from each subject after explaining the objective of the study. The present study was part of a project approved by the institutional ethics committee. The subjects were divided into two groups – quid-chewers (n = 168) and non-chewers (n = 197) – for comparison purposes. About 80.5% of the subjects were male. The mean age (± SE) of the quid-chewers and non-chewers was 32.5 ± 0.7 and 30.4 ± 0.8 years, respectively. About 22.62% of quid-chewers and 5.06% of non-chewers were smokers. The subjects were examined at the Government Dental College, Ahmedabad, under artificial light using a mouth mirror, explorer and curved probe.

Data related to bleeding of the gums, halitosis, ability to swallow solid food, presence of a burning sensation in the soft tissues, etc., were collected by questionnaire, and the presence of ulcers in the oral cavity was checked clinically. These data were considered to be possible indicators of the presence and extent of lesions. In addition, each subject was asked to open his/her mouth in order to confirm whether there was any difficulty with mouth opening.

Oral Hygiene Status

The oral hygiene status of the enrolled subjects was determined by using the Simplified Oral Hygiene Index (OHI-S). The OHI-S, introduced by Greene and Vermilion (11) in 1964 and quoted by Peter (2004), comprises the Simplified Debris Index (DI-S) and Simplified Calculus Index (CI-S). Each of these indices is based on numerical determinations representing the amount of debris or calculus on six pre-selected tooth surfaces.

Debris Index (DI-S):

DI-S was used for evaluating the extent of debris present on the six pre-selected tooth surfaces, i.e. buccal surface of the selected upper first molars, lingual surface of the selected lower first molars, and labial surface of the upper right and lower left central incisors. The surface area covered by debris was estimated by running the side of Shepard crook explorer along each tooth surface.

Debris Index – Simplified – Scoring System

Score

0: Absence of debris

1: Soft debris covering less than the cervical one-third of the tooth surface.

2: Soft debris covering more than the cervical one-third of the exposed tooth surface but less than the cervical two-thirds.

3: Soft debris covering more than the cervical two-thirds of the exposed tooth surface.

Calculus Index – Simplified (CI-S):

An explorer was used for scoring of calculus. The same tooth as those for evaluation of the debris index was examined. The surface area covered by calculus was detected supragingivally, and subgingival calculus was explored on a randomly selected tooth quadrant.

Calculus Index – Simplified – Scoring System:

Score

0: Absence of calculus

1: Calculus covering less than the cervical one-third of the exposed tooth surface.

2: Supragingival calculus covering more than the cervical one-third, but not more than the cervical two-thirds of the exposed tooth surface, or presence of individual flecks of subgingival calculus around the cervical portion of the tooth.

3: Supragingival calculus covering more than the cervical two-thirds of the exposed tooth surface, or a continuous heavy band of subgingival calculus around the cervical portion of the tooth.

The Simplified Oral Hygiene Index score for each individual was obtained by combining the Simplified Debris Index and the Calculus Index. Totaling the debris score per tooth surface and dividing by the number of the surfaces examined yielded the Simplified Debris Index (DI-S) score for an individual. The same method was used to obtain the CI-S

Thus,

OHI-S = DI-S + CI-S

The Simplified Oral Hygiene Index (OHI-S) values range from 0 to 6. The clinical levels of oral hygiene that can be associated with group OHI-S scores are as follows; Good: 0.0 to 1.2; Fair: 1.3 to 3.0; Poor: 3.1 to 6.0

Gingival Recession:

Assessment of gingival recession was done to specifically determine its extent, i.e. displacement of the gingival margin at least 1 mm apical to the cemento-enamel junction in all the subjects.

Statistical analysis

Logistic regression analysis, Student's *t* test and chi-squared test were employed according to which hypotheses were being tested.

Results

Various oral hygiene measures practiced routinely by the quid-chewers and non-chewers are shown in Table 1. The data show that quite a large number of quid-chewers (87.5%) and non-chewers (90.86%) used paste/powder regularly for maintenance of oral hygiene. However, 8.93% of chewers did not use toothpaste or powder, as compared to 5.08% of non-chewers. There was no significant difference between quid-chewers and non-chewers with respect to oral hygiene measures adopted. About 49.2% of non-chewers had good oral hygiene status, as compared to only about 14.9% of quid-chewers (Table 2). The oral hygiene status of non-chewers was significantly better than that of chewers. Poor oral hygiene status was also observed in a higher proportion of quid-chewers (17.86%) than in non-chewers (11.17%). The mean oral hygiene index of chewers was 2.12 ± 0.86 while that of non-chewers was 1.54 ± 1.12, the difference being statistically significant ($P < 0.001$).

Table 3 shows the different complaints of the subjects pertaining to the oral cavity. The incidence of bleeding gums was significantly higher in quid-chewers than in non-chewers, and more chewers (58.3%) had halitosis. About 22.6% chewers complained of difficulty in mouth-opening, as compared with only about 1% of non-chewers. Furthermore, 10.1% chewers had difficulty in swallowing solid food, whereas none of the non-chewers had this

Table 1 Oral hygiene measures adopted by subjects

Oral Hygiene Measures	Non-chewers-197	Chewers-168	Total- 365
Do not use brush/powder	10 (5.08)	15 (8.93)	25
Use brush/powder occasionally	8 (4.06)	6 (3.57)	14
Use brush/powder regularly	179 (90.86)	147 (87.50)	326
Total	197	168	365

Figure in parenthesis is the percentage of oral hygiene measure

problem. A burning sensation in the soft tissues was also found in a higher proportion of quid-chewers than in non-chewers. Similarly, ulcers on the oral mucosa were present in about 6.5% of chewers, as compared to 0.51% of non-chewers. Logistic regression analysis revealed that, in general, chewers had significant odds ratios for the various oral complaints studied with respect to non-chewers after adjustment for age, sex and smoking (Table 3). Sex and smoking did not have any significant impact on the odds ratio. Furthermore, age had no significant impact on the odds ratio for difficulty in mouth-opening, difficulty with swallowing, burning sensation in soft tissues, and ulceration.

An effect of quid-chewing on the periodontium, i.e. the occurrence of periodontal pockets, gingival lesions and gum recession, was observed clinically. Periodontal pockets, occurrence of gingival lesions, as well as gum recession also had a higher incidence in quid-chewers than in non-chewers (Table 4). Gingival recession was present in about 50% and 26% of chewers and non-chewers, respectively. Logistic regression analysis also showed significant odds ratios for these conditions for chewers as compared with non-chewers (Table 4). This analysis showed that quid-chewers are at higher risk for the various conditions studied, irrespective of sex, indicating a causative role of areca nut and tobacco in periodontal diseases.

Table 2 Oral hygiene status of the chewers and non-chewers

Oral hygiene status	Non-chewers-197	Chewers-168
Good	97 (49.24)	25 (14.88)*
Fair	78 (39.59)	113 (67.26)
Poor	22 (11.17)	30 (17.86)
Total	197	168

Figure in parenthesis shows the percentage of oral hygiene status
* $P < 0.001$ on comparing with non-chewers

Table 3 Distribution of subjects according to their complaints

Complaints of subjects	Non-chewers (197)	Chewers (168)	*Odds-ratio	95% CI
Bleeding gums	52 (26.40)	67 (39.88)	1.381	(1.08, 1.77)
Bad odor (halitosis)	67 (34.01)	98 (58.33)	1.566	(1.23, 1.99)
Difficulty in opening mouth	2 (1.02)	38 (22.62)	4.843	(2.32, 10.1)
Difficulty in swallowing	0 (0.0)	17 (10.12)	-	-
Burning sensation of soft tissue	1 (0.51)	47 (27.98)	9.998	3.55, 28.15
Ulceration	1 (0.51)	11 (6.55)	-	-

Figure in parenthesis is the percentage of complaints
- Indeterminate
* Age, sex and smoking adjusted

Table 4 Periodontal condition of chewers and non-chewers

Periodontal condition	Non-chewers	Chewers	*Odds-ratio	95% CI
Periodontal pocket	61 (30.96)	92 (54.76)	1.643	(1.26, 2.14)
Gingival lesions	2 (1.02)	10 (5.95)	2.868	(1.24, 6.65)
Gingival recession	52 (26.40)	85 (50.60)	1.729	(1.32, 2.32)

Figure in parenthesis is the percentage of periodontal condition
*Age, sex and smoking adjusted odds ratio of chewers against non chewers

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Discussion

This study revealed no significant difference between quid-chewers and non-chewers with respect to oral hygiene measures adopted. However, the mean value of the OHI among chewers was higher than among non-chewers. This suggests that quid-chewers had a poorer oral hygiene status than non-chewers, even though both groups undertook almost the same oral hygiene measures, and that quid-chewing plays a significant role in deterioration of oral hygiene. Complaints such as bleeding gums, halitosis, difficulty with mouth-opening and swallowing solid food, and a burning sensation in the soft tissues were significantly more common among chewers than among non-chewers. These data indicate a potential role of areca nut and tobacco-chewing in oral health status. Previously, Ling et al. reported that betel quid-chewing was associated with a higher prevalence of bleeding where higher clinical disease existed, and with a likelihood of higher subgingival infection with *A. actinomycetemcomitans* and *P. gingivalis* (12). However, in the present study we were unable to determine whether the subjects had these infections or diabetes.

The hardness of the areca nut and interactions among the various ingredients of chewing materials with periodontal tissues might be responsible for the poor periodontal status of chewers. Areca nut, which contains alkaloids such as arecoline, might have a significant causative role in periodontal diseases along with other variables such as the level of oral hygiene, dietary factors, general health and dental status, and tobacco-smoking. This lends support to the earlier *in vitro* findings of Chang et al. (10), who reported that areca extracts containing arecoline inhibit the growth and attachment of, and protein synthesis in, human cultured periodontal fibroblasts. On the basis of these findings, they proposed that areca might be cytotoxic to periodontal fibroblasts and may exacerbate pre-existing periodontal disease as well as impairing periodontal reattachment. The present data on periodontal status confirm the earlier findings of Waerhaug (13), who reported that more areca consumers had periodontitis than non-consumers, even when comparative levels of oral hygiene were present. He suggested that areca nut consumption might act as a factor that lowers resistance to local irritants. The present study also indicated deterioration of periodontal condition among quid-chewers. Periodontal pockets, gingival lesions and gingival recession were more prevalent among chewers than among non-chewers, even though both groups adopted approximately the same oral hygiene measures. Furthermore, loss of periodontal attachment and greater calculus formation has also been reported in areca nut-chewers (14,15), and Baelum et al. have reported a higher prevalence of attachment loss in older age groups than in younger age groups (16), suggesting that age could be a factor affecting such changes. The present study also suggests that age has a significant impact on the prevalence of oral complaints and periodontal conditions. The age-, sex- and smoking-adjusted odds ratios for quid-chewers against non-chewers were statistically significant for various complaints and conditions, suggesting a role of the chewing habit in the deterioration of periodontal status as well as various oral conditions in quid-chewers compared with non-chewers. Furthermore, areca nut might be cytotoxic to periodontal fibroblasts and thus exacerbate pre-existing periodontal disease as well as impairing periodontal reattachment. Recently, Chatrchaiwiwatana reported that betel quid-chewing was directly associated with periodontitis in the presence of several confounding factors (17). The present study indicated that chewing areca nut and tobacco has a potentially causative role in the development of oral lesions, and deterioration of oral hygiene and periodontal status, as higher odds ratios were observed for various lesions and periodontal status after adjustment for age and sex.

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Annexure 15

Oral melanin pigmentation in smoked and smokeless tobacco users in India. Clinico-pathological study.

Sarswathi TR, Kumar SN, Kavitha KM.

Indian J Dent Res. 2003 Apr-Jun;14(2):101-6.

Abstract

Tobacco used as smoked and smokeless form induces oral mucosal changes in which intra-oral mucosal pigmentation is one of the clinical manifestations. The melanocyte activity responsible for pigment changes is not well documented in the literature. The present study is undertaken to observe clinical and histological changes in oral buccal and labial mucosa of 41 tobacco users and compared with 8 controls. 95.24% of smokers showed pigmentation of both labial and buccal mucosa. Labial mucosa showed a high degree fo pigmentation (81%) than the buccal mucosa (33.3%). 93.3% of alcoholics showed a high degree of pigmentation. Hypermelanocytosis and melanosis were observed in smokers. Pigmentation at the site of quid placement was absent in smokeless tobacco users but mild pigmentation was observed away from the site of quid placement with the concurrent increase in the number of melanocytes and melanocytic activity.

Impact of gutkha chewing & smoking on microbial environment of oral cavity: a case study on slum dwellers of selected areas in Visakhapatnam.

Avasn Maruthit Y, Rao RS, Palivela H, Thakre S.

J Environ Sci Eng. 2004 Oct;46(4):268-73.

Abstract

Oral diseases are still a neglected epidemic. During the recent years, in India, both in urban and rual, consumption of tobacco in the form of direct chewing of gutkha is alarmingly increasing especially in the young adults as which is major reason for subsistence of oral cancer. In the present investigation an attempt was made to find out the relationship between gutkha chewing including smoking and oral micro flora in some slum dwellers of Visakhapatnam. The subjects were randomly selected and their health data was collected by distributing questionnaire to control and effected subjects. The oral saliva samples were collected from both gutkha chewers, smokers and from control groups by using saline swabs and inoculated on suitable nutrient media. The results revealed that decrease in salivation and mucous formation in gutkha chewers, which further resulted in reduction in number of oral micro flora. Aspergillus species appeared only in gutkha chewers and smokers. Gutkha chewing and smoking thus, may lead to an increase in the oral pathogens by reducing the normal symbiotic microbial flora.

Annexure 78

Tobacco habits and oral health status in selected Indian population.

Vellappally S, Jacob V, Smejkalova J, Shriharsha P, Kumar V, Fiala Z

Cent Eur J Public Health. 2008 Jun;16(2):77-84.

Abstract

This cross-sectional study was aimed at possible relationships between tobacco habits and selected behavior characteristics in an adult sample from India. Contemporaneous clinical examination comprised an intra-oral examination with specific emphasise to dental caries status in the form of DMFT (Decayed, Missing, and Filled Teeth) index. The study comprised 805 subjects in the age group from 30 to 69 years (72% of males and 28% of females). The participants were divided into regular smokers, occasional smokers, ex-smokers, tobacco chewers and non-tobacco users. The highest prevalence of oral mucosal lesions were found in tobacco chewers (22.7%) followed by regular smokers (12.9%), occasional smokers (8.6%), ex-smokers (5.1%) and non tobacco users (2.8%) ($p < 0.001$). The mean number of decayed teeth was highest in tobacco chewers (6.96) followed by regular smokers (6.44) and ex-smokers (5.5) ($p < 0.001$). The mean number of missing teeth was highest in the group of regular smokers (1.9) and lowest in non-tobacco users (1.53), but the results were not statistically significant ($p = 0.529$). The mean number of filled teeth were highest in the group of tobacco chewers (3.67) followed by regular smokers (3.29) ($p < 0.001$). DMFT value of tobacco chewers, regular smokers and ex-smokers is higher when compared to non-tobacco users ($p < 0.001$). The study documents that chewing tobacco and smoking can present significant risk factors for dental caries. However, the conclusions are burdened by some limitations. Further studies for investigation of the effect of tobacco using on dental caries are needed.

Periodontal health status in pan chewers with or without the use of tobacco.

Sumanth S, Bhat KM, Bhat GS.

Oral Health Prev Dent. 2008;6(3):223-9.

Abstract

BACKGROUND: Betel nut and tobacco chewing is a common practice in south-east Asia. In India, betel nut is commonly chewed in the form of pan, with or without tobacco. Numerous studies have shown the carcinogenic potential of betel nut and tobacco. Betel nut and tobacco are also known to have deleterious effects on the oral tissues.

PURPOSE: The aim of our study was to evaluate and compare the periodontal effects of pan chewing with or without the use of tobacco as an ingredient.

MATERIALS AND METHODS: The periodontal status of 300 subjects (150 subjects were pan chewers with tobacco and 150 subjects were pan chewers without tobacco) was evaluated using the community periodontal index (CPI). The subjects were selected by the stratified random sampling method. The oral hygiene status of the subjects was evaluated using the simplified oral hygiene index.

RESULTS: CPI code-4, with a probing depth of 6 mm or more, was seen in 30% of pan chewers with tobacco compared with 7.3% of pan chewers without tobacco. It was found that pan chewers with tobacco had 4.7 times more risk of having pockets than pan chewers without tobacco. The higher codes of loss of attachment were seen in pan chewers with tobacco compared with pan chewers without tobacco. It was found that pan chewers with tobacco had 7 times more risk of having loss of attachment when compared with the pan chewers without tobacco.

CONCLUSIONS: The results show higher incidence of periodontal diseases in pan chewers who use tobacco compared with pan chewers who do not use tobacco. Based on the results, it was concluded that, although betel nut has deleterious effects on the periodontium, the addition of tobacco leads to a synergistic effect between betel nut and tobacco on the periodontal tissues.

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Community Dent Oral Epidemiol. 2005 Feb;33(1):45-52.

Assessment of risk factors for oral leukoplakia in West Virginia.

Fisher MA, Bouquot JE, Shelton BJ.

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Abstract

OBJECTIVE: To assess risk factors associated with oral leukoplakia in a US population with high use of smoked tobacco and smokeless tobacco.

METHODS: The RJ Gorlin Leukoplakia Tissue Registry was used to identify individuals with oral leukoplakia in West Virginia, USA. This case-control study consisted of 90 cases with oral leukoplakia and 78 controls with periapical cysts. Univariate-univariable (one dependent variable and one independent variable) and univariate-multivariable (one dependent variable and multiple independent variables) logistic regression modeling quantified the association between oral leukoplakia and potential explanatory variables.

RESULTS: Unadjusted measures of association indicate that those with oral leukoplakia were more likely to be older [odds ratio of crude: OR(Crude) = 2.72; 95% confidence interval (CI): 1.45-5.11], more likely to currently use smokeless tobacco (OR(Crude) = 3.16; 95% CI: 1.10-9.07), and more likely to currently use snuff (OR(Crude) = 8.32; 95% CI: 1.83-37.80). Individuals currently using smokeless tobacco or currently using snuff were more likely to have oral leukoplakia [adjusted odds ratio, OR(Adj) = 9.21 and 30.08; 95% CI: 1.49-57.00 and 2.67-338.48, respectively], after simultaneously adjusting for age, gender, currently using smoked tobacco, currently using alcohol daily, and dental prostheses use.

CONCLUSIONS: Generalizability is an issue when studying risk factors associated with oral leukoplakia because of geographical variations in the composition of smokeless tobacco (i.e. betel, lime, ash, and N-nitrosamines) and cultural variations in the use of tobacco (i.e. reverse smoking). Snuff was the main smokeless tobacco product currently used in West Virginia, and was strongly associated with oral leukoplakia, after adjusting for potential explanatory variables.

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Annexure 61

AJH 1998;11:1153–1163

Ambulatory 24-h Blood Pressure Monitoring in Healthy, Middle-aged Smokeless Tobacco Users, Smokers, and Nontobacco Users

Gunilla Bolinder and Ulf de Faire

Ambulatory 24-h blood pressure monitoring was conducted in 135 healthy, normotensive, middle-aged (35 to 60 years) men, with no antihypertensive medication, to study the influence of habitual smokeless tobacco use (n = 47) and smoking (n = 29) on diurnal blood pressure and heart rate. Comparisons were made with nonusers of tobacco (n = 59). Adjustments were made for differences in age, body mass index, waist-hip ratio, physical fitness, and alcohol intake.

Daytime ambulatory heart rates were significantly ($P < .05$) elevated in both smokeless tobacco users and smokers compared with nonusers (69 ± 14 and 74 ± 13 beats/min, respectively, versus 63 ± 12 beats/min). In subjects ≥ 45 years old, ambulatory daytime diastolic blood pressures were significantly elevated, on average by 5 mm Hg, in both smokeless tobacco users and smokers ($P < .001$) compared with nonusers. Clinical measurements of heart rate and systolic blood pressure in smokers were significantly lower compared with the ambulatory mean values. Nighttime measurements showed only minor differences between the tobacco habit groups.

The higher heart rates and blood pressures noted during the daytime in smokers and smokeless tobacco users were most likely due to the effects of nicotine. A strong positive relationship was found between cotinine (major nicotine metabolite) and blood pressure in smokeless tobacco users (systolic blood pressure, r = 0.48, $P < .001$; diastolic blood pressure, r = 0.41, $P = .005$), whereas an inverse relationship was found in smokers (systolic blood pressure, r = −0.12, $P = .47$; diastolic blood pressure, r = −0.03, $P = .84$), indicating additional and more complex influences on vascular tone in smokers than the influence of nicotine in smokeless tobacco users. Am J Hypertens 1998; 11:1153–1163 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: **Ambulatory blood pressure, smoking, smokeless tobacco, nicotine.**

A large number of epidemiologic studies consistently show lower blood pressures in smokers compared with nonsmokers.[1] This finding is regarded as a paradox, because nicotine has potent sympatomimetic effects, affecting blood pressure levels and heart rate.[2–4] However, a few cross-sectional studies of smokeless tobacco users (one of which comprised >5000 smokeless tobacco users) suggested that smokeless tobacco users had higher blood pressures compared with both

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TABLE 1. CLASSIFICATION OF THE STUDY POPULATION INTO MAJOR TOBACCO HABIT GROUPS

	Nonusers (n = 59)	Smokeless Tobacco Users (n = 47)	Smokers (n = 29)	Years of Tobacco Use, Median (25th, 75th percentiles)
Never-users of tobacco	36			0
Exusers for ≥5 years*	14			12 (10–20)
Exusers for ≤5 years†	9			24 (19–29)
Smokeless tobacco users‡		27		25 (18–28)
Exsmokers, now smokeless tobacco§		20		24 (17–30)
Smokers‖			24	29 (20–30)
Smoking + smokeless tobacco use#			3	30 (23–35)
Former smokeless tobacco users, now smoking**			2	32 (30–35)

* *Stopped smoking or using smokeless tobacco >5 years prior to examination.*
† *Stopped smoking or using smokeless tobacco <5 years prior to examination.*
‡ *Current daily smokeless tobacco use for >6 months.*
§ *Stopped smoking >6 months ago, current daily smokeless tobacco users for >6 months.*
‖ *Current daily smoking for >6 months.*
\# *Current daily smoking plus daily or occasional smokeless tobacco use.*
** *Stopped using smokeless tobacco >6 months ago, current daily smokers for >6 months.*

smokers and nonusers.[5–9] Thus, there is a controversy as to whether the use of tobacco should be regarded as a risk factor for the development of established hypertension or not, although smoking is associated with a substantial increase in cardiovascular morbidity,[10] and hypertensive smokers multiply their cardiovascular risk compared to normotensive smokers.[11] Increased mortality from cardiovascular disease has been shown also in smokeless tobacco users compared with nonusers, although not to such a degree as in smokers.[12]

Ambulatory blood pressure monitoring in smokers and nonsmokers has been performed in a few studies, most of which indicate slightly higher blood pressure values in smokers, particularly during the daytime and in age groups >45 years.[13–16] However, in a study of normotensive Danish adults 20 to 79 years old, smokers exhibited slightly lower ambulatory blood pressure recordings compared with nonsmokers.[17] No ambulatory blood pressure monitoring of smokeless tobacco users has been performed up to now.

The use of oral smokeless tobacco results in blood levels of nicotine similar to those observed in cigarette smokers,[2,18] but smokeless tobacco users are not exposed to most other components of smoked tobacco. The more isolated exposure to nicotine in smokeless tobacco users makes it suitable to study blood pressure effects associated with long term nicotine exposure, and might help to elucidate the role of nicotine in the development of hypertension.

The aim of the present study was to use 24-h ambulatory blood pressure recordings to investigate whether the use of smokeless tobacco among healthy middle aged men, is associated with any alteration in blood pressure and heart rate during daytime and nighttime, compared with smokers and nonusers of tobacco, and to relate the findings of ambulatory blood pressure recordings to clinical blood pressure measurements.

METHODS

Subjects In 1993 there were 269 firefighters, 35 to 60 years old, in the Stockholm City Fire Brigade. In connection with the annual compulsory fitness test they were offered an extended health examination including 24-h ambulatory blood pressure monitoring. Of the 269 firefighters, 203 subjects (75%) were willing to participate, and 151 of these were called for investigation within the time limits of the study. Nonparticipating subjects (both nonresponders and those who were willing to come) were equally distributed amongst the nine different fire departments. All subjects were informed of the nature, purpose, and possible risks of the study prior to giving their voluntary consent to participate. The study protocol was approved by the ethics committee of Karolinska Hospital.

Subjects were divided into different tobacco habit groups as presented in Table 1. For intergroup comparisons nonusers, smokeless tobacco users, and smokers, defined according to the definitions in Table 1, were used. No subject was on antihypertensive medication. The recordings of 16 subjects were omitted because of inadequate technical quality (9 nonusers, 3 smokeless tobacco users, and 4 smokers), leaving 135 subjects for evaluation.

Physical Examination Body height and weight were measured and body mass index was determined (BMI in kilograms/square meter). Waist and hip circumferences were measured and the waist/hip ratio was calculated. Self-reported alcohol and coffee habits were registered as none, low, medium, or high consumption. Information on family history of hypertension was registered as answers to yes/no questions, as were questions about ongoing medication. Physical fitness was assessed by the maximal oxygen uptake as determined by a maximal exercise test, and dichotomized into ≥2.8 L/min or <2.8 L/min (the fire department limit for approving smoke-helmet equipment).

Blood Sampling Subjects were examined at 7:30 to 8:00 AM after overnight fasting and >8 h abstention from use of tobacco. Blood samples were drawn from an antecubital vein for the determination of nicotine and cotinine levels (the primary metabolite of nicotine). Cotinine levels were used to estimate the intake of nicotine. Cotinine, with a half life of about 18 h, is a good quantitative indicator of habitual nicotine intake.[19,20]

Casual Blood Pressure Measurement Blood pressure was determined, in the morning at 8:00 to 8:30 AM the day after the ambulatory monitoring was completed, by a standard mercury manometer with the cuff size adjusted to the circumference of the arm. Systolic (SBP) and diastolic (DBP) blood pressure was defined by the Korotkoff sounds phase I and V to the nearest 2 mm Hg after 5 min rest in a supine position, as the mean of two separate measurements. Heart rate (HR) was registered by palpation.

Ambulatory 24-h Blood Pressure Recording Ambulatory blood pressure was recorded using the Suntech Accutracker II (Suntech Medical Instruments Inc., Raleigh, NC). The method of measurement is auscultatory through a microphone over the brachial artery, using simultaneous electrocardiogram (ECG) recordings for R wave gating. Systolic and diastolic blood pressure was determined from phase I and V Korotkoff sounds. Blood pressure was recorded every 15 min during daytime (06:00 to 24:00) and every 30 min during the night (00:00 to 06:00), resulting in approximately 84 recordings per individual. Artifacts were defined as SBP > 250 mm Hg, DBP > SBP, DBP < 30 mm Hg, or DBP > 150 mm Hg. Data were analyzed as means of SBP, DBP, HR over 24 h, daytime, nighttime, and the averages of consecutive 3 h periods. Blood pressure variability was defined as the standard deviation of the mean value of the systolic or diastolic blood pressure during the time space referred to (24 h, daytime, nighttime, or 3-h periods) for each individual.

Diary The 24-h ambulatory recordings were all carried out during a weekday free from periods of normal firefighter duties or shiftwork, with daily activities recorded as periods of sleeping hours, unusual physical effort, smoking/smokeless tobacco use, alcohol intake, meals, and driving. The diary notations were principally used to register sleeping hours, and to identify exposure to unusual physical effort, like hard training or sport activities. Tobacco users were instructed to consume tobacco ad libitum according to their usual habits. Tobacco consumption data were analyzed only to confirm tobacco use during the registration period, because blood cotinine measurements before the ambulatory monitoring were used to estimate the habitual daily nicotine intake.

Statistics Means and standard deviations were calculated for all the anthropometric measurements and for blood pressure and heart rate recordings for the different time spaces, respectively. Intergroup comparisons were made for never-users of tobacco with smokeless tobacco users and smokers, using analysis of variance (ANOVA) and Fisher's PLSD (protected least significant difference) test for post hoc significance tests. Odds ratios (OR) and 95% confidence intervals were calculated for self-reported questionnaire answers in the three tobacco habit groups with the never-users as a reference group. Univariate linear regression was used to analyze the nature of relationships between blood pressure measurements, anthropometric data, and lifestyle factors. Covariates that might influence blood pressure were also entered in a multivariate regression model to adjust for their influence on the ambulatory blood pressure measurements.

RESULTS

Study Population Table 2 presents the basic characteristics of the study population. Waist-hip ratios were significantly higher in smokers, whereas no significant differences were found for age, body mass index, or sleeping hours in the three groups. In Table 3 the results of the questionnaire and physical exercise data are shown. Smokers consumed more alcohol and coffee and had significantly lower physical exercise capacity than both nonusers and smokeless tobacco users. Approximately one-third of the subjects exhibited a family history of hypertension in each of the three examined groups.

Blood Pressure Recordings There was a strong correlation between clinical and ambulatory recordings ($r = 0.69$ for SBP; $r = 0.47$ for DBP; $P < .001$). The results of the clinical measurements and the 24-h monitoring, after adjustments for differences in age, body mass index, waist-hip ratio, physical fitness, and alcohol consumption are shown in Table 4. Casual blood

TABLE 2. BASIC CHARACTERISTICS OF THE STUDY POPULATION

	Never-Users of Tobacco (n = 59)	Smokeless Tobacco Users (n = 47)	Smokers (n = 29)	P*
Anthropometric data				
Age (years)	45.1 ± 6.6	44.3 ± 6.4	47.2 ± 5.7	
BMI (kg/m²)	25.7 ± 2.4	25.5 ± 2.2	25.0 ± 2.1	
Waist/hip ratio (cm/cm)	0.89 ± 0.05	0.89 ± 0.05	0.92 ± 0.06	
Sleeping hours (n)	7.1 ± 0.8	7.0 ± 0.9	6.8 ± 0.9	<.001
Tobacco use				
Number of cigarettes/day	0	0	18 ± 11	
Grams of smokeless tobacco/day	0	27 ± 15	0	
Plasma nicotine (μg/L)†	0.2 ± 0.3	4.5 ± 5.8	3.4 ± 2.7	
Plasma cotinine (μg/L)†	3.4 ± 2.7	359 ± 173	258 ± 161	

Values are means ± SD. n, number in each group. BMI, body mass index.

** Comparisons between smokers and never-users with analysis of variance (ANOVA), Fishers PLSD test for significance, significance level P < .05. No significant differences were found on comparing smokeless tobacco users with never-users.*

† After overnight abstension.

pressures were similar in nonusers and smokeless tobacco users and slightly, but not significantly, lower in smokers. During 24-h monitoring, smokeless tobacco users and smokers exhibited systolic blood pressures (in smokers also diastolic blood pressures) significantly higher compared with nonusers. This was most obvious during the daytime. The unadjusted mean values of the hourly recordings in the three tobacco habit groups are illustrated in Figure 1. If subjects ≥45 years old were considered, ie, 56% of the study population, there were significantly higher diastolic blood pressures (approximately 5 mmHg) found in both smokeless tobacco users and smokers, as compared with nonusers (Figure 2). Data on the 3-h mean values of systolic and diastolic measurements in subjects ≥45 years old, including ANOVA comparisons between the three tobacco habit groups are presented in Table 5. All daytime diastolic and most of the systolic blood pressure recordings in smokeless tobacco users were significantly elevated ($P < .05$) compared with nonusers. These differences were even more pronounced in smokers ($P < .001$) when compared with nonusers. Nighttime blood pressure recordings in subjects ≥45 years old did not, however, reveal any significant differences in the three tobacco habit groups, except for slightly elevated systolic blood pressures in smokers at the beginning of the night ($P = .04$) and for diastolic blood pressures in smokeless tobacco users at the end of the night ($P = .03$).

Blood Pressure Variability Comparisons of the blood pressure variability did not show any significant differences between the three tobacco habit groups, except for the nighttime systolic blood pressures in smokers ($P = .02$) compared with nonusers, as shown in Table 4. In Figure 3 the change in mean systolic and diastolic blood pressures from daytime to nighttime, expressed as a percentage, is shown. Both

TABLE 3. LIFE STYLE RELATED DATA ON THE STUDY POPULATION

	Never-Users of Tobacco (n = 59)	Smokeless Tobacco Users (n = 47)			Smokers (n = 29)		
	%	%	OR	CI	%	OR	CI
Coffee intake high*	19	21	1.2	0.5–3.0	31	2.0	1.7–5.4
Alcohol intake medium/high*	45	34	0.8	0.3–2.0	93	4.2	0.9–19
Physical capacity, low†	10	11	1.1	0.3–3.6	55	10.9	3.6–33
Family history of hypertension‡	34	26	0.7	0.3–1.6	38	1.2	0.5–3.0

** Alcohol and coffee intake dichotomized according to self-reported data: no or low intake = low; medium or high intake = high.*

† Assessed by maximal oxygen uptake < 2.8 L/min during exercise test.

‡ Self-reported known hypertension in either of the parents.

OR, odds ratio, comparisons made with never-users as reference group. CI, 95% confidence interval.

TABLE 4. BLOOD PRESSURE VALUES AT CLINICAL EXAMINATION AND THROUGH 24-h AMBULATORY MONITORING IN DIFFERENT TOBACCO HABIT GROUPS

Blood Pressure	Nonusers of Tobacco (n = 59)	Smokeless Tobacco Users (n = 47)	P*	Smokers (n = 29)	P*
SBP Casual†	124 ± 12	123 ± 13	ns	119 ± 18	ns
DBP Casual†	78 ± 7	78 ± 10	ns	78 ± 11	ns
Mean SBP, 24-h	123 ± 7	127 ± 9	<.05	128 ± 12	<.05
Mean DBP, 24-h	77 ± 9	79 ± 9	ns	81 ± 11	ns
Mean SBP, daytime	126 ± 8	131 ± 10	<.05	131 ± 12	<.05
Mean DBP, daytime	79 ± 9	81 ± 10	ns	83 ± 11	<.05
Mean SBP, nighttime	108 ± 8	106 ± 10	ns	110 ± 12	ns
Mean DBP, nighttime	66 ± 9	67 ± 10	ns	68 ± 12	ns
SBP Variability 24-h	13 ± 2	14 ± 3	ns	14 ± 3	ns
DBP Variability 24-h	11 ± 2	11 ± 3	ns	11 ± 2	ns
SBP Variability daytime	11 ± 2	11 ± 2	ns	12 ± 3	ns
DBP Variability daytime	10 ± 2	10 ± 2	ns	10 ± 2	ns
SBP Variability nighttime	9 ± 3	9 ± 3	ns	11 ± 3	<.05
DBP Variability nighttime	8 ± 2	8 ± 3	ns	9 ± 3	ns

All values are means and standard deviations adjusted for differences in age, body mass index, waist-hip ratio, physical training level, and alcohol consumption. Variability is calculated as the mean of the SD of each individual BP recording. n, number in each group; SBP, systolic blood pressure; DBP, diastolic blood pressure. Daytime, 06:00 to 24:00; Nighttime, 00:00 to 06:00; ns, not significant.

** Comparisons between tobacco users and never-users, after adjustments, using Student t test. Significance level P < .05.*

† Measured at 8:30 AM, after 5 min of supine rest.

tobacco user groups showed greater change from day to night blood pressures compared with nonusers. Significant changes, however, were only recorded in diastolic blood pressures in smokeless tobacco users ($P = .01$).

Heart Rate Recordings Heart rate was significantly elevated in both smokeless tobacco users and smokers during day- and nighttime, compared with nonusers (69 ± 14 and 74 ± 13 beats/min, respectively, compared with 63 ± 12 beats/min). Mean values, adjusted for differences in age, body mass index, waist-hip ratio, physical fitness, and alcohol consumption are shown in Table 6. Compared to the clinical recordings after 5 min of rest, the mean heart rate during the 24-h ambulatory monitoring was on average 10% higher in nonusers and smokeless tobacco users and 20% higher in smokers. The unadjusted hourly mean heart rate values of the three tobacco habit groups are illustrated in Figure 4.

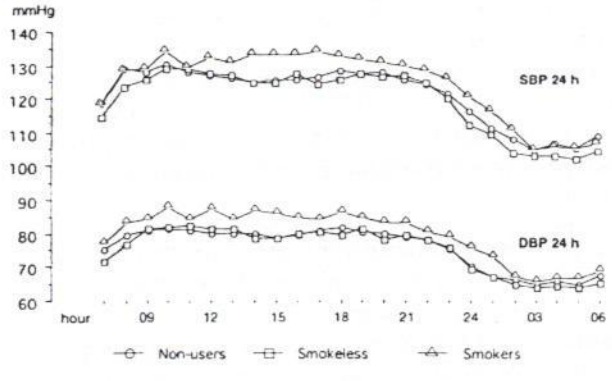

FIGURE 1. *Ambulatory blood pressure mean values (unadjusted) over 24 h in the three tobacco habit groups.*

Heart Rate Variability The mean heart rate variability was 11 ± 3 beats/min (10 ± 3 in the daytime and 6 ± 3 beats/min at night). Intergroup comparisons for the three tobacco habit groups exhibited a slightly greater variability in tobacco users (Table 6).

Physical Fitness, Heart Rate, and Blood Pressure The correlation between maximal oxygen uptake (liters/minute), as determined by a maximal exercise test, and 24-h heart rate demonstrated a highly significant correlation in the whole study group, showing a decreasing heart rate with increasing oxygen uptake ($r = -0.51$, $P < .001$). This finding was significant in all tobacco habit groups. There was a much weaker, but still significant, correlation between diastolic blood pressure but not systolic blood pressure and maximal oxygen uptake ($r = -0.21$, $P = .01$).

Confounding Factors Although there were no significant differences between the three tobacco habit groups regarding anthropometric measurements or age, there were still differences between the groups in physical fitness and other lifestyle related factors. When adjustments were made for all mean blood

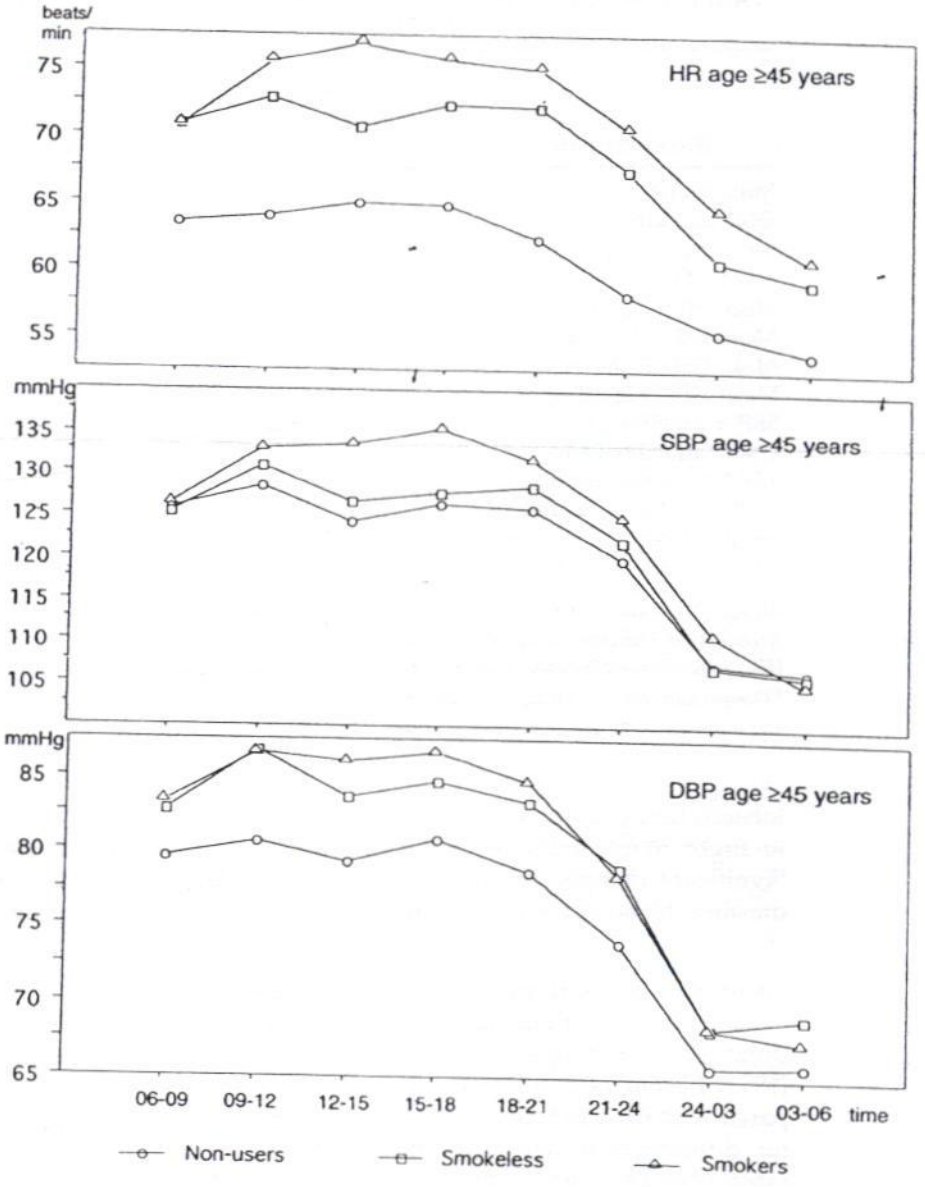

FIGURE 2. *Heart rate (HR) and systolic (SBP) and diastolic (DBP) blood pressure in subjects ≥45 years old (nonusers: n = 34; smokeless tobacco users: n = 23; smokers: n = 18). Mean values during 3-h periods of 24-h ambulatory blood pressure registration.*

pressure and heart rate values for the possible influences of age, body mass index, waist-hip ratio, physical fitness, and alcohol intake, by multivariate regression analysis, only physical fitness and body mass index had a significant influence on heart rate and blood pressure measurements. Adjusted values were generally slightly higher regarding blood pressure measurements and slightly lower regarding heart rate in the two tobacco user groups, but the differences remained essentially unchanged compared with nonusers.

Relationship Between Blood Pressure Measurements and Tobacco Consumption A linear regression analysis showed a highly significant correlation between blood cotinine values (the main metabolite of nicotine) and 24-h systolic and diastolic blood pressures of smokeless tobacco users (SBP, r = 0.48, $P < .001$; DBP, r = 0.41, $P = .005$), whereas smokers showed no such correlations (SBP, r = −0.12, $P = .47$; DBP, r = −0.03; $P = .84$), as shown in Figure 5. The relationship remained essentially unchanged even when controlling for differences in age and body mass index.

Relationship Between Family History of Hypertension and Ambulatory Blood Pressure In the whole study population, 32% had reported a family history of hypertension, and mean ambulatory systolic and diastolic blood pressures were significantly higher ($P < .05$) in these subjects: 126/81 mm Hg compared with 122/77 mm Hg in subjects without a family

TABLE 5. MEAN VALUES OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURES IN SUBJECTS ≥45 YEARS OLD DURING 3-h PERIODS OF AMBULATORY BLOOD PRESSURE MONITORING, COMPARING TOBACCO USERS WITH NONUSERS OF TOBACCO

Hour		Nonusers of Tobacco (n = 34)	Smokeless Tobacco Users (n = 23)	P*	Smokers (n = 18)	P*
06:00 to 09:00	SBP	126 ± 14	125 ± 14	.59	126 ± 16	.73
	DBP	80 ± 12	83 ± 14	.003	83 ± 13	<.001
09:00 to 12:00	SBP	128 ± 14	131 ± 15	.03	133 ± 16	<.001
	DBP	81 ± 13	87 ± 15	<.001	87 ± 14	<.001
12:00 to 15:00	SBP	124 ± 15	134 ± 18	.08	134 ± 18	<.001
	DBP	79 ± 13	84 ± 17	<.001	86 ± 13	<.001
15:00 to 18:00	SBP	126 ± 14	128 ± 14	.34	135 ± 19	<.001
	DBP	81 ± 13	85 ± 14	<.001	87 ± 13	<.001
18:00 to 21:00	SBP	126 ± 13	129 ± 13	.02	132 ± 17	<.001
	DBP	79 ± 12	83 ± 13	<.001	85 ± 12	<.001
21:00 to 24:00	SBP	120 ± 12	122 ± 16	.1	125 ± 18	<.001
	DBP	74 ± 12	79 ± 16	<.001	78 ± 14	<.001
00:00 to 03:00	SBP	107 ± 11	107 ± 15	.91	110 ± 17	.04
	DBP	66 ± 11	68 ± 16	.09	68 ± 14	.09
03:00 to 06:00	SBP	107 ± 11	106 ± 12	.6	105 ± 15	.3
	DBP	66 ± 11	69 ± 12	.03	67 ± 14	.3

n, number in group; SBP, systolic blood pressure; DBP, diastolic blood pressure. All values are means and standard deviations.

ANOVA comparisons are made with nonusers as reference group.

** Fishers PLSD test for significance (P < .05 was considered significant).*

history of hypertension. In a linear regression analysis, the relationship of a family history of hypertension and ambulatory blood pressure values was strongest in smokers (r = 0.37, $P = .05$).

DISCUSSION

Comments on the Results Related to Tobacco Use

The main findings of the present study were the significant increase in heart rate in both smokeless tobacco users and smokers, indicating a persistent nicotine effect, together with the significant elevation of blood pressure in both smokers and smokeless tobacco users >45 years of age, which might be taken as a reason for long term tobacco use as a contributing factor in the development of sustained hypertension. Although the peak cardiovascular responses to nicotine have been shown to decline to normal values within 2 h after a given dose despite only small differences in nicotine levels, recurrent doses of nicotine always involve momentary stress effects on the cardiovascular system.[2, 3] It should be noted that Swedish smokeless tobacco does not contain licorice, a substance which, some American studies suggest, contributes to blood pressure elevation.[7, 21]

There are two paradoxes regarding vascular tone and the pharmacologic effects of nicotine: the constant finding of lower resting blood pressures in smokers together with a negative dose-response relationship with lower blood pressures observed as the number of cigarettes smoked increased[1,22–24]; and the lower prevalence of angina pectoris in smokers compared with nonsmokers.[25] Neither of these findings are compatible with the prominent increase in cardiovascular morbidity in smokers. As shown in the present study, the more isolated exposure to nicotine in smokeless tobacco users seems to involve significant effects on heart rate and blood pressure in healthy subjects. Smokers also exhibited a similar influence during 24-h monitoring, demonstrated also by other investigators.[13–16] There might, therefore, be a more complex influence involving other inhaled pharmacologically vasoactive substances when smoking, entailing a transient decline in blood pressure following cessation of smoking analogous to a type of withdrawal phenomenon.[1] A possible autonomic imbalance with increased vagal influence in resting positions, or endothelial dysfunction influenced by nitric oxide, carbon monoxide, or other combustion products in tobacco smoke might be responsible for these effects. Blunted postural responses in autonomic cardiac regulation in smokers have been demonstrated.[26] A finding in the present study, supporting a multipharmacologic influence of smoking is the lack of correlation between blood cotinine levels and blood pressure measurements in smokers, demonstrated also by others,[24] whereas smokeless tobacco users exhibited a strong relationship.

Nicotine values, as shown in Table 2, were rather

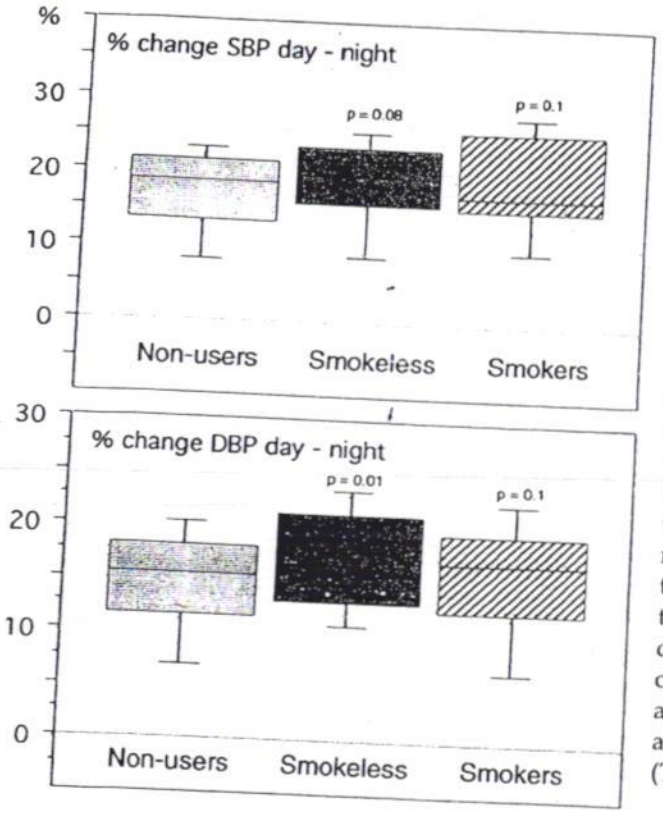

FIGURE 3. *Percent change from mean systolic (SBP) and diastolic (DBP) daytime blood pressures to mean nighttime blood pressures in the three tobacco habit groups. Box plots showing the 10th, 25th, 50th, 75th, and 90th percentiles. Comparisons with nonusers (ANOVA and Fisher's PLSD test) were significant P < .05) only for change in diastolic blood pressure in smokeless tobacco users.*

similar in smokeless tobacco users and smokers. The higher blood cotinine content in smokeless tobacco users is regarded as an indication of additional nicotine intake through the gastrointestinal mucosa by swallowing, and not reaching the central circulation until inactivated by first pass liver metabolism. It has been suggested that cotinine might have a relaxant effect on vascular smooth muscle,[13,24] and consequently smokeless tobacco users would most likely exhibit even lower blood pressures than smokers, according to their higher cotinine levels. This has not been demonstrated in any of the presented studies up to now.

Comments on the Results of the Whole Study Population All subjects in this study were normotensive and without medication. A metaanalysis of 23 studies of ambulatory blood pressure monitoring in >3000 healthy normotensive subjects[27] reported a mean daytime blood pressure of 123/76 mm Hg and a mean nighttime blood pressure of 106/64 mm Hg. Normotension was regarded as a blood pressure level lower than 140/90 mm Hg. In the present study the 24-h, daytime, and nighttime mean values were significantly higher compared with the results of the metaanalysis, but very similar to the findings of a study of a healthy population 20 to 70 years old in Sweden[28] (Table 7).

Family history of hypertension was found to be significantly correlated to higher ambulatory blood pressure values in this study, in accordance with previous studies.[29,30] The strong correlation of physical fitness, as determined by maximal oxygen uptake, and heart rate, found in all tobacco habit groups, are in accordance with previous studies.[31]

Comments on Methods The advantages of 24-h blood pressure monitoring include studying the diurnal variations in blood pressure levels resulting from the influence of lifestyle elements, such as mental stress, tobacco, coffee, alcohol, food, etc, and also

TABLE 6. HEART RATE VALUES AT CLINICAL EXAMINATION AND THROUGH 24-h AMBULATORY MONITORING IN THE DIFFERENT TOBACCO HABIT GROUPS

Heart Rate	Nonusers of Tobacco (n = 59)	Smokeless Tobacco Users (n = 47)	P*	Smokers (n = 29)	P*
Casual (beats/min)†	57 ± 9	60 ± 7	ns	58 ± 9	ns
Mean HR, 24-h (beats/min)	62 ± 12	65 ± 14	<.05	69 ± 14	<.05
Mean HR, daytime (beats/min)	63 ± 12	69 ± 14	<.05	74 ± 13	<.05
Mean HR, nighttime (beats/min)	54 ± 9	56 ± 12	<.05	58 ± 11	<.05
Variability, 24-h	9 ± 2	11 ± 3	<.05	11 ± 3	ns
Variability, daytime	9 ± 2	11 ± 3	ns	10 ± 2	ns
Variability, nighttime	6 ± 3	5 ± 3	ns	6 ± 3	ns

During the 24-h monitoring, on average 84 measurements/individual were performed. All values are means and standard deviations adjusted for differences in age, body mass index, waist-hip ratio, physical training level, and alcohol consumption. Variability is calculated as the mean of the SD of each individual heart rate recording.

* *Comparisons between tobacco users and never-users, after adjustments, using Student t test. Significance level P < .05.*

† *Measured at 8:30 AM, after 5 min of supine rest.*

Daytime, 06:00 to 24:00; Nighttime, 00:00 to 06:00; HR, heart rate, ns, not significant.

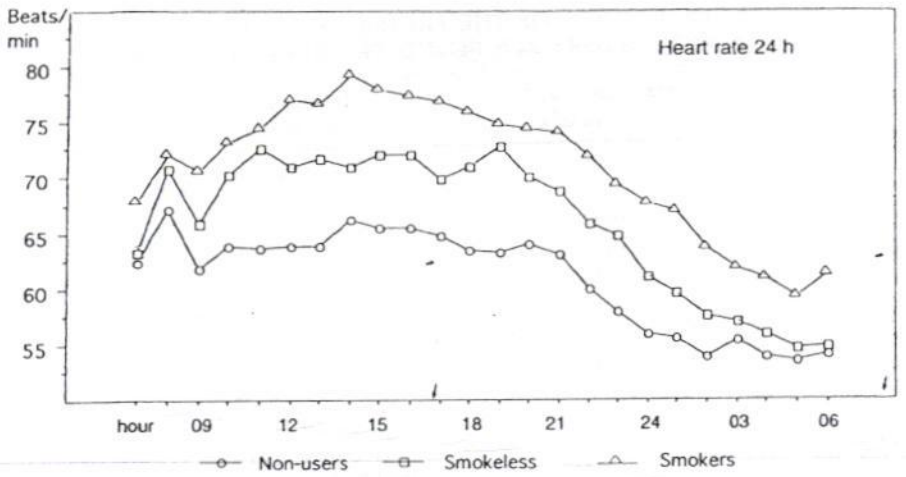

FIGURE 4. *Hourly mean values of heart rate during 24-h ambulatory blood pressure measurements, in the three tobacco habit groups. Smokeless tobacco users showed significant differences (P < .001) during all daytime measurements, but not at night, compared to nonusers. Smokers had significantly (P < .001) elevated heart rate compared to nonusers both by day and at night.*

studying pharmacologic treatment patterns.[16,32] However, ambulatory monitoring has limitations as conditions are less controlled than measurements taken at a clinic. Changes in physical activity during the period of monitoring account for about a third of the overall variance of blood pressure.[33] In the present study only ordinary daily activities without high physical demands were performed and there was no diary-reported difference in activity patterns between the three tobacco habit groups. Still, this study was performed on physically very well trained middle-aged men, and significant differences in physical performance were observed only comparing nonusers with cigarette smokers.[34] The findings of the present study might therefore underestimate the cardiovascular effects of smokeless tobacco, because all subjects were more physically fit than a random sample of the population.

The standardized choice of 00:00 to 06:00 as sleeping hours can, of course, give rise to questions of misclassification of awake and sleeping recordings. As there were no significant differences in sleeping hours between the three tobacco habit groups, and as 90% of all subjects reported being asleep during the nighttime registration period, there is reason to believe that any possible misclassifications should be equally distributed in the three tobacco habit groups.

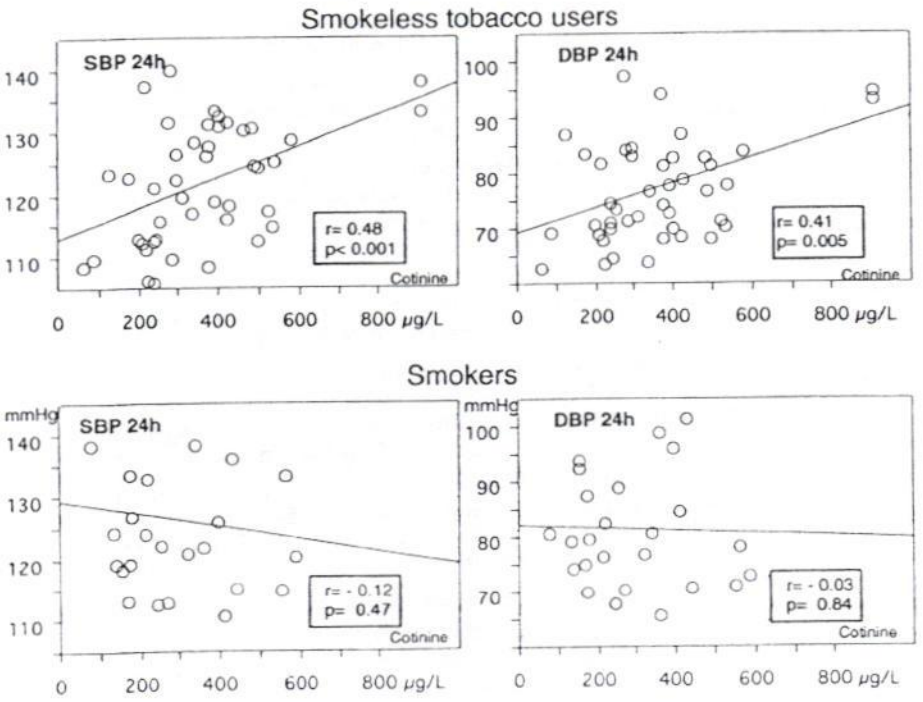

FIGURE 5. *Linear regression analysis of the relationship between mean 24-h ambulatory systolic (SBP) and diastolic (DBP) blood pressures and blood cotinine values in smokeless tobacco users (n = 47) and smokers (n = 29); P < .05 are regarded as statistically significant.*

TABLE 7. COMPARISONS OF THE RESULTS OF THE PRESENT INVESTIGATION WITH STUDIES ON NORMAL VALUES OF AMBULATORY 24-h BLOOD PRESSURE MONITORING IN MEN

	Stæssen et al[27] (n = 1683*)	Nyström et al[28] (n = 100*)	Present Study, 1997 (n = 135)
Age (years)	20–79	20–70	35–60
Blood pressure (BP)			
24-h BP (mm Hg)	118/72	124 ± 9/76 ± 6	124 ± 9/78 ± 10
Daytime BP (mm Hg)	123/76	129 ± 9/80 ± 7	126 ± 10/80 ± 10
Nighttime BP (mm Hg)	106/64	110 ± 10/64 ± 8	107 ± 10/66 ± 10

Values are means ± SD (when available). n, number in each group.

** Information on men is calculated from data presented in the paper.*

CONCLUSION

Mild but long-standing blood pressure elevation can cause structural changes to both heart and blood vessels, thus contributing to the development of sustained hypertension.[35] There is no doubt that smoking cessation has tremendous effects on cardiovascular morbidity.[36] However, to stop smoking by switching over to smokeless tobacco does not seem to avert all of the cardiovascular risks associated with smoking. The finding of increased blood pressure in smokers during 24-h registration is contradictory to most reports on clinical blood pressure measurements but supports the results of several[13–16] although not all,[17] studies of ambulatory blood pressure recordings in smokers. The findings of elevated ambulatory blood pressures in smokeless tobacco users supports the results of earlier investigations.[8] The use of smokeless tobacco is increasing continuously in both the US and Sweden. Thus, it is important to consider that a proportionately small increase in cardiovascular morbidity due to the habit has obvious effects at a public health level, because cardiovascular disease remains the leading cause of death in these countries.

ACKNOWLEDGMENTS

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Smokeless Tobacco, Cardiovascular Risk Factors, and Nicotine and Cotinine Levels in Professional Baseball Players

David Siegel, MD, MPH, Neal Benowitz, MD, Virginia L. Ernster, PhD, Deborah G. Grady, MD, MPH, and Walter W. Hauck, PhD

ABSTRACT

Background. The use of smokeless tobacco (ST), which has increased in popularity over the past 2 decades, results in considerable systemic exposure to nicotine. Nicotine might contribute to atherosclerosis by an effect on cardiovascular risk factors.

Methods. The effects of ST use on cardiovascular risk factors and cotinine and nicotine levels were studied in 1061 professional baseball players during spring training in 1988 and 1989.

Results. Of the study participants 477 (45%) were users. ST use was more common among Whites (55%) than among Blacks (29%) or Hispanics (21%), and users reported heavier consumption of alcohol ($p < .001$) and had higher mean serum caffeine levels ($p < .001$) than nonusers. ST users did not differ from nonusers in adjusted levels of systolic and diastolic blood pressure, pulse, and total or HDL-cholesterol. Among ST users, participants using snuff had higher mean serum cotinine levels than those who used chewing tobacco ($p < .001$). There was no association between serum cotinine levels and adjusted levels of any cardiovascular risk factor studied. However, higher diastolic blood pressures were associated with higher mean serum nicotine levels ($p = .02$).

Conclusions. Smokeless tobacco use has at most a modest effect on cardiovascular risk factors in young physically fit men. (*Am J Public Health.* 1992;82:417–421)

Introduction

The use of smokeless tobacco (ST)—oral snuff or chewing tobacco—increased in popularity in the 1970s and 1980s. Approximately 10 million Americans used ST in the past year; 3 million were less than 21 years of age.[1] Among young men, the use of moist snuff has become particularly widespread.[2] Smokeless tobacco use results in considerable systemic exposure to nicotine.[3,4] The results of studies of cigarette smokers have led to concern that nicotine may increase the risk of atherosclerotic vascular disease.[5] Nicotine may contribute to atherosclerosis by affecting lipid metabolism, coagulation, hemodynamic status, or all three. Smokers have higher levels of low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) cholesterol and lower levels of high-density lipoprotein (HDL) cholesterol than do nonsmokers.[6–8] Cigarette smoking or the administration of nicotine acutely increases heart rate and blood pressure, although in habitual cigarette smokers blood pressure tends to be lower than in nonsmokers.[9] Circulating leukocytes, primarily neutrophils, are higher in smokers than in nonsmokers, and leukocyte counts return toward nonsmoking levels after smoking cessation.[10,11] Neutrophils may generate oxygen-free radicals and other substances that promote thrombosis, and they may accelerate endothelial cell growth, both of which could contribute to the acceleration of atherosclerotic vascular disease.[5,12] Whether nicotine exposure from ST use has similar effects on lipid metabolism, neutrophils, blood pressure, and heart rate, and thus predisposes to atherosclerotic vascular disease, has not been established.

In studies performed on a research ward, ST use resulted in systemic absorption of nicotine and cardiovascular effects similar to those observed with cigarette smoking.[13] In reports of small numbers of individuals, ST use has been associated with hypertension, perhaps related to ST's salt content or to nicotine-related catecholamine release.[13–15] One recent study reported an association between ST use and elevated levels of total serum cholesterol.[8]

We recently completed a comprehensive study of the health effects of ST use in professional baseball players.[16] A part of the study's purpose was to determine whether ST use was associated with changes in cardiovascular risk profiles. Specifically, we measured blood pressure, heart rate, total serum cholesterol, HDL cholesterol, and white blood cell counts. We also quantitated nicotine intake from ST by measuring plasma nicotine and its metabolite cotinine in plasma.

Methods

Study Population

A detailed discussion of the study methods and highlights of findings from

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Editor's Note: See related Commentary by Connolly on page 351.

the first year of the project have been presented elsewhere.[16] We report here detailed findings from the first 2 years of the study on cardiovascular risk factors and nicotine and cotinine levels in the participants.

During February and March of 1988 and 1989, we studied 1061 members of the seven major league professional baseball teams and their associated minor league teams that conduct spring training in the greater Phoenix and Tucson, Ariz, area. All players and coaches on the teams were invited to participate in the study.

After giving informed consent, all participants completed a questionnaire that provided demographic data and information about cigarette smoking and coffee and alcohol consumption. There were only 41 current cigarette smokers and they were excluded from analyses. Detailed information concerning patterns of ST use, including type and brand used most often, was collected. Analyses of type (snuff or chewing tobacco) and brand were based on the type and brand usually used. The amount of ST used was based on the number of cans of snuff or pouches of chewing tobacco reportedly used per week. Because many participants who usually used one type of ST occasionally used the other type, the combined number of hours that tobacco of either type was held in the mouth per day was also calculated. Recency of use was determined as hours since ST was last used.

The participants were classified on the basis of their self-reported ST use as nonusers (those who had never used ST or who had used ST in the past but never more frequently than once a month) and users (those who had used ST within the past week). Former users (those who had used ST more than once a month in the past but had not used ST within the previous month) and infrequent current users (those who had used ST within the past month but not within the past week) were excluded from analyses. For any player for whom we had data from both 1988 and 1989, we used only the data from the year for which the data were most complete. If data from both years were equally complete, 1989 data were used for that player. Data from a total of 477 ST users and 584 nonusers are included in this report.

Blood Pressure and Pulse

After the participants completed the questionnaire, their heart rate and blood pressure were measured twice, several minutes apart, in a sitting position. Systolic blood pressure was recorded at the level when phase 1 Korotkoff sounds were first heard and diastolic blood pressure was recorded at the beginning of phase 5 with the disappearance of sounds. To avoid the effects of physical activity, we included in our analysis of blood pressure and pulse rates only measurements from individuals who had not come to the examination directly from the playing field.

Biochemical Measurements

Blood was drawn to measure total serum cholesterol; HDL cholesterol; nicotine, cotinine, and caffeine levels; and white blood cell count. Biochemical validation of self-reported ST use included measurement of cotinine (the primary metabolite of nicotine) and thiocyanate (a marker of tobacco smoke exposure) by gas chromatography.[17] Low serum cotinine level (<12 ng/mL) together with normal serum thiocyanate levels (<85 mmol/L) was considered biochemical evidence of nonuse of tobacco.[18] This standard, applied in an initial analysis of participants from whom blood was obtained in 1988 and who reported that they neither used ST nor smoked cigarettes, indicated that 95% (357 of 376 for whom blood samples were obtained in 1988) were correctly classified biochemically as nonusers. Given the high accuracy of use status based on self-report and the fact that blood samples were not obtained from all players presented here, the results shown in Tables 1, 2, and 4 are based on self-report. Serum caffeine was measured simultaneously with nicotine and cotinine; 7-ethyl theophylline, 5-methylnicotine, and 1-methyl-5-(2-pyridyl)-pyrrolidine, respectively, were used as internal standards.

Statistical Analysis

Estimated odds ratios were calculated and adjusted for covariates by means of multiple logistic analyses.[19] All logistic analyses were done with the CATMOD procedure on PC-SAS (SAS Institute, Cary, NC) with confidence intervals based on standard errors of the log odds ratios. Significance levels for analyses of covariance were determined with PC-SAS's GLM procedure. The means reported are least squares means, that is, estimates of the means for each use group adjusting for differences between groups in the covariates. For categorical covariates we created the appropriate indicator variables so that the least squares means are distributed around the overall mean, corresponding to the usual method of adjusting for confounding.

Results

Demographic Characteristics

The distribution of current ST users and nonusers by self-reported age, race, educational level, and alcohol consumption is presented in Table 1. Most participants (77%) in both groups were between 20 and 29 years of age and were white (67%). Participants were relatively well educated—94% had graduated from high school and 74% had completed at least some college.

Twenty-four percent reported no alcohol consumption and 7% reported an average of more than two drinks per day. Smokeless tobacco use varied by age; current-week use was reported by 26% of participants younger than 20 years, 49% of those aged 20 to 29 years, and 38% of those aged 30 years and older. Whites were more likely to report ST use during the past week (55%) than Blacks (29%) or Hispanics (21%). Current-week ST users were heavier consumers of alcohol than were nonusers ($P < .001$), and had higher mean serum caffeine levels (512 ng/ml versus 331 ng/ml, data not shown; $P < .001$) when adjusted for age and race.

Of the ST users, 75% used primarily oral snuff, the others chewing tobacco. Among current users of snuff, 70% used Copenhagen, 21% Skoal, and 6% Hawken. Of the chewers, 48% used Levi-Garett and 42% used Redman (data not shown).

Cardiovascular Risk Factors

There were no significant differences between ST users and nonusers in systolic and diastolic blood pressure, pulse, and total or HDL cholesterol levels when adjusted for age, race, alcohol use, and serum caffeine (Table 2). ST users had lower mean white blood cell counts than nonusers ($P < .01$). There were also no significant differences among ST users in systolic and diastolic blood pressure, pulse rate, white blood cell count, and total or HDL cholesterol levels when evaluated by different measures of use—years of use, hours of use per day, and hours since last use (data not shown).

Cotinine, Nicotine, and Caffeine Levels

Serum cotinine measurements were obtained in 230 of the current users. Table 3 presents cotinine levels in relation to type and patterns of ST use. Participants who used snuff had higher adjusted mean serum cotinine than participants who used

chewing tobacco ($P < .001$). Only 1% of the participants who used chewing tobacco, compared with 24% of those who used snuff, had serum cotinine levels of ≥250 ng/mL (data not shown). Participants who reported using ST more hours per day, as well as those who reported more recent use, also had higher adjusted mean serum cotinine levels ($P < .001$). Similar statistically significant results were found for adjusted mean serum nicotine levels (data not shown). Participants who had used ST for more years had higher adjusted mean serum caffeine levels than those who had used ST for a shorter period ($P = .03$, data not shown).

Cotinine and Nicotine Levels and Cardiovascular Risk Factors

There was no difference in adjusted systolic and diastolic blood pressure, pulse rate, white blood cell count, and total or HDL cholesterol levels between participants who used snuff exclusively and those who used chewing tobacco exclusively (Table 4). We examined the association between the above measures and serum cotinine and serum nicotine levels, adjusting for age, race, alcohol use, and serum caffeine (data not shown). There was no association between serum cotinine levels and any of these measures. Interestingly, we failed to confirm our previous finding of a weak inverse association between serum cotinine levels and serum HDL cholesterol levels.[16] However, higher mean serum nicotine levels were associated with higher diastolic blood pressure levels ($P = .02$), and there was a trend toward higher pulse rates ($P = .09$), total cholesterol levels ($P = .10$), and white blood cell counts ($P = .15$) with higher mean serum nicotine levels.

TABLE 1—Characteristics of Study Sample According to Smokeless Tobacco Use

	Nonuser, % (n)	User, % (n)	Total, % (n)
Age, y			
<20	13.0 (78)	5.7 (27)	10.0 (105)
20–24	49.7 (288)	56.9 (269)	52.9 (557)
25–29	21.9 (127)	26.0 (123)	23.7 (250)
30–34	7.8 (45)	7.0 (33)	7.4 (78)
35–39	2.1 (12)	1.9 (9)	2.0 (21)
>40	5.2 (30)	2.5 (12)	4.0 (42)
Race			
White	54.6 (319)	81.6 (389)	66.7 (708)
Hispanic	25.2 (147)	8.2 (39)	18.0 (186)
Black	18.0 (108)	9.4 (45)	14.4 (153)
Asian/Other	1.7 (10)	0.8 (4)	1.1 (14)
Educational level			
Elementary school	2.9 (16)	0.6 (3)	1.8 (19)
Some high school	5.2 (29)	3.4 (16)	4.4 (45)
High school graduate	22.6 (127)	16.3 (76)	19.7 (203)
Some college	46.4 (261)	58.0 (268)	51.0 (529)
College graduate	23.0 (129)	22.1 (103)	22.6 (232)
Alcohol consumption*			
Nondrinker	34.7 (200)	9.9 (47)	24.0 (247)
1–13 drinks per week	61.8 (356)	78.0 (372)	69.3 (728)
14–20 drinks per week	1.2 (7)	5.3 (25)	3.0 (32)
>20 drinks per week	2.3 (13)	6.3 (30)	4.1 (43)

Note. Total *n* was 1061; because not every participant answered every question on the questionnaire, the numbers in each category will not add to the total.
*$P < .001$ for trend users versus nonusers.

TABLE 2—Adjusted* Mean Levels of Systolic and Diastolic Blood Pressure, Pulse Rate, Total Cholesterol, HDL Cholesterol, and White Blood Cell Count by Smokeless Tobacco Use

	Nonuser		User		
	Mean	n	Mean	n	95% CI for Difference
Blood pressure (mm Hg)					
Systolic	117.1	176	117.1	127	−2.48, 2.53
Diastolic	72.1	176	71.5	127	−1.62, 2.79
Pulse (beats/min)	65.6	175	65.4	126	−2.67, 3.13
Total cholesterol (mmol/L)	4.42	489	4.39	396	−0.09, 0.15
HDL cholesterol (mmol/L)	1.30	485	1.31	395	−0.05, 0.04
WBCs × 10^9/L	6.6	419	6.2†	332	0.12, 0.64

Note. HDL indicates high density lipoprotein; WBC, white blood cells; CI, confidence interval. CIs for users minus nonusers.
*Adjusted for age, race, alcohol use, and serum caffeine level.
†$P < .01$ compared with nonusers.

Discussion

This group of professional baseball players is the largest population of ST users in which nicotine and associated cardiovascular risk factors have been examined. The large sample size and the high prevalence of ST use provided ample power to detect relatively minor effects of ST use on the cardiovascular risk factors studied. Despite this, we did not find differences in systolic and diastolic blood pressure, total and HDL cholesterol, and white blood cell count between ST users and nonusers. These findings are similar to those that we reported after the first year of the study[16] and contrast with the results of experimental studies of ST users in which ST use throughout the day produced the same cardiovascular effects as cigarette smoking.[13] Additionally, we analyzed the effect of ST use on serum nicotine and cotinine levels and their association with cardiovascular risk factors.

Cotinine is the major metabolite of nicotine and has a much longer half-life than nicotine.[12] For these reasons cotinine is widely used as a biochemical marker of average daily intake of nicotine. Determination of serum cotinine, however, is a relatively insensitive way to detect exactly when tobacco was last used. The mean serum cotinine level was 144 ng/mL for snuff users and 82 ng/mL for chewers. The average cotinine levels for snuff users were similar to those previously reported in a group of college athletes, but were considerably lower than those measured in a research ward study of ST use and cigarette smoking.[3,13] These cotinine levels are also lower than the average level of 300 ng/mL found in cigarette smokers.[12] Since a cotinine level of 100 ng/mL corresponds to a nicotine intake of about 12 mg,[12] we estimated that daily intake of nicotine was 17.0 mg for snuff users and 9.9 mg for chewing tobacco users. The low

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TABLE 3—Adjusted[a] Mean Levels of Serum Cotinine in Smokeless Tobacco Users by Type of Smokeless Tobacco Use, Years of Use, Hours of Use Per Day, and Hours Since Last Use

	n	Mean Serum Cotinine (ng/ml) (SE)
Type of smokeless tobacco[b]		
Snuff	182	143.9 (7.4)
Chewing tobacco	48	82.1 (15.1)
Years of use		
3 or less	31	91.1 (18.1)
4–6	97	145.6 (10.2)
7–9	54	123.9 (13.9)
10 or more	48	135.2 (14.6)
Hours of use per day[b]		
0.0–0.5	73	104.3 (12.2)
0.5–1.0	49	131.7 (14.2)
1.0–1.5	33	134.8 (17.6)
1.5–2.0	22	120.8 (21.4)
2.0–4.0	38	165.3 (16.3)
>4.0	15	178.1 (26.5)
Hours since last use[b]		
0–1	61	174.0 (13.1)
1–12	60	185.6 (13.2)
12–24	78	87.9 (11.4)
>24	31	49.1 (19.2)

[a]Each analysis is adjusted for other variables in the table.
[b]$P < .001$; for the two "hours" variables, this P is from trend tests using the continuous form of the variables.

TABLE 4—Adjusted[a] Mean Levels of Systolic and Diastolic Blood Pressure, Pulse Rate, Total and HDL-Cholesterol, and White Blood Cell Count by Type of Smokeless Tobacco Use[b]

	Snuff		Chewing Tobacco		
	Mean	n	Mean	n	95% CI for difference
Blood Pressure					
Systolic	115.3	69	119.3	26	−9.10, 1.07
Diastolic	71.9	69	70.9	26	−2.19, 5.14
Pulse	64.5	69	65.4	25	−4.22, 6.05
Total Cholesterol	4.34	180	4.39	48	−0.33, 0.21
HDL-Cholesterol	1.33	179	1.33	48	−0.11, 0.09
White Blood Cell Count	6.1	154	6.2	33	−0.66, 0.49

Note. Same abbreviations and units as in Table 2.
[a]Adjusted for age, race, alcohol use, serum caffeine level, hours of smokeless tobacco use per day, time since last ST use and years of ST use.
[b]Subjects included in this table are exclusive users of either snuff or chewing tobacco.

cotinine levels in our subjects were consistent with relatively light use of ST, as reflected by an average of 1.1 hours of snuff use per day and 0.7 hours of chewing tobacco use per day. As expected, serum cotinine levels tended to be higher with greater duration of ST use and greater number of hours of ST use per day, and was lower with greater number of hours since the last dose of ST. Overall, the serum cotinine data indicate that baseball players are relatively light users of ST compared with other populations. Our data also indicate that ST use in baseball players is seasonal; about 50% of the baseball players in our study who reported current-week ST use indicated that they use ST primarily during the baseball season and rarely use it during the off season. The pattern of ST use and low levels of nicotine intake suggests that baseball players may be less dependent on nicotine than are other tobacco users.

Our finding that cotinine levels were lower with chewing tobacco use than with snuff use was surprising in light of the observation that nicotine intake for a single chew is substantially greater than that from a single use of snuff, and daily nicotine levels with ad lib use of both in an experimental study have been found to be similar.[4,13] Our results suggest that chewers use ST in a manner that does not extract as much nicotine from ST as snuff users. The relationship between hours of use per day and serum cotinine was not highly correlated, suggesting that nicotine intake may be more efficient with shorter periods of daily use than with longer periods of use. This type of dose response could be observed if ST is held in the mouth for long periods of time, since the most rapid absorption of nicotine through ST occurs in the first 15 to 20 minutes.[4]

We found an association between higher serum nicotine levels and increased diastolic blood pressure and trends between higher plasma nicotine levels and increased heart rate and white blood cell count. Serum nicotine reflects the recency of tobacco use, and changes in blood pressure, pulse rate, and white blood cell count might reflect a direct pharmacologic response.[12] Our diastolic blood pressure finding is consistent with findings from other studies showing that ST use acutely increases blood pressure.[20,21]

The smokeless tobacco users in this study drank more alcohol than did nonusers. This finding is similar to those of other studies of ST use, in both adolescents and adults.[22] We also found that plasma caffeine levels were higher in ST users than nonusers, perhaps reflecting a tendency toward more psychoactive drug use in ST users. Other studies have found that cigarette smokers drink more caffeine-containing beverages than do nonsmokers.[23] Thus, future studies of the cardiovascular effects of ST should control for the potentially confounding effects of caffeine and alcohol.

Although our findings did not show major adverse effects of ST use on cardiovascular risk factors, we cannot exclude the possibility that daily ST use for many years may have an adverse effect on the cardiovascular system. Previous reports have described long-term harmful effects of ST use, including a strong association with oral cancer.[24–26] Our participants differed from those in other studies of ST use in that their ST use was generally seasonal and of short duration (less than 10 years). Our participants were also professional athletes who exercised regularly and who were generally physically fit, factors that might minimize the harmful effects of ST on the cardiovascular system. Similar large studies should be done in older populations of more sedentary in-

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dividuals to detect the impact of ST use in individuals more prone to cardiac disease. □

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Annexure 83

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Risk of hypertension amongst Swedish male snuff users: a prospective study

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Abstract. Hergens M-P, Lambe M, Pershagen G, Ye W (Karolinska Institutet and Stockholm County Council; Stockholm, Sweden). Risk of hypertension amongst Swedish male snuff users: a prospective study. *J Intern Med* 2008; **264**: 187–194.

Background. The scientific evidence on whether long-term use of snuff is associated with high blood pressure is limited, inconsistent and based only on cross-sectional data.

Objective. We aimed at studying the risk of hypertension in relation to long-term use of snuff based on longitudinal data.

Design. Repeated health check-ups were offered to all employees in the Swedish construction industry between 1978 and 1993. Blood pressure was measured at the health check-up and information on tobacco use and other risk factors was collected through questionnaires.

Setting. In total, 120 930 never smoking men with information on blood pressure and snuff use at baseline were included. The association of high blood pressure and snuff use at baseline was estimated by logistic regression. Further, 42 055 men were identified as normotensive at baseline and had at least one subsequent health check-up. Through repeated blood pressure measurements and linkage to the Swedish National Inpatient Register, information on hypertension was obtained. Relative risk estimates were derived from Cox proportional hazards regression model.

Results. Almost 30% of all men had used snuff. The adjusted odds ratio of high blood pressure amongst snuff users at baseline was 1.23 (95% CI 1.15–1.33) compared to never snuff users. The relative risk of high blood pressure during follow-up was 1.39 (95% CI 1.08–1.79) amongst snuff users and 1.36 (95% CI 1.07–1.72) for hypertension as recorded in the Inpatient Register.

Conclusion. Use of Swedish moist snuff appears to be associated with a moderately increased risk of hypertension.

Keywords: cohort, hypertension, snuff.

Background

Moist snuff (snus) is a type of smokeless tobacco widely used by men in Sweden; approximately 20% of adult men are daily snuff users [1]. The adverse cardiovascular health effects from cigarette smoke are well known; however, the evidence on snuff use and cardiovascular outcomes is limited. Results from some studies show an elevated risk of cardiovascular mortality and morbidity amongst snuff users and other smokeless tobacco products, but the evidence appears inconsistent [2–8].

The acute effects, probably mainly due to nicotine exposure, from smokeless tobacco use on blood pressure and pulse rate, have been documented both in

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animal and human experiments. Several studies reported increases in cardiac output as well as vascular constriction [9–14]. One Swedish study observed that pulse rate and blood pressure were approximately 5–10% higher amongst those who used snuff within 2 h before measurements compared to those who were not exposed [15]. Another study found that snuff users had higher pulse rate and blood pressure at rest compared to those who were not exposed, but no differences were observed during exercise [16].

Hypertension is a major risk factor for the development of cardiovascular disease; however, evidence on the possible long-term effects of snuff use on blood pressure is limited. A large Swedish cross-sectional study reported a higher prevalence of high blood pressure amongst snuff users compared to subjects who never used tobacco [17], and in a case–control study an increased risk of hypertension amongst snuff users was observed in the control group [6]. A third Swedish study showed a higher mean systolic blood pressure during a 24-h period amongst snuff users compared to nontobacco users [18]. On the other hand, several cross-sectional studies from both Sweden and the United States did not find an association between long-term use of snuff and the risk of hypertension [12, 15, 19–22]. There are no longitudinal studies on snuff use and risk of hypertension.

In this prospective study, our aim was to assess the risk of high blood pressure and hypertension amongst male long-term users of snuff, particularly based on longitudinal data.

Material and methods

Setting

Between 1969 and 1993, the Swedish Construction Industry's Organization offered free health check-up to both blue-collar and white-collar employees. These health check-ups were voluntary and with no limits as to how many times an individual could attend. The mean number of visits was 3 but some employees had up to 13 visits. Approximately 25% of the workers did not attend at any time. There is no information on whether the nonattendants did not get an invitation or whether they were unwilling to participate. At each visit resting blood pressure was measured in a supine position, in addition to heart rate, height and weight. The workers also completed a questionnaire regarding medical history, working environment and detailed history of smoking and snuff use.

The cohort

Approximately 390 000 individuals were registered in the cohort between 1971 and 1993. No information was available on tobacco use between the years 1975 and 1977, therefore we chose to use exposure information (snuff use) from the first visits after 1 January 1978. To avoid confounding from smoking we excluded all persons who had ever smoked, using information from all visits available from 1971 to 1993. The Swedish personal registration number, an individually unique identifier, enabled follow-up through record linkage to several national registers, i.e. the Inpatient Register, the Causes of Death Register, the Migration Register and the Total Population Register. Subjects were further excluded because of other inconsistencies or missing information on area of domicile, weight, height or snuff use. In all, approximately 1.4% of the men were lost to follow-up because of inconsistent personal registration numbers. The final population consisted of 120 930 men. The exclusion criteria and the number of subjects included in the different analyses are outlined in detail in Fig. 1.

Outcome

Cases of hypertension were identified in the Inpatient Register using discharge diagnoses in which hypertension was coded as the underlying cause or as co-morbid condition. The definition included malignant and benign hypertension with or without heart and kidney failure (ICD-7: 440–447, ICD-8: 400–404, ICD-9: 401–405 and ICD-10: I10–I15). A systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the health visit was classified as high. Only subjects with repeated measurements of blood pressure were included when calculating the

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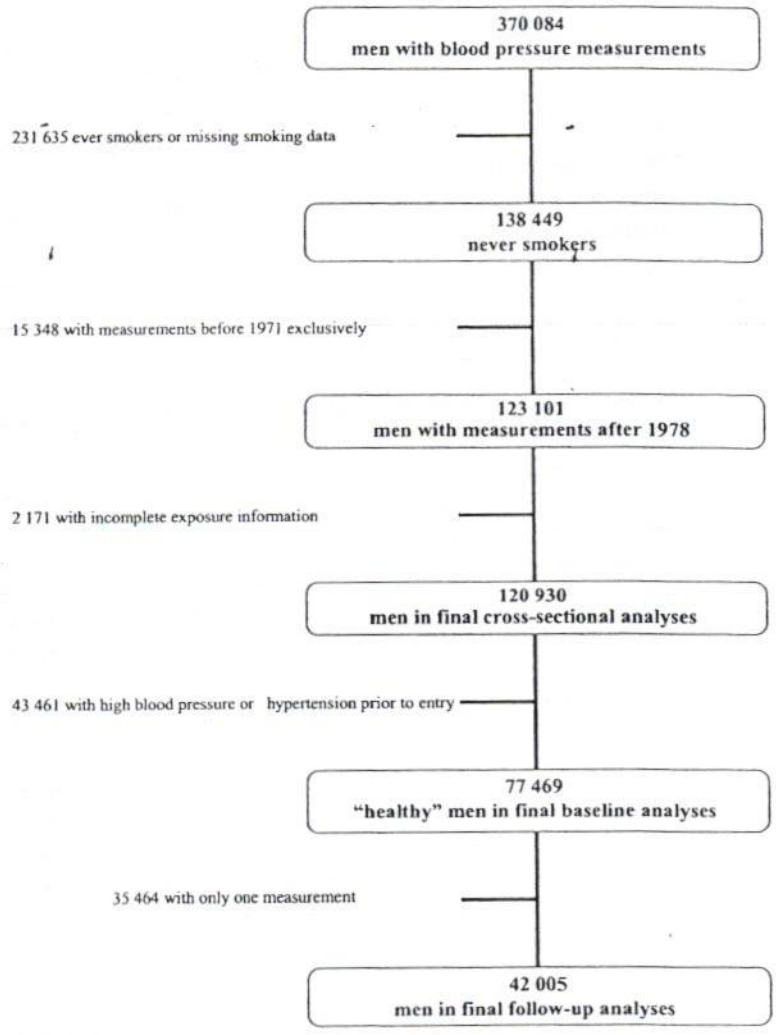

Fig. 1 Flowchart of the Construction Workers Cohort.

mean systolic and diastolic blood pressure over time. For those with two measurements at one health visit the mean was used. A 'healthy' cohort was created for the follow-up analyses including only those with systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg at the first visit along with those never registered with hypertension in the In-patient Register prior to baseline (see Fig. 1).

Information on snuff dipping and other risk factors

From 1978 information on the amount of snuff use (g week^{-1}), duration of snuff dipping, and time since cessation of snuff dipping (years) was obtained. Regular snuff use was defined as consumption of at least 1 g day^{-1} for at least 1 year. Former snuff users were those subjects who had stopped using snuff more than 1 year before enrolment. The mean consumption reported amongst current snuff users was 22.5 g day^{-1}. We only used snuff information from the first visit registered as the repeat visits varied in number and timing because of self-selection. For this reason and the fact that duration was age dependent we did not use this information in the analyses. Current users were divided into four groups according to the amount of daily snuff intake (g week^{-1}): <12.5 g day^{-1}, 12.5–24.9 g day^{-1}, 25–49.9 g day^{-1} and 50 or more g day^{-1}.

Body mass index [BMI, weight (kg)/height (m^2)] was calculated using information from the health check-up. Area of domicile at baseline was established by linkage to the Total Population Register and the Register of Domestic Migration. We grouped the residence areas of participants into northern, middle and southern Sweden. No information on alcohol, diet or physical activity was available.

Statistical analysis

At baseline the relationship between snuff use and high blood pressure was measured as odds ratios through logistic regression models with adjustment for age, BMI and region of residence. The cohort members contributed person-years from the entry date until the date of first diagnosis (hypertension in the Inpatient Register or high blood pressure at subsequent health visit), death, emigration out of Sweden or the end of year 2004 (1993 for analyses of high blood pressure), whichever occurred first. If an individual was living in a county with incomplete coverage of the Inpatient Register, the entry date was reset to the date of complete coverage to ensure complete follow-up for hypertension. The association between snuff use and risk of hypertension was estimated by relative risks derived from Cox proportional hazards models with adjustment for attained age (as time scale) [23], BMI and region of residence. Repeated blood pressure measurements on individuals allowed us to study the effect of snuff on change in high blood pressure (binary outcome variable) over time. Repeated measurements on individuals are usually correlated and the Generalized Estimation Equation was used to adjust for this within-individual correlation [22]. Age at entry was considered as a potential confounder and was included in the analyses. All analyses were conducted using SAS, version 9.1 (Cary, NC, USA). This study was approved by the Regional Ethics Committee at Umeå University.

Results

In all, 120 930 never smoking men with information on blood pressure and snuff use at baseline were included, and 42 005 of those had more than one measurement on blood pressure and were normotensive at baseline (Fig. 1). Approximately 30% of the men were ever snuff users. More than 5900 men had high blood pressure (systolic ≥160 mmHg or diastolic ≥100 mmHg) at baseline. Amongst the normotensive men with repeated measurements 949 cases with high blood pressure or hypertension were observed. The prevalence of snuff use and number of men with high blood pressure/hypertension is presented in Table 1.

Table 1 Use of snuff and high blood pressure or hypertension amongst nonsmoking men in the Swedish Construction Workers Cohort

	Baseline cohort (N = 120 930)		Healthy baseline (N = 77 469)		Healthy baseline with repeated measurements (N = 42 005)		
	n (%)	High blood pressure[a]	n (%)	Hypertension[b]	n (%)	High blood pressure[a]	Hypertension[a]
Never snuff use	85 413 (71)	4815	52 456 (68)	581	29 892 (71)	337	397
Ever snuff use	35 517 (29)	1100	25 013 (32)	158	12 093 (29)	124	91
Former snuff use	2487 (2)	90	1631 (2)	12	858 (2)	10	7
Current snuff use	32 973 (27)	1010	23 382 (30)	146	11 235 (27)	114	84
<12.5 g day^{-1}	7175 (6)	280	4828 (6)	37	2641 (6)	34	22
12.5–24.9 g day^{-1}	14 832 (12)	435	10 637 (14)	66	5252 (13)	51	36
25–49.9 g day^{-1}	7529 (6)	183	5479 (7)	30	2366 (5)	18	17
>50 g day^{-1}	3437 (3)	112	2438 (3)	13	976 (3)	11	9

[a]Cases identified at health check-up for those with more than one health check-up. End of follow-up 1993.
[b]Cases identified in the Inpatient Register.

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The odds ratios for high blood pressure (SBP >160 mmHg or DBP >100 mmHg) amongst ever snuff users was 1.23 (95% CI 1.15–1.33) compared with nontobacco users following adjustment for age, BMI and region of residence (Table 2). Following stratification for age, slightly higher odds ratios for high blood pressure were observed amongst ever snuff users in the older age groups.

Amongst subjects with normal blood pressure at baseline no clear risk of hypertension was observed in snuff users compared with nonsnuff users (Table 4). However, amongst the normotensive with repeated measurements, the relative risk of high blood pressure at a subsequent health visit was 1.39 (95% CI 1.08–1.79) amongst ever snuff users (Table 4). In this group the relative risk of hypertension was 1.36 (95% CI 1.07–1.72). The risk estimates were generally higher amongst current users, although no clear dose–response effect was detected (Tables 3 and 4). The effect of snuff on the risk of high blood pressure increased with time ($P = 0.02$).

Discussion

Our findings indicate that the prevalence of high blood pressure is increased amongst ever snuff users. We also observed an increased risk of high blood pressure and hypertension during follow-up amongst snuff users with normal blood pressure at baseline.

Table 2 Prevalence of high blood pressure (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg) at baseline (N = 120 930) in different age groups according to snuff use amongst Swedish male construction workers

Age at baseline (years)	Never used snuff	Ever used snuff		Former snuff users		Current snuff users	
	n (%)	*n* (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)
All	4815 (5.63)	1106 (3.11)	1.23 (1.15–1.33)	90 (3.69)	1.04 (0.83–1.31)	1010 (3.07)	1.25 (1.16–1.35)
<45	1174 (1.83)	529 (1.61)	1.18 (1.06–1.32)	41 (1.85)	0.98 (0.72–1.35)	487 (1.59)	1.20 (1.08–1.34)
45–49	505 (8.28)	110 (12.00)	1.37 (1.10–1.72)	14 (11.63)	1.42 (0.80–2.51)	95 (12.06)	1.35 (1.07–1.72)
50–54	763 (13.97)	116 (19.02)	1.37 (1.10–1.71)	8 (15.52)	1.12 (0.52–2.39)	107 (19.38)	1.39 (1.10–1.75)
55–59	1157 (20.90)	168 (28.19)	1.35 (1.11–1.63)	11 (17.46)	0.73 (0.38–1.43)	156 (29.46)	1.43 (1.17–1.75)
60–64	1114 (27.27)	176 (32.06)	1.20 (0.98–1.45)	16 (32.69)	1.30 (0.70–2.40)	158 (31.99)	1.19 (0.97–1.46)
≥65	102 (34.58)	7 (53.85)	2.20 (0.70–6.95)	0	–	7 (53.85)	2.20 (0.70–6.95)

[a]OR, odds ratio derived from logistic regression model; CI, confidence interval; adjusted for age at entry, body mass index [weight (kg)/height (m^2), categorized into <20, 20–24.9, 25–29.9 and ≥30] and region of residence (northern, middle and southern Sweden).

Table 3 Prevalence of high blood pressure (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥100 mmHg) at baseline in different age groups according to snuff use amongst Swedish male construction workers

Age at baseline (years)	OR[a] (95% CI)			
	<12.5 g day^{-1}	12.5–24.9 g day^{-1}	25–49.9 g day^{-1}	≥50 g day^{-1}
All	1.12 (0.98–1.28)	1.31 (1.17–1.46)	1.25 (1.07–1.47)	1.45 (1.18–1.78)
<45	1.18 (0.96–1.44)	1.12 (0.96–1.31)	1.30 (1.07–1.58)	1.36 (1.06–1.75)
45–49	1.24 (0.80–1.90)	1.62 (1.17–2.26)	1.01 (0.57–1.83)	1.22 (0.62–2.42)
50–54	1.11 (0.74–1.65)	1.37 (0.97–1.96)	1.68 (1.01–2.8)	2.18 (1.11–4.3)
55–59	1.15 (0.83–1.6)	1.73 (1.29–2.31)	1.31 (0.76–2.25)	1.61 (0.75–3.46)
60–64	0.96 (0.72–1.29)	1.65 (1.22–2,23)	0.61 (0.29–1.29)	1.83 (0.70–4.80)
≥65	1.78 (0.38–8.36)	4.57 (0.44–47.6)	1.36 (0.08–24.0)	–

[a]OR, odds ratio derived from logistic regression model; CI, confidence interval; adjusted for age at entry, body mass index [weight (kg)/height (m^2), categorized into <20, 20–24.9, 25–29.9 and ≥30] and region of residence (northern, middle and southern Sweden).

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Table 4 Relative risk of high blood pressure or hypertension amongst Swedish male construction workers using snuff

	Healthy baseline (N = 77 469)	Healthy baseline with repeated measurements (N = 42 005)	
	Hypertension[b]	High blood pressure[a]	Hypertension[b]
	RR[c] (95% CI)	RR[c] (95% CI)	RR[c] (95% CI)
Never snuff use	Ref.	Ref.	Ref.
Ever snuff use	1.08 (0.89–1.29)	1.39 (1.08–1.79)	1.36 (1.07–1.72)
Former snuff use	0.78 (0.43–1.41)	1.49 (0.76–2.90)	0.85 (0.40–1.79)
Current snuff use	1.10 (0.91–1.33)	1.34 (1.03–1.74)	1.43 (1.12–1.83)
<12.5 g day^{-1}	1.03 (0.74–1.43)	1.49 (0.97–2.27)	1.18 (0.77–1.82)
12.5–24.9 g day^{-1}	1.15 (0.88–1.49)	1.24 (0.86–1.80)	1.43 (1.01–2.02)
25–49.9 g day^{-1}	1.15 (0.79–1.69)	1.19 (0.69–2.05)	1.77 (1.08–2.90)
>50 g day^{-1}	1.03 (0.59–1.79)	1.67 (0.86–3.28)	1.76 (0.90–3.42)

[a]Cases identified at health check-up for those with more than one health check-up. End of follow-up 1993.

[b]Cases identified in the Inpatient Register.

[c]RR, relative risk derived from Cox proportional hazard regression model; CI, confidence interval; adjusted for age (age at follow-up was used as time scale), body mass index [weight (kg)/height (m^2), categorized into <20, 20–24.9, 25–29.9 and ≥30) and region of residence (northern, middle and southern Sweden).

Our findings are in line with two previous studies on snuff use and hypertension, of which one was based on an earlier subset of the present cohort [17] whilst the other was a case–control study showing an increased prevalence of hypertension amongst controls using snuff [6]. However, several studies have failed to find such an association [12, 15, 19–23]. These apparent discrepancies could have several explanations: the age distribution in the study populations is different, three of them (including ours), have an older/middle aged study population [6, 17, 22] whilst others have restricted the study population to young and healthy athletes [12, 15, 19, 20, 23]. In some studies adjustment was made for potential confounding factors, such as smoking, BMI and physical activity [6, 12, 17, 19, 21], whilst others did not [20, 23]. All previous studies on snuff use and hypertension were cross-sectional studies, which limits the possibility of evaluating causality. Our study is the first study using a prospective design for assessing the long-term effect of snuff use on blood pressure and hypertension. We were able to restrict the cohort to a normotensive study population for follow-up both by blood pressure measurements at health check-ups and in-patient care for hypertension.

Smokeless tobacco and snuff have a documented acute hypertensive effect lasting up to 90 min after intake [13]. This effect is presumably the result of nicotine exposure. Studies have shown that snuff users have serum nicotine concentrations comparable to those of cigarette smokers [9, 10, 24]. Nicotine infusion can increase systolic blood pressure by activating the sympathetic nervous system [25, 26], an effect which is observed at relatively low blood levels of nicotine, and the effect reaches a maximum even if the nicotine level in the blood is further increased; and persists as long as the nicotine levels are moderate, including overnight. This means that a snuff user can have a sympathetic activation 24 h per day [26]. The results of the present study may thus partly be due to a short-term effect from snuff use. However, subjects were not allowed to use tobacco during the health check-up and the blood pressure was measured after 5 min of rest in supine position. Another way of limiting any bias from short-term effect is to use a high cut-off for the definition of high blood pressure. A review article indicates that the maximal elevation in blood pressure after snuff intake ranges from 4 to 15 mmHg for systolic blood pressure and 6–11 mmHg for diastolic blood pressure [13]. For the

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purpose of the present study, we defined high blood pressure as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg. These cut-off points for high blood pressure exceed those which are currently recommended. The increase in blood pressure from the direct effect of snuff is unlikely to rise above this cut-off value in a normotensive person. It should also be noted that the effect of former snuff use on high blood pressure in the present study was not as consistent, or statistically significant as for current snuff users, which may imply that the effect of snuff use decreases after cessation.

Strengths of the present study include the prospective design, the large sample size and a homogeneous study population. During prolonged follow-up, misclassification of exposure might happen because of subsequent changes in tobacco use. The data on snuff exposure have not been validated in the present study. However, a previous study on the Construction Workers Cohort showed that the inconsistency over time was only 2.6% regarding tobacco smoking [27]. Another Swedish study found that once snus use was initiated, more men continued using snus rather than quit tobacco completely [28]. Although we lacked individual level information by which to control for education, diet and physical activity, the variability of these factors is expected to be less amongst construction workers than in the general population. We were able to adjust directly for BMI. This is an important risk factor for hypertension, and to some extent helps control caloric intake and physical inactivity. As we did not have any information on the nonattendants, we do not know whether there would be a potential selection bias and how this would influence the results.

It is important to point out that the identification of cases of hypertension in this study is not optimal. One report indicates that only 17% of all patients with hypertension can be identified in the Inpatient Register [29]. Such misclassification of outcome is probably nondifferential, i.e. both snuff users and nonsnuff users have the same probability of presence in the register. If anything, this bias would primarily contribute to a dilution of the effect from snuff use on hypertension but the magnitude may be unimportant if mainly the sensitivity (underdiagnoses) is affected [30].

In conclusion, we found an increased risk of elevated blood pressure and hypertension amongst snuff users. These results are of potential public health importance as the prevalence of snuff use is high in Sweden and that hypertension is one of the major risk factors for cardiovascular disease.

Conflict of interest statement

No conflict of interest was declared.

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Annexes 8:

Use of smokeless tobacco: blood pressure elevation and other health hazards found in a large-scale population survey.

Bolinder GM, Ahlborg BO, Lindell JH

J Intern Med. 1992 Oct;232(4):327-34.

Abstract

Health hazards associated with the use of smokeless tobacco were evaluated in a cross-sectional study of 97,586 Swedish construction workers undergoing health examinations in 1971-74. All users of smokeless tobacco only (5014 subjects) and all exclusive smokers of > or = 15 cigarettes daily (8823 subjects) were compared with all non-users of any tobacco (23,885). Both smokeless tobacco users and smokers showed higher prevalences of circulatory and respiratory disorders. Hypertension was most common in smokeless tobacco users. In the 45- to 56-years age group, the odds ratio for a diastolic blood pressure of > 90 mmHg was 1.8 (95% CI, 1.5-2.1), and for a systolic blood pressure > 160 mmHg, 1.7 (95% CI, 1.3-2.1). Smokers showed the lowest prevalence of hypertension. Disability pensions due to cardiovascular disease were nearly 50% more frequent in both smokeless tobacco users and smokers. These findings indicate that an increased cardiovascular risk is also associated with the use of smokeless tobacco.

Annexure 85

Tobacco Induced Diseases

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Research

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Association of exclusive smokeless tobacco consumption with hypertension in an adult male rural population of India

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Abstract

Introduction: Tobacco consumption is a major source of mortality and morbidity in India . Prevalence of smokeless tobacco (ST) consumption in India is around 20%. Studies have shown increased prevalence of cardiovascular disease risk factors and an increased incidence of adverse cardiovascular events among the ST consumers. This is a cross-sectional study done to look into the association of exclusive smokeless tobacco consumption with hypertension, in an adult male rural population of north India.

Methods: All male residents of a village in north India above 15 years of age, who did not have any acute or chronic morbidity were included after taking an informed consent. Subjects were interviewed regarding their demographic profile, socioeconomic status and tobacco consuming habits. Current smokeless tobacco user was defined as one who has ever consumed tobacco orally in past 1 month. Blood pressure of the subjects was also recorded. Cut offs used for systolic and diastolic hypertension were 140 mm hg and 90 mm Hg respectively.

Results: 443 subjects were included in the study. Prevalence of exclusive ST users was 21% while 19.4% consumed both forms and 26.6% did not take any form of tobacco. Mean systolic and diastolic BP were significantly higher in exclusive ST users(systolic BP=139.2+17.4,diastolic BP = 86.8+11.5)as compared to the non users(systolic BP= 135.7+18.8 , diastolic BP= 82.6 +11.5; p value < 0.05). The prevalence of diastolic hypertension was significantly higher in exclusive ST users as compared to non users (40.9%, 22.9% ;p value = 0.01) . The OR for diastolic hypertension in male ST users was 2.3(95% C.I. = 1.3-4.3). Prevalence of systolic hypertension was higher in exclusive ST users too though this was not statistically significant (43%,36.4%;p value = 0.39.).

Conclusion: ST consumption is associated with increased prevalence of high BP in the adult male rural population.This is an indicator of increased predisposition to major adverse cardiac events later in their life time. Prevention of ST consumption could be an important intervention in preventing the ongoing upswing in prevalence of chronic heart disease.

Introduction

Tobacco consumption is a major source of mortality and morbidity in India. According to estimates there are approximately 5 million deaths due to tobacco consumption annually which is expected to reach 10 million by 2025. Currently over 20% of worldwide tobacco related mortality occurs in India [1,2].

In developing countries like India, tobacco consumption is mainly done in two forms: smoked tobacco products and smokeless tobacco. Most commonly used smokeless tobacco products include - tobacco pan masala, tobacco with lime, tobacco with pan and betel quid [3]. Prevalence of smokeless tobacco consumption in India is 20%. It is significantly higher in males than in females (28% in males and 12% in females) and in rural population as compared to urban population [4]. Easy affordability, lesser cost and misconceptions regarding its useful health effects are important contributory factors for increased smokeless tobacco consumption.

Association of smokeless tobacco consumption with occurrence of adverse cardiovascular events like myocardial infarction, stroke, and ischemic heart disease has been studied in detail in western population. Results from these studies paint a mixed picture with some showing increased incidence of these adverse events [5-8] while others showing no such association [9-12]. Similarly, contradictory results have been seen in studies evaluating increased risk factors for cardiovascular diseases in smokeless tobacco consuming population [13-17]. In India, limited studies have shown that tobacco chewing is associated with increased prevalence of cardiovascular risk factors like dyslipidemia, hypertension, and ECG abnormalities as compared to non tobacco users [16-18].

This is a cross-sectional study done to look into the association of exclusive smokeless tobacco consumption with hypertension, a well known risk factor for development of cardiovascular disease, in an adult male rural population of north India.

Materials and methods

A community based cross sectional study was carried out in the village Piayala of Faridabad district in Haryana state in north India over a period of one month. The site of study was chosen by random selection. All male residents of the village above 15 years of age were included after taking an informed consent. Exclusion criteria for the subjects included presence of any self reported acute illness, diagnosed cardiac, renal or hepatic disease, any current treatment for cardiac or blood pressure related morbidities and history of heavy alcohol or recreational drug use. Convenience sampling was used by approaching the subjects for interviewing in the morning before they left for their work.

A peer reviewed, pretested proforma was used to interview the study subjects. The proforma contained questions pertaining to the demographic profile, socioeconomic characteristics, and tobacco consumption habits. For the study, smokeless tobacco was defined as form of tobacco consumed orally and not smoked, and included moist oral snuff, chewing tobacco and tobacco used with betel quid, areca nut, Pan Masala. Current tobacco user was defined as one who has ever consumed tobacco in any form in past one month. Current smokeless tobacco user was defined as one who has ever consumed tobacco orally in past 1 month. A never user was defined as one who has never consumed tobacco in any form. The subjects were interviewed in Hindi on a one to one basis. We also measured the blood pressure of the patient using an electronic BP measuring instrument (OMERON M4) in the right arm standing position. The B.P was recorded on 2 different occasions at 5 minute intervals and the average of the two values was calculated. Systolic hypertension was defined as systolic blood pressure more than 140 mm Hg and diastolic hypertension was defined as diastolic blood pressure more than 90 mm Hg.

Data was entered using Microsoft excel spread sheet and analyzed using SPSS 17.00 version statistical analysis software. Age adjusted Odds ratio was calculated to look into association between the desired variables using logistic regression models. Chi square test was used to test the association between categorized variables and independent T test was used to compare means of continuous variables.

Results

The male population of the village with age greater than 15 yrs was 554 out of which 36 (6.5%) were not available at the time of interview. 44 (7.9%) were excluded due to lack of consent and 31(5.6%) were excluded due to presence of either acute illness (n = 7) or a history of pre existing cardiovascular disease (n = 9) or current blood pressure medication (n = 11) or chronic alcoholism (n = 4). Finally, 443 subjects were included in the study. Prevalence of consumption of different forms of tobacco (smoked vs. smokeless) is shown in Table 1. The demographic profiles exclusive smokeless tobacco users and non users of tobacco are shown in Table 2. Multivariate logistic regression analysis showed a statistically significant correlation between exclusive smokeless tobacco consumption and less than 5 years of education among the subjects (Table 3). Also odds of exclusive smokeless tobacco use were significantly higher in unskilled or semiskilled workers like farmers, factory workers and daily laborers (Table 3). Prevalence of risk factors for hyperten-

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Table 1: Prevalence of consumption of different forms of tobacco in rural male population

Mode of tobacco consumption	% Distribution (n = 443)
Non user of tobacco	26.6%(n = 118)
Exclusive Smokeless tobacco user	21% (n = 93)
Exclusive smoker of tobacco	33% (n = 146)
Both smoker and smokeless tobacco user	19.4%(n = 86)

sion, mean values of B.P and the prevalence of systolic and diastolic hypertension in the population are shown in Table 4. No statistically significant difference was seen in prevalence of any risk factor among exclusive smokeless tobacco user and non user population. Mean systolic and diastolic blood pressure were higher in exclusive smokeless tobacco user population as compared to the non users. Prevalence of systolic hypertension was higher in exclusive smokeless tobacco consumers as compared to non users. However this difference was not statistically significant (p value = 0.39). The Odds Ratio adjusted to age, BMI, exercise and family history of hypertension for systolic Hypertension among the exclusive smokeless tobacco users was found to be 1.4(95% C.I. = 0.8-2.7). The prevalence of diastolic hypertension was found to be significantly higher in exclusive smokeless tobacco user male population as compared to non users of tobacco(p value = 0.01). The adjusted odds ratio for diastolic hypertension in male smokeless tobacco users was found to be 2.7(95% C.I. = 1.4-4.9)

Discussion

Smokeless tobacco consumption is associated with increased prevalence of high blood pressure in the adult male rural population. This finding is similar to some previous studies done in Indian [16-18] as well as western population [19-24]. Significantly higher prevalence of diastolic blood pressure in the smokeless tobacco users as compared to non-users corroborates with findings in previous studies [16,19]. However many studies have failed to show an association between smokeless tobacco use and hypertension [14,25-28]. This could be due to difference in subject population included in these studies. Also, differences in the study designs (cross sectional vs. prospective) and in adjustment for various confounding factors could be contributing to the variability in the results. Other possible reasons for this population based difference in the effect of smokeless tobacco on blood pressure could be due to difference in the composition of the smokeless tobacco used as well as difference in predisposition to HTN in populations of different origins. Availability of Data for Indian population, in this regard, is very limited. Studies have shown that smokeless tobacco acutely increases blood pressure and heart rate similar to tobacco smoking [20]. Acute Nicotine exposure from smoking cigarettes is a well known factor for causing adverse cardiovascular outcomes [29]. Evidence suggests that chewing tobacco leads to blood nicotine levels similar to that seen in smoking. Moreover, due to prolonged absorption, high levels of nicotine are achieved for longer durations of time. The sympathicoadrenal activating properties of nicotine and high sodium content of oral tobacco preparations could be the main contributing factors for high B.P in tobacco chewers [29]. This high content of sodium could be more contributory to the diastolic

Table 2: Demographic details of exclusive smokeless tobacco users and non users of tobacco

Baseline characteristics	Exclusive smokeless tobacco user(n = 93)	Non users of tobacco (n = 118)
Mean Age	35.4 ± 11.2 yrs	36.3 ± 13.1 yrs
age group distribution	<20: 14% 20-40: 60.2% 40-60: 16.2% >60: 9.6%	<20: 17.7% 21-40: 55.9% 41-60: 15.2% >60:16.1%
Marital Status	Married: 77.4% Unmarried:22.6%	Married: 72.2% Unmarried: 27.8%
Literacy	<5 yrs: 62.3% 6 yrs or more: 38.7%	<5 yrs: 52.4% 6 yrs or more: 48.6%
Occupation	Farmer: 21.1% Factory worker: 20.2% Laborers: 25.3% Students: 5.2% Other: 25.1%	Farmer: 23.2% Factory worker: 15.5% Laborers: 11.4% Students: 10.3% Others: 36.3%

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Table 3: Logistic regression analysis of exclusive smokeless tobacco consumption and demographic characteristics

Characteristic	Chi square	Odds ratio for exclusive ST consumption	P value
Age: <45 (RC) >45	0.034	0.91(0.36-2.28)	0.85
Marital status Unmarried(RC) Married	0.797	1.33(0.71-2.50)	0.37
Literacy: < 5 yrs of Education(RC) >5 yrs of Education	6.85	0.48(.27-0.83)	0.009
Occupation: Unskilled/Semiskilled (RC) Others	6.01	0.49(0.27-.87)	0.014

P value < 0.05 is considered significant. RC: reference category; Unskilled and semi skilled workers include farmers, daily laborers, and factory workers

blood pressure than systolic as shown in our study results. Further studies are warranted to gain insight and understanding of this matter.

Limitations

This study included the study population of one village only, thus leading to some degree of selection bias. Differences in dietary habits of the subject, like amount of salt intake, have not been taken into account which could be a potential confounding factor. Also, recall bias could have been there in self reporting of illnesses by the subjects.

Conclusion

An increased prevalence of high blood pressure is seen amongst asymptomatic males who are exclusive smokeless tobacco users. This is an indicator of increased predisposition to major adverse cardiac events later in their life time. Prevention of Smokeless tobacco consumption could be an important intervention in preventing the

Table 4: Comparison of blood pressure and other relevant parameters among exclusive smokeless tobacco users and nonusers

	Exclusive ST user (N = 93)	Non user of tobacco (N = 118)	O.R.* (95%C.I)	P value
Mean body weight (Kg)	51.8 ± 10.4	53.2 ± 12.5	-	0.386
Family history of HTN	5.4% (n = 5)	6.77% (n = 8)	-	0.779
regular exercise	12.9% (n = 12)	11.86% (n = 14)	-	0.835
Mean systolic B.P(mmHg)	139.2 ± 17.4	135.7 ± 18.8	-	0.16
Mean diastolic B.P(mmHg)	86.8 ± 11.5	82.6 ± 11.5	-	0.01
Systolic HTN prevalence	43% (n = 40)	36.4% (n = 43)	1.4 (0.8-2.7)	0.39
Diastolic HTN prevalence	40.9% (n = 38)	22.9% (n = 27)	2.7 (1.4-4.9)	0.0018

Mean systolic and diastolic blood pressures in exclusive smokeless tobacco users and non users of tobacco along with prevalence of systolic, diastolic hypertension, and other associated variables in the population

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ongoing upswing in prevalence of chronic heart disease that is threatening to engulf every region of the world.

Abbreviations

ST: smokeless tobacco; BP: Blood pressure.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

This study was done as a part of curriculum for final year of medical school by students of 2003 MBBS batch of All India Institute of Medical Sciences. AP and NP contributed equally to the study. They were involved in the study designing, literature review, data collection, and analysis and manuscript preparation. MS, KS, AKV were involved in data collection and data analysis part of the study. SS was involved in data analysis and manuscript writing. SP was involved in supervision of the study and helped with designing the study. All the authors have read and approved the final manuscript.

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Original Article

Cardiovascular Risk Factors in Tobacco-chewers: A Controlled Study

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Abstract

Background : Influence of habitual tobacco chewing on cardiovascular risk has not been well studied. To determine prevalence of major cardiovascular risk factors in subjects who habitually chew tobacco we performed a controlled study.

Methods : A population based case-control study was performed in Bikaner in North-western India where the prevalence of tobacco-chewing is high. Successive 200 subjects who agreed to participate in the evaluation and had a history of isolated tobacco-chewing (range 10-60 years) were enrolled (Group III). The prevalence of major coronary risk factors- obesity, truncal obesity, hypertension, fasting hyperglycemia, and lipid levels were estimated using current guidelines. Electrocardiogram was also performed in all subjects. Chest radiography and treadmill stress test was done in subjects when indicated by symptoms. 200 age- and gender-matched controls who did not use tobacco in any form (Group I) and 200 subjects who had history of smoking bidis or cigarettes for more than 10 years (range 10-55 years) (Group II) were also evaluated.

Results : The body-mass index and obesity were lowest in smoker group. Tobacco chewers had a significantly higher ($p<0.001$) systolic blood pressure (BP), diastolic BP, resting heart rate, total cholesterol, LDL cholesterol and triglycerides as compared to controls and was similar to smoker group. There was a significantly greater ($p<0.01$) prevalence of hypertension, hypercholesterolemia, hypertriglyceridemia, radiographic cardiomegaly and positive stress test in Group III as compared to controls. Prevalence of these risk factors was similar among Group II and Group III subjects. HDL cholesterol levels were the lowest in tobacco-chewing group (44.3±8.1 mg/dl) as compared to the Group I (48.4±7.8) and Group II (47.4±7.5) ($p<0.001$).

Conclusions : There is a significantly greater prevalence of multiple cardiovascular risk factors obesity, resting tachycardia, hypertension, high total and LDL cholesterol, and low HDL cholesterol, and electrocardiographic changes in tobacco users, chewing or smoking, as compared to tobacco non-users. Chewing tobacco is associated with similar cardiovascular risk as smoking. ©

Introduction

According to the World Health Report (2002) tobacco is the most important preventable cause of overall mortality as well as cardiovascular mortality worldwide.[1] While cigarette smokers are found worldwide smokeless tobacco use is restricted to certain geographic areas.[2] Tobacco use is widely prevalent in India and many developed countries. Multiple studies have reported that all forms of tobacco use (smoked, smokeless and other forms) is highly prevalent in youth and adult and in both men and women in India.[3] Tobacco chewing is a unique habit of Indian subcontinent and is consumed in form of *pan, gutka, mawa, khaini, mainpuri*, etc. Because of its easy availability tobacco chewing is rapidly increasing and affecting all age groups, genders and has become a major public and social health concern. It is roughly estimated that about 5 to 10 million people are tobacco-laced *pan masala* addicts in India.[4]

Cigarette smoking is a major risk factor for coronary heart disease and ischaemic stroke, lung cancer, chronic obstructive lung disease and premature morbidity and mortality.[5] In India smoking has been correlated with increased mortality from pulmonary tuberculosis.[6] Nicotine is one of the important substances present in tobacco and has direct toxic effects on cardiovascular system.[5,7] Tobacco chewing is well known to increase risk of oral and gastrointestinal cancers but whether it increases the risk of cardiovascular diseases is not well studied.[4] To study the cardiovascular risk factor profile in subjects chronically exposed to chewing tobacco and to compare the risk factors in smokers and control subjects we performed a study.

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METHODS

The study was approved by the institutional ethics committee and was conducted in the department of medicine, SP Medical College and Associated Group of Hospitals, Bikaner, Rajasthan. Fifteen health check-up camps were organised in the city of Bikaner in years 2001 and 2002 to evaluate cardiovascular risk factors in community. Preliminary talks were held with local community leaders who were explained the aims, objectives and methodology of the study. Volunteers who agreed to use of chewing tobacco and non-smokers, smokers who did not chew tobacco and non-tobacco users were invited for participation in the study.

Successive subjects who consumed tobacco in chewable form (*gutka, paan, khaini*, are the most popular forms in this region) for more than 10 years were included in the study. These subjects did not use smoke and were not suffering from any major illness. The prevalence of risk factors in these subjects was compared with smokers of more than 10 years (cigarette or *bidis*) who did not consume chewable tobacco (n=200), and healthy controls (n=200). Exclusion criteria were subjects with history of alcohol intake, ingestion of recreational drugs or any drug with cardiovascular effects. Patients with known diabetes mellitus, renal disease, hepatic disease or endocrinal disorder were also excluded from the study.

After taking consent the subjects were advised to report to the camp site after 8 hours fasting and abstaining from tobacco use in any form. All the subjects were evaluated with detailed history, complete general and cardiovascular physical examination, and fasting blood sample for glucose, urea, creatinine, cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol. Electrocardiogram was also performed in all subjects. Chest radiography and treadmill stress test was done in subjects when indicated by symptoms.

Cardiovascular risk factors were compared in 200 successive subjects who agreed to consume chewing tobacco and not smoking for more than 10 years (Group III), with 200 subjects who did not chew tobacco but smoked tobacco in any form (Group II), and 200 subjects who did not consume tobacco in any form (Group I).

Statistical analysis: Numerical variables are reported as mean ± 1 SD and ordinal variables in percent. Unpaired t-test or chi-square test were used to compare two groups while analysis of variance and chi-square tests were used to compare multiple groups. P value less than 0.05 was considered significant.

RESULTS

The baseline demographic variables are shown in Table 1. The groups were matched for age and gender distribution. Among smoker Group II, the average consumption of cigarette/*bidis* per day was 18.5/day (range 10-40/day) and mean duration of smoking was 23.4 years (range 10-55 years). In Group III subjects, the average consumption of tobacco was 5.7 g/day (range 3-20 g) and mean duration of tobacco use was 21.1 years (range 10-60 years). There were no significant differences in the socioeconomic status and educational status of the subjects. The prevalence of leisure-time physical activity was lower in smokers and tobacco chewers although this was not statistically significant. Significantly greater tobacco using subjects agreed to family history of tobacco use. Although no subject presented with any symptom, upon direct questioning many subjects agreed to symptoms of chest pain (17%, 32.5%, 39%), breathlessness (2.5%, 15%, 13.5%), abdominal pain (0.5%, 1%, 5%), backache (1%, 4%, 3%), headache (1.5%, 2%, 5%), palpitations (1.5%, 5%, 6%)

Table 1 : Demographic profile of the study subjects

Variable	Control Group N=200	Smokers N=200	Tobacco Chewers N=200	P value
Age (yr)	46.8±13.3 (Range 25-76)	48.5±12.2 (Range 25-70)	46.8±13.0 (Range 23-70)	0.312
Male : Female	163/37 (4.4:1)	173/27 (6.4:1)	161/39 (4.1:1)	
Married	194 (97.0)	198 (99.0)	192 (96.0)	0.234
Socioeconomic status				0.976
High	3 (0.2)	3 (0.2)	3 (0.2)	0.848
Middle	69 (34.5)	63 (31.5)	71 (35.5)	
Lower middle	95 (47.5)	94 (47.0)	98 (49.0)	
Lower	33 (16.5)	40 (20.0)	28 (14.0)	
Educational Status				
Illiterate	33 (16.5)	47 (23.5)	32 (16.0)	0.081
Primary	35 (17.5)	46 (23.0)	32 (16.0)	
Secondary	73 (36.5)	55 (27.5)	77 (38.5)	
College	59 (29.5)	52 (26.0)	59 (29.5)	
Family history of tobacco use	66 (33.0)	120 (60.0)	114 (57.0)	0.002*
Leisure-time physical activity	45 (22.5)	35 (17.5)	33 (16.5)	0.402

Numerical values are mean ± 1SD. Numbers in parentheses are percent. * significant.

and recurrent stomatitis (0%, 1%, 6%). As compared to control subjects in Group I, in Group II and Group III subjects the symptoms of chest pain (34 vs. 63 vs. 78, $p<0.01$), breathlessness (5 vs. 30 vs 27, $p<0.01$), headache (3 vs. 4 vs. 10, $p<0.05$) and palpitations (3 vs. 10 vs. 12, $p<0.05$) were significantly greater.

The mean body-mass index (BMI) was significantly lower in smokers (22.1±4.4 kg/m2) as compared to controls (24.6±6.9) and tobacco chewers (24.4±4.2) (Table 2). The waist-hip ratio was similar in all the three groups and there was no difference in the prevalence of truncal obesity. Mean systolic BP and diastolic BP were the lowest in control subjects and were significantly greater and identical in Groups II and III. Systolic BP was 129.0±14.7 mm Hg in Group I, 133.5±14.1 in Group II and 131.5±17.1 in Group III and diastolic BP was 82.4±10.7, 85.4±7.7 and 87.0±9.8 mm Hg respectively ($p<0.01$ on within group and inter-group comparison). Prevalence of systolic as well as diastolic hypertension was also significantly greater in Group II and III subjects as compared to controls. Resting tachycardia was also significantly greater in Group II and III subjects (Table 2).

Biochemical variables are shown in Table 3. There was no significant difference in mean fasting blood glucose levels. Mean levels of total cholesterol, LDL cholesterol and triglycerides were significantly greater and not significantly different in Group II and Group III subjects as compared to controls ($p<0.001$). Levels of HDL cholesterol were not significantly different. Prevalence of hypercholesterolemia and hypertriglyceridemia was also significantly greater in tobacco consuming groups. Prevalence of abnormal electrocardiograms as well as coronary heart disease diagnosed by Rose-questionnaire angina or ECG changes (Q-waves, ST segment changes, T-wave changes) was also greater in Group II and III subjects as compared to controls. Radiographic cardiomegaly was seen more frequently in Group II

Table 2 : Cardiovascular risk factors

Variable	Control Group N=200	Smokers N=200	Tobacco Chewers N=200
Weight (Kg)	66.5±12.9	61.0±13.6**	66.2±12.4
Height (Meters)	1.65±0.1	1.66±0.1	1.68±0.1
Body-mass index (Kg/m²)	24.6±6.9	22.1±4.4**	24.4±4.2
Overweight/obesity. BMI ≥25 Kg/m²	80 (40.0)	44 (22.0)**	78 (39.0)
Waist:hip ratio	0.91±0.1	0.92±0.4	0.90±0.1
Truncal obesity. WHR >0.9 (men), >0.8 (women)	119/163; 33/37 (76.0)	140/173; 27/27 (83.5)	118/161; 37/39 (77.5)
Systolic BP mm Hg	129.0±14.7	133.5±14.1**	131.5±17.1*
Diastolic BP mm Hg	82.4±10.7	85.4±7.7**	87.0±9.8**
Systolic HTN (≥140 mm Hg)	50 (25.0)	90 (45.0)**	74 (37.0)*
Diastolic HTN (≥90 mm Hg)	58 (29.0)	96 (48.0)*	103 (51.0)**
Heart rate (per min)	79.9±6.7	79.4±10.6	81.5±11.4
Tachycardia >90/min	13 (6.5)	38 (19.0)**	36 (18.0)**

BMI body-mass index; WHR waist-hip ratio; BP blood pressure; HTN hypertension; ECG electrocardiogram. Numerical values are mean ± 1SD. Numbers in parentheses are percent. * $p<0.05$, **$p<0.001$ (Statistical comparison between control and smokers or tobacco chewers)

Table 3 : Lipids and other biochemical factors

Variable	Control Group N=200	Smokers N=200	Tobacco Chewers N=200
Glucose (fasting) (mg/dl)	82.3±9.4	80.3±9.6	83.2±4.4
Cholesterol (mg/dl)	169.4±28.5	186.0±39.2**	182.0±42.1**
High cholesterol ≥200 mg/dl	30 (15.0)	66 (33.0)**	57 (28.5)**
LDL cholesterol (mg/dl)	99.1±28.1	115.9±38.5**	114.1±36.9**
High LDL cholesterol ≥130 mg/dl	22 (11.0)	64 (32.0)**	56 (28.0)**
HDL cholesterol (mg/dl)	48.4±7.8	47.4±7.5	44.3±8.1**•
Low HDL cholesterol <40 mg/dl	34 (17.0)	34 (17.0)	56 (28.0)**
Triglycerides (mg/dl)	105.4±29.1	122.5±50.6**	116.0±43.8**
High triglycerides ≥150 mg/dl	18 (9.0)	50 (25.0)**	41 (20.5)**
Urea (mg/dl)	25.1±4.2	23.9±16.9	25.1±4.2
Creatinine (mg/dl)	0.75±0.8	0.77±0.5	0.79±0.3
Abnormal ECG	22 (11.0)	42 (21.0)*	34 (17.0)
Coronary heart disease	8 (4.0)	16 (8.0)	5 (10.0)*
Positive stress test	6/44 (13.6)	20/67 (29.8)*	15/62 (24.2)*

LDL low density lipoprotein; HDL high density lipoprotein. Numerical values are mean ± 1SD. Numbers in parentheses are percent.
* $p<0.05$, ** $p<0.001$ (Statistical comparison between control and smokers or tobacco chewers)
• $p<0.003$ (Statistical comparison between smokers and tobacco chewers)

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and Group III although the numbers of subjects where radiographs were obtained was small. Treadmill stress test using standard Bruce protocol was performed in 44 subjects in Group I, 67 subjects in Group II and 62 subjects in Group III. As compared to control Group I (6 subjects, 13.6%), the treadmill stress test was indicative of ischemic response (ST depression >1.0 mm in ≥ 2 leads) in a significantly greater proportion of subjects in Group II (20 subjects, 29.8%) and Group III (15 subjects, 24.2%) ($p<0.01$).

Statistical comparison of various parameters shows greater prevalence of various cardiovascular risk factors in tobacco users, smokers or chewers as compared to tobacco non-users but the comparison between tobacco chewers and smoker was found to be insignificant statistically except in HDL where we found significantly low values of HDL in tobacco chewers as compared to smokers ($p<0.003$) (Table 4).

Table 4 : Odds ratios of abnormal values of various cardiovascular risk variables

Variable	Control v/s Smokers	Control v/s Tobacco chewers	Smokers v/s Tobacco Chewers
BMI	0.4230	0.9590	0.4415
Waist hip ratio (males)	1.5686	1.0146	1.5459
Heart rate	3.3741	3.1575	1.0685
Systolic BP	2.4545	1.7619	1.3931
Diastolic BP	2.2599	2.5997	0.8693
Total cholesterol	2.7910	2.2587	1.2356
LDL	3.8074	3.1464	1.2100
HDL	1.0000	1.8986	0.5266
Triglyceride	3.3703	2.6072	1.2926

Discussion

The habit of chewing tobacco is increasing because of its free availability, cheaper cost and increasing education about well established hazards of smoking. Studies have confirmed that use of smokeless tobacco is as harmful as smoked tobacco.[7] Chewing tobacco could result in significantly greater deleterious cardiovascular effects due to a larger overall exposure owing to prolonged absorption.[8,9]

Gajalakshmi *et al*[6] performed a large case-control study in Chennai recently and reported that tobacco is a major risk factor for mortality. Gupta *et al* performed[10] a prospective cohort study of tobacco use and mortality in Mumbai and found similar results. Our study shows that tobacco-chewers are at a high risk of mortality from cardiovascular diseases due to greater prevalence of multiple cardiovascular risk factors.

In the present study it is observed that tobacco chewing as well as smoking was more prevalent among the lower socioeconomic status subjects (Table 1). There was also a greater incidence of family history of tobacco use among these groups. This is similar to previous Indian studies.[11,12] The BMI in smokers was significantly lower as compared to tobacco chewers and non-smokers. This could be due to the fact that chewing tobacco does not interfere with eating as much as smoking does and the subjects that chew tobacco may have different eating habits. We have not inquired dietary details of the study subjects and cannot comment on this aspect. Systolic as well as diastolic BP was greater in tobacco consuming groups although the diastolic BP was significantly greater in tobacco chewers. This could be due to a more prolonged absorption of tobacco when chewed accompanied with more prolonged vascoconstriction. Greater sodium content of smokeless tobacco may also be a contributing factor. Greater hypertension and mean BP levels among cigarette and bidi smokers has been reported from India and association of non-smoked tobacco with hypertension is recognized.[13,14] Both smokers as well as tobacco chewers have a higher total and LDL cholesterol and triglyceride levels as compared to controls. Dietary factors to explain this difference need further studies. The higher levels of cholesterol and triglycerides in tobacco chewers may be attributed to tobacco induced stimulation on metabolism of free fatty acids in peripheral tissue.[5] Similar findings have been reported earlier.[15]

The World Health Report (2003)[16] concludes that consumption of tobacco products are the world's leading preventable cause of death, responsible for about 5 million deaths a years mostly in poor countries and poor populations. The toll will double in 20 years unless available and effective interventions are urgently and widely adopted.

Removal of major risk factors such as tobacco could increase healthy life expectancy in every region of the world and would reduce the differences between different regions.[17] 20 major risk factors for ill-health and death contribute globally to 47% of premature deaths and 39% of total disease burden in the year 2000.[18] Removal of these risk factors which includes tobacco addiction would increase global healthy life expectancy by 9.3 years (17%) ranging from 4.4% (6%) in the developed countries and 16.1 years (43%) in developing countries of Africa.

We also found a significantly greater prevalence of multiple cardiovascular risk factors obesity, resting tachycardia, hypertension, high total and LDL cholesterol, and low HDL cholesterol, and electrocardiographic changes in tobacco users, chewing or smoking as compared to tobacco non-users. Chewing tobacco is associated with similar cardiovascular risk as that of smoking. Tobacco use in any form should be the major area of concern in India and elsewhere.

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Book Review

Yoga Book for Doctors

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Antar Prakash Centre for Yoga
Email: prakashmalshe@rediffmail.com

Price (Paperback): Rs.120/-
(Hard bound): Rs.140/-

Yoga is currently much discussed and debated in both the print and electronic media. Reactions of the medical profession on health, utility range from positive to extremely negative with enormous skepticism. Many of the attitudes could result from lack of adequate exposure to underline physiological facts pertaining to yogasanas.

Dr. Prakash C. Malshe, a physician himself has chosen, after learning initial steps from Swami Adhyatmanand ji and practice for around two decades, to share with the medical fraternity the facts that are useful focusing on the physical aspects of yoga without feeling compelled to pursue the higher spiritual goals, i.e. the enlightenment.

The book is suitably divided into 9 chapters commencing with normal human physiology followed by Prayer, Asanas, Pranayams and Internal Cleansing processes. There are photographs of actual performance postures and original Sanskrit quotations with appropriate English translations that follows. There is reference to common lifestyle diseases such as Diabetes Mellitus, Hypertension, Ischaemic Heart Disease.

The author has stated that this book is an attempt to scientifically validate the facts about yoga that so fare we have just believed in; and provide clear idea what a particular asana, mudra or pranayama can do; and how. In this handy form and for the uninitiated, I must say that he has succeeded.

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Annexure 87

LIPPINCOTT
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EUROPEAN
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Review Paper

Is smokeless tobacco a risk factor for coronary heart disease? A systematic review of epidemiological studies

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Background There is on-going debate about the wisdom of substituting smokeless tobacco products for cigarette smoking as a 'harm reduction' strategy. It is generally believed that health risks associated with smokeless tobacco use (ST) are lower than those with cigarette smoking. However, the population attributable risk of smoking is higher for cardiovascular diseases than for any cancers, and few studies or reviews have considered the cardiovascular outcomes of ST use. A systematic review was therefore carried out to highlight the gaps in the evidence base.

Methods Electronic databases were searched, supplemented by screening reference lists, smoking-related websites, and contacting experts. Analytical observational studies of ST use (cohorts, case–control, cross-sectional studies) were included if they reported on cardiovascular disease (CVD) outcomes, or risk factors. Data extraction covered control of confounding, selection of cases and controls, sample size, clear definitions and measurements of the health outcome and ST use. One or two independent reviewers carried out selection, extraction and quality assessments.

Results A narrative review was carried out. Very few studies were identified; only three from Sweden consider CVD outcomes and these are discrepant. There may be a modest association between use of Swedish snuff (snus) and cardiovascular disease (e.g., relative risk=1.4, 95% confidence interval 1.2–1.6) in one prospective cohort study. Several other studies have considered associations between ST use and intermediate outcomes (CVD risk factors).

Conclusions There may be an association between ST use and cardiovascular disease. However, further rigorous studies with adequate sample sizes are required. *Eur J Cardiovasc Prevention Rehab* 11:101–112 © 2004 The European Society of Cardiology.

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Keywords: cardiovascular disease, smokeless tobacco, smoking, systematic review

Introduction

Coronary heart disease (CHD) is the most common cause of death in the UK, and many developed countries [1]. It is projected to be the single leading cause of death and disability worldwide by 2020 [2]. The major risk factors for CHD are smoking, high blood pressure, high cholesterol levels, and lack of physical activity. Estimates of relative risk (RR) for smoking and CHD vary between studies, but tend to be between 1.5 and 3.0 [3,4].

The biological mechanisms through which smoking causes CHD are still debated. Smoking appears to increase CHD risk primarily through thrombosis (blood clotting) [5], but may also influence atherosclerosis [6,7]. Evidence suggests that the blood nicotine levels from smokeless tobacco (ST) use are similar to those of smoking [8]. Nicotine itself has been shown to have acute and systemic cardiovascular effects [9–12], but other aspects of tobacco smoke may be more responsible for oxidative damage [13].

Smoking 'harm reduction'

There is increased interest in the concept of 'harm reduction', persuading resistant smokers to reduce their smoking levels [14], or to switch

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to alternative less harmful products [15]. Nicotine addiction is the main hurdle to quitting smoking among those motivated, hence swapping to another less harmful form of nicotine delivery may benefit public health [16].

What is ST and how is it used?

Smokeless tobacco is tobacco consumed orally and not smoked, and includes moist oral snuff, chewing tobacco, and tobacco used with betel quid, areca nut, and other ingredients [17–19]. Its use increased in the latter half of the twentieth century in certain countries [19], particularly the US and Sweden (where 20% of young males use snuff) [20]. Forms of ST are also very commonly used in the Indian sub-continent [21].

Population attributable risks of tobacco use and cardiovascular disease

Recent Swedish studies have not found high risks of cancers associated with oral moist snuff use, but the incidence of oral cancers is very low [22]. In contrast, the incidence of cardiovascular diseases is very high [1] and increasing in many countries [2,23], and the population attributable risk of cigarette smoking is higher for cardiovascular disease than for most cancers [24–26]. Smokeless tobacco contains many of the same potentially noxious substances (nitrosamines and nicotine) as smoked tobacco. The potential cardiovascular health risks of ST use have been overlooked to date. A systematic review was therefore carried out to summarize and highlight gaps in the knowledge base. This review expands on a larger report, which considered a range of health effects associated with ST use [27].

Methods

Criteria for considering studies for this review

Study types

Analytical epidemiological studies (prospective and retrospective cohort, case–control and cross-sectional studies) were included. These must contain users of a form of ST and a group who use no tobacco products or smoke cigarettes only.

Outcome measures

Studies reporting on cardiovascular disease outcomes were included. Studies reporting on 'intermediate' outcomes (cardiovascular risk factors) such as blood pressure or lipid levels were excluded from the original review [27], but have been reported here for completeness.

Exclusions

The 'acute' effects of nicotine and tobacco on the cardiovascular system, including increases in blood pressure and heart rate, have been well-described elsewhere [13,28–35].

Search strategy for identification of primary studies

A comprehensive search strategy was developed, as part of a larger review [27]. This included electronic databases, websites, contact with experts, and checking reference lists. A few non-English language studies were identified, but not included (appendices available from author on request).

Results of searches

Each of the 2923 records identified were scanned by at least one reviewer to identify potentially relevant studies. A conservative approach was utilized i.e., all papers were retrieved unless sufficient details were available to decide the study was definitely not relevant. A second reviewer independently screened the first 1557 articles (from MEDLINE) to double-check and minimize errors. Agreement between the two reviewers was high (kappa = 0.74) (see Figure 1 for a summary of study searching, inclusion, data extraction and quality assessment). The inclusion criteria and data extraction forms were developed for the review, adapted from a form used previously [36], and pilot tested. Once initially identified, two reviewers extracted data from included studies.

Assessment of methodological quality

Unlike for randomized controlled trials, there are no generally accepted lists of appropriate quality criteria for observational studies [37] and there is little empirical research relating aspects of study quality to results [38]. Specific aspects of quality, such as control of confounding factors, selection of cases and controls, sample size, clear definitions of the CHD and ST use, evidence of a dose–response relationship were therefore detailed for each study. Table 1 describes each study in the order of reference.

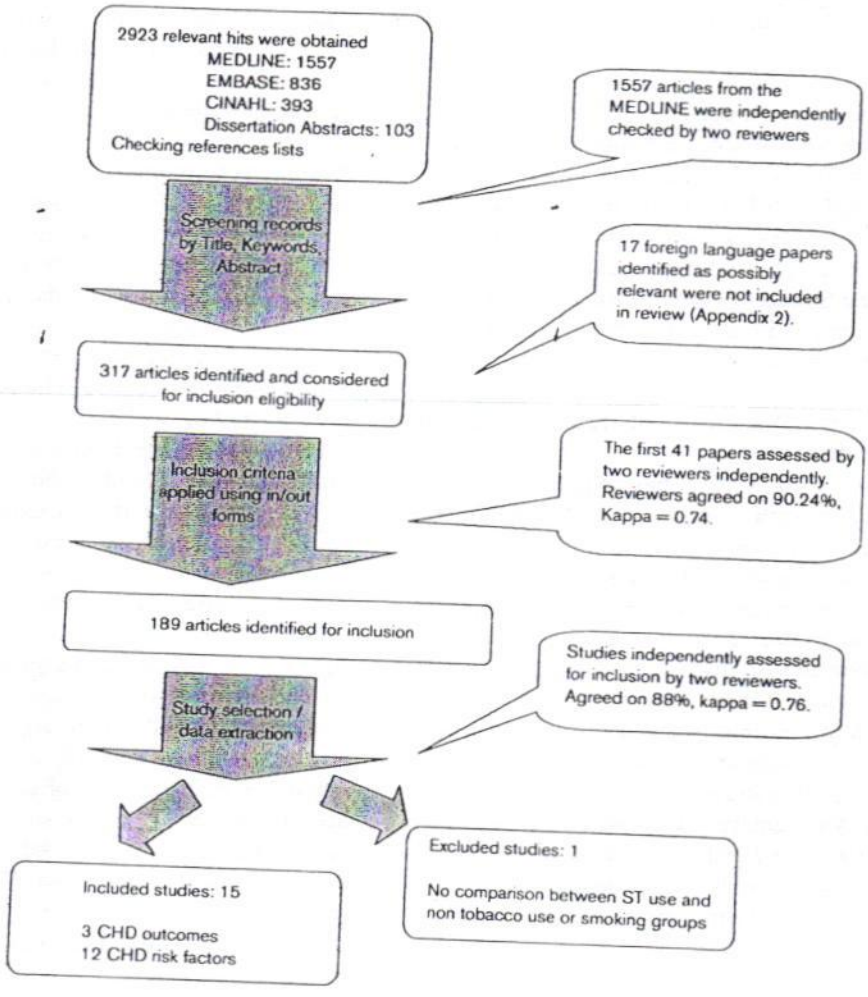
Results

Studies of cardiovascular disease outcomes

Prospective cohort study

One cohort study of ST use and cardiovascular disease was carried out in several different regions of Sweden. Bolinder *et al.* [39] followed up Swedish construction workers (135,036 men) for mortality outcomes from cardiovascular disease (CVD) and other causes for 10 years. The ST use was defined as current use of ST only and ST users were never-smokers. Also, cigarette smokers did not use any other forms of tobacco. Across all age groups, there was a 40% excess risk of both CVD death and all-cause mortality among ST users [RR = 1.4, 95% confidence interval (CI) 1.2–1.6 for all CVD; RR = 1.4, 95% confidence interval (CI) 1.3–1.8 for all cause mortality]. Among younger men aged 35–54, the age and regional origin-adjusted RR of ST use for CHD mortality was 2.0 (95% CI 1.49–2.9); for stroke, the RR was 1.9 (95% CI 0.6–5.7), and for all CVD deaths the RR was 2.1 (95% CI 1.5–2.9). There were no statistically significant associations between ST and CVD in the older

Fig. 1



Flowchart of search and selection strategy. CHD, coronary heart disease; ST, smokeless tobacco.

(55–64) age group, and the authors suggest this may be 'a healthy worker effect'. Equally, this may result from 'selective mortality' (earlier deaths among snuff users) or simply chance.

Most of the major CVD risk factors [age, body mass index (BMI), blood pressure, diabetes and history of heart symptoms or blood pressure medication at the time of entering study] were taken into account in these estimates, except cholesterol and alcohol use. Relative risks were not altered after control of these confounders (though no numerical data is shown).

We calculated the population attributable risks (PAR) for snus use and cigarette smoking using RR estimates from this study, and estimates of prevalence of cigarette smoking and snus use among men in Sweden [40]. This suggests that roughly twice as many cardiovascular disease deaths could be attributed to cigarette smoking, compared with snuff use, however 95% CIs are wide and almost overlap (Table 2).

Case–control studies

Two case–control studies of CVD were included [41,42]. Both recruited cases from the MONICA (Monitoring Outcomes in Cardiovascular Disease) Sweden Project, but the authors state that participants were different in each study. The first paper used group-matched population controls [41]. Snuff dippers had no increased risk of myocardial infarction (MI) compared to non-tobacco users (see Table 1). No dose–response relation was

Table 1 Description and quality assessment of studies

Study and type of ST	Subjects, setting and years of recruitment	Sample size and number of ST users	Measurement of exposure, outcomes and confounders	Findings or results	Comments
Cardiovascular disease outcomes: prospective cohort study					
Bolinder, 1994 [39] ORAL SNUFF USE	Swedish construction workers who had health check-ups in 1971–1974.	135 036 workers. Women workers (less than 0.05%) were excluded from the study. 1672 of those aged 35–54 years and 1734 of 55–65 years were ST users. In total, there were 6297 ST users, 14 983 smokers of <15 cigarettes per day, 13 518 smokers of >15 cigarettes per day. 6761 recent ex-smokers (quit smoking 1–5 years previously) and 9800 ex-smokers who quit more than 5 years previously. There were 32 546 non-users of tobacco.	ST use was defined as present ST usage to reduce misclassification. Non-users in this study had never used any tobacco. ST users had never smoked. Cigarette smokers did not use any other tobacco forms. Outcomes clearly defined with ICD codes. Most of CVD risk factors adjusted for ST-outcome association except cholesterol and alcohol use. Also age and regional origin adjusted.	**Age group 35–54** RR of ST use for IHD: RR = 2.0, (95% CI 1.49–2.9). Stroke: RR = 1.9 (95% CI 0.6–5.7). All CVD: RR = 2.1 (95% CI 1.5–2.9). All cancer: RR = 1.2 (95% CI 0.8–1.9). All cause RR = 1.9 (95% CI 1.6–2.4). **Age group 55–65** Adjusted RR of ST use for IHD: RR = 1.2 (95% CI 1.0–1.5). Stroke: RR = 1.2 (95% CI 0.7–1.8). All CVD: RR = 1.1 (95% CI 1.0–1.4). All cancer: RR = 1.0 (95% CI 0.8–1.3). All cause RR = 1.2 (95% CI 1.0–1.3). **Over all age groups** RR of ST used for all CVD: RR = 1.4 (95% CI 1.2–1.6). RR smoking <15 cigarettes per day: RR = 1.8 (95% CI 1.6–2.0). RR smoking ≥ 15 cigarettes per day: RR = 1.9 (95% CI 1.7–2.2).	25% of the workers did not come for checkups, the reason is not clear. Statistical power of the study is high (in total 6297 users of ST were followed up and 172 IHD deaths occurred in this group). Healthy worker effect may play a role in ST CVD mortality association. When potential confounding due to age, area of domicile, BMI, blood pressure, diabetes and history of heart symptoms or blood pressure medication at the time of entering the study was analysed according to Mantel–Haenzel procedure, the RR of death from CVD remained essentially unchanged. *Reference category is male never users of tobacco.
Case–control studies					
Huhtasaari 1992 [41] ORAL SNUFF	First MI cases and population controls from Northern Sweden, 1989–1991.	585 cases (first MI) and 589 controls. 59 of cases and 87 of controls were regular snuff dippers. 32 cases and 31 controls were concomitant smokers and snuff users.	ST was defined clearly (at least once daily), and dose–response relation was analysed. Outcomes clearly defined (MONICA protocol). Blood pressure, cholesterol and diabetes prevalence were similar in cases and controls so they were not included in the model. Confounders adjusted for were age and smoking (by 'excluding' snuff users who also smoked). Low levels of education were also considered separately as a risk factor for MI.	Age adj. OR of snuff dipping vs. no tobacco for MI: 35–54 years: OR = 0.96 (95% CI 0.56–1.67) 55–64 years: OR = 1.24 (95% CI 0.67–2.30) All ages: OR = 0.89 (95% 0.62–1.29) Snuff dippers had no increased risk of MI compared to non-tobacco users. Snuff ≤ 2 cans weekly OR = 0.63 (95% CI 0.41–0.98). >3 more cans weekly OR = 0.93 (95% CI 0.61–1.41). In a logistic regression model for MI, with smoking, snuff dipping, low level of education, and age as predictors, snuff dipping was not significant.	The study was planned within Northern Sweden MONICA project. Cases were identified according to MONICA protocol. Controls were selected from population and they were only group matched. Response rate in controls was 81.6%. A telephone survey was conducted to check non-participants smoking habits and they were found to be similar to participants. Of the original set of case-controls 21.8% were excluded because of missing smoking information. This was common amongst the fatal case pairs. To check the validity of ST information obtained from spouses of fatal MI cases, spouses of surviving cases were interviewed by telephone 2 months later. The agreement was high for snuff use (98%). Information on duration of use was not high quality. Median age of starting snuff was 31.5 years explained by the fact that many had started snuff in conjunction with quitting smoking. Proper statistical analyses were carried out.

Huhtasaari 1999 [42] ORAL SNUFF From same study pop as Huhtasaari 1992 [41] But participants differed in each study	First MI cases and population controls from Northern Sweden, 1991–1993.	687 first MI men cases and 687 matched controls from same country. The cases were MONICA Sweden project. 59 cases and 90 controls were current snuff users and -non current smokers; 20 cases and 11 controls were both smokers and snuff users. 11 of the cases and 13 of the controls were former snuff users but non-smokers.	Detailed information about ST (present use, previous use, amount, type of preparation, age of onset and whether or not snuffing was associated with quitting smoking) obtained. Median consumption of snuff was 2 boxes per week in both cases and controls. Outcomes clearly defined (MONICA protocol) Confounders adjusted for include hypertension, low level of education, not being married or cohabitant, diabetes, known high cholesterol and heredity.	OR for different combinations of snuff user for MI: Current snuff user-non smoker: 0.96 (95% CI 0.65 to 1.41) Current smoker, no current snuff use: 3.65 (2.67–4.99) Current snuff user and smoker: 2.66 (95% CI 1.24 to 5.71) Former snuff user, never smoked: 1.23 (95% CI 0.54 to 2.82) In conditional regression model, regular use of snuff was adjusted Adjusted OR of snuff use for all MI: 0.58 (95% CI 0.35 to 0.94). Adjusted OR of snuff use for all MI: 0.58 (95% CI 0.35 to 0.94). Adjusted OR of snuff use for fatal MI: 1.50 (95% CI 0.45 to 5.03).	Of the original set of case–controls 21.8% were excluded because of missing smoking information. This was common amongst the fatal case pairs. To check the validity of ST information obtained from spouses of fatal MI cases, spouses of surviving cases were interviewed by telephone 2 months later. The agreement was high for snuff use (98%). Information on duration of use was not high quality. Median age of starting snuff was 31.5 years explained by the fact that many had started snuff in conjunction with quitting smoking. Proper statistical analyses were carried out.
'Intermediate' outcomes (cardiovascular risk factors) cross-sectional studies					
Bolinder 1992 [11] ORAL SNUFF From same study as Bolinder 1994 [39]	16–65 years old Swedish construction workers, 1971–1974.	97 586 construction workers who had voluntary health checkups. 5014 of the participants were ST users who had never been regular smokers.	ST users were daily users. Confounding: persons who had mixed tobacco habits were excluded from the analyses to increase validity, also adjusted for age.	Reason for disability pension among 46–55 years old: OR of ST use vs non-users for CVD diagnosis: 1.6 (95% CI 0.7–3.5) for hypertension: 3.0 (95% CI 1.9–4.9). Among 56–65 year olds: OR of ST use vs non-users for CVD diagnosis: 1.5 (95% CI 1.1–1.9). Age adjusted RR of 'frequent sick leave' (1 day or more for four times or more per year) for all kind of diagnosis was 1.1 (95% CI 1.0–1.2) for ST users compared to non-users. Age adjusted RR 'Longer sick leave' (30 days in a year) was 1.2 (95% CI 1.1–1.2) for ST users compared to non-users.	The aim of the study was to evaluate ST effect on blood pressure and other health hazards. In this cross-sectional study, reference group was those who had never used any tobacco form. The outcomes were questionnaire reported symptoms, physical examination and disability pension due to cardiovascular and musculoskeletal diagnoses. Healthy worker effect highly possible.
Eliasson *et al.*, 1991 [44] ORAL SNUFF	Male volunteers <31 years, recruited from University students and schoolteachers.	21 snuff dippers, 18 non-tobacco users, 21 cigarette smokers	Snuff use clearly defined (at least one can 50 g per week). Measurement of outcomes clearly described. No attempt to adjust for important confounders (see comments).	Snuff users and cigarette smokers had higher serum insulin levels. Snuff users had no significant elevations of other risk factors such as serum cholesterol or triglycerides, diastolic blood pressure (BP), haemoglobin concentration, white cell count.	Sample size is very small. Considerable lifestyle differences exist between cigarette smokers and non-tobacco users e.g., physical activity levels lower, higher alcohol and coffee consumption among tobacco users then non-users (risk profile worst for smokers, intermediate for snuff dippers, best for non-tobacco users). Also substantial social class differences – non-tobacco users and snuff dippers were male volunteers, of similar social class, but 35% of smokers were blue-collar workers.

Table 1 (*Continued*)

Study and type of ST	Subjects, setting and years of recruitment	Sample size and number of ST users	Measurement of exposure, outcomes and confounders	Findings or results	Comments
Eliasson *et al.*, 1995 [45] SNUFF DIPPING (MOIST ORAL SNUFF)	Part of MONICA project – population sample of men aged 25–64 in Northern Sweden, 1990.	604 men, of whom 92 dipped snuff regularly.	ST measurements clearly defined, snuff dippers did not use other tobacco products. Blood analyses clearly described, with overnight fasting and glucose tolerance test. Also anthropometry (BMI, WHR) & BP. Multiple regressions: predictors included age, BMI, WHR, height, cholesterol, HDL cholesterol, triglycerides, and blood pressure.	There were no differences in plasma fibrinogen, fibrinolytic variables (tPA activity, PAI-1 activity), or glucose intolerance among snuff dippers compared with non-tobacco users. Men who smoked cigarettes had higher fibrinogen levels than non-tobacco users, and evidence of a dose–response relationship was found.	Snuff use clearly defined, but limited to males only (too few female snuff users). Reasonable participation rate (79.2%). Smokers were slightly older and had a longer duration of tobacco use than snuff dippers. Potentially important confounders, such as socio-economic status, educational level, and physical activity were not considered.
Siegel *et al.*, 1992 [46] ORAL SNUFF AND CHEWING TOBACCO	1061 members of seven major league baseball teams and their associated minor league teams, Phoenix and Tucson Arizona, spring 1989.	1061, of whom 473 were ST users.	ST use included type, brand, and quantity (number of cans of snuff or pouches of chewing tobacco reportedly used per week). Self-reported use biochemically validated Heart rate and pulse measured twice, sitting. Blood samples taken. Confounding: $n=41$ cigarette smokers were excluded. Other covariates adjusted by multiple logistic regression (age, race, alcohol consumption, serum caffeine).	No significant differences between ST users and non-users in systolic or diastolic BP, pulse, total or LDL cholesterol. No dose–response relationships were found (e.g., with years of use, or hours of use per day, but data not shown). ST users had lower mean white cell counts than non-users.	The aim of the study was to evaluate ST effect on blood pressure and other risk factors. Study limited to young, fit, males (77% aged between 20 and 29). Predominantly white and well educated.
Tucker, 1989 [8] ST USE (NOT DEFINED)	Adult males who were employees of over 25 companies participating in a Health Examination Programme. Time period of study not stated.	2840, of whom 93 were ST users.	ST measurements not described, no dose–response information. Physical measurements include body fat (skin-fold callipers), physical fitness (step test), blood samples (cholesterol). M–H adjustments for age, educational level, physical fitness and smoking.	The adjusted RR of hypercholesterolaemia (defined as total cholesterol >6.2 mmol/l) was 2.51 (95% CI 1.47–2.29 for ST use). This compared with RR of 1.51 (95% CI 1.14–2.0) for smoking 1–20 cigarettes daily, and 1.98 (95% CI 1.29–3.03) for smoking >20 cigarettes daily.	ST use not defined or described. ST users were younger and less educated than non-tobacco users. Limited to males only.
Khurana *et al.*, 2000 [47] CHEWING TOBACCO (NOT DEFINED)	Patients attending 'medical outdoor', SMS Medical College and Hospital, Jaipur, India, and volunteers from society. Patients with diabetes, hypertension, renal disease, hepatic impairment, endocrine disorders, alcoholics, menopausal women, and those on certain medications all excluded. No other details given.	30 current smokers, 30 current tobacco chewers (both of >10 years duration), 30 non-smokers and non-chewers.	Methods of measuring lipid profiles clearly described. No details of types of tobacco chewers. No information on confounding – states no significant difference in mean age between groups, that participants ate 'average India diet', and had body weight 'in normal range'.	Current smokers had significantly lower HDL (high density lipoprotein) than non-smokers, and significantly higher VLDL (very low density lipoprotein) and TG (triglycerides). TC (total cholesterol) and LDL (low density lipoprotein) were both also higher among smokers, but the difference was not statistically significant. Tobacco chewers also had significantly lower HDL, and significantly higher VLDL and TG. For example, HDL was 39.80 ± 5.62 in smokers, 37.55 ± 5.81 in chewers, and 44.38 ± 3.86 in non-tobacco users. Similarly, TG was 154.44 ± 43.98 in smokers, 160.33 ± 47.76 in chewers, 96.49 ± 25.78 in non-tobacco users. There were no statistically significant differences between smokers and tobacco chewers.	Sample size small (30 in each of three groups), unclear precisely how patients and volunteers were selected. Very little information provided on these participants (no information on sex, very limited information on age, and other potential confounders). Validity of results is therefore questionable.

Bolinder *et al.*, 1997 [48] SNUFF USE	Male firemen aged 35–60 years.	143, of whom 28 were long-term ST users, 40 never-users of tobacco, and 29 smokers.	ST user clearly defined (daily use for more than 6 months). Outcome: ultrasonographic examination of carotid artery clearly described and carried out blind to tobacco use status. Annual compulsory fitness test, BP, blood analyses. Confounders considered included biochemical risk factors, age, BMI, blood pressure.	Snuff users did not differ significantly from those who had never used tobacco, in terms of intima medial wall measurements or lumen diameters of common carotid or bulb area. Significant increases in wall thickness were found for smokers. Plaques were found in two ST users and no never-users, but this difference was not significant.	Small sample size–biochemical risk factors (serum cholesterol, LDL cholesterol, triglycerides, fibrinogen) all tended to be slightly higher (and HDL cholesterol lower) among ST users compared with never-users, but differences not statistically significant.
Bolinder *et al.*, 1997 [51] ORAL SNUFF	Male firemen aged 35–60, Stockholm City.	144, of whom 50 were ST users, 68 non-tobacco users, and 33 smokers.	ST use clearly defined, as above. Graded exercise test on a bicycle ergometer, until exhaustion. Continuous recording of HR, ECG respiratory rate, O_2 uptake and CO_2 production, and respiratory rates. Fasting blood sample. Test results adjusted for differences in age, BMI, WHR, alcohol, physical training, occupational physical activity.	No significant differences in maximal work or oxygen uptake for ST users compared with non-tobacco users. Smokers performed significantly worse in terms of maximal workloads and oxygen uptake. For example VO_2 max (mL/min/kg) for non-users was 3.51 ± 0.51, 3.48 ± 0.49 for ST users, and 2.88 ± 0.49 for cigarette smokers. No dose–response relationships observed with quantity of tobacco used for ST users, but in smokers a statistically significant negative correlation between maximal workload and number of cigarettes smoked per day was observed.	Study population may overlap with the study above, Bolinder *et al.*, 1997 [55]. 'Healthy worker' effect is possible: it may be harder to investigate potentially deleterious effects of ST use among healthy and physically fit males.
Schroeder and Chen, 1985 [52] TYPES OF ST NOT DESCRIBED	Volunteers, not specified.	1663 volunteers over 18, 710 males, 923 females. 69 males were ST users, but blood pressure reported for only 19 males aged 18–25.	Not described	Mean BP of 19 current male ST users was 143.7/80.7 mmHg, 23 male cigarette smokers 127.7/70.0 mmHg, non-users of tobacco 131.6/72.8 mmHg. This was statistically significant for tobacco users combined versus non-users (7.9 mmHg, $P < 0.01$), but no significance test was carried out for ST users versus non-tobacco users.	Letter only–very limited details. Unclear why analyses limited to those aged 18–25, which much reduces the sample size available.
Westman and Guthrie, 1990 [53] CHEWING LEAF TOBACCO AND SNUFF	Men attending rural county fairs in Kentucky, US.	32 leaf tobacco users (25 light users, less than 1 pouch/day, seven heavy users), 15 snuff users, 27 non-ST users.	Exposure measured by questionnaire and clearly described. Outcome measurements not described. Confounders not mentioned.	Mean systolic BP of heavy tobacco chewers was 15.1 mmHg higher than that of non-users ($P = 0.007$). Systolic BP: 139.3 ± 25.1 in heavy users, 122.9 ± 10.9 in light users, 124.2 ± 13.5 in non-users and 125 ± 9.8 in snuff users. Diastolic BP: 31.3 ± 16.9 in heavy users, 79.3 ± 9.0 in light users, 74.0 ± 13.6 in non-users and 74.3 ± 6.8 in snuff users. Plasma renin concentrations, and excretion of sodium and potassium tended to be higher in heavy users.	Letter only, ST use clearly described but few other details. Most notably selection is not described; heavy tobacco chewers were substantially older than non-chewers (37.3 ± 14.9 vs. 27.5 ± 8.9 for non-users, 30.3 ± 9.9 for light users, and 26.1 ± 9.32 for snuff users). It is also unclear whether non-ST users used other forms of tobacco. Clearly, apart from age, other lifestyle differences between the groups could account for the differences in blood pressure.

Table 1 (*Continued*)

Study and type of ST	Subjects, setting and years of recruitment	Sample size and number of ST users	Measurement of exposure, outcomes and confounders	Findings or results	Comments
Stegmayr *et al.*, 1995 [54] ORAL SNUFF	Part of MONICA project, Northern Sweden, 1990. Men aged 40–49.	17 snuff dippers, 26 cigarette smokers, 54 non-tobacco users.	Snuff use clearly defined. Measurements of outcomes described in detail. Men with 'mixed' tobacco habits were excluded, but no other attempts to adjust for confounders.	Levels of plasma vitamins were similar in snuff-dippers and non-tobacco users. Regular smokers had significantly lower plasma levels of ascorbate ($P<0.001$), lipid-standardized α-tocopherol ($P=0.032$), α-carotene ($P<0.001$) and ascorbate, lipid-standardized α-tocopherol, α-carotene and β-carotene than non-tobacco users e.g. β-carotene 0.37 μmol/l (95% CI 0.32–0.42) in non-tobacco users, 0.31 (95% CI 0.22–0.40) in snuff users, and 0.26 (95% CI 0.2–0.32) in smokers.	Small sample size, limited to males only. Response rates reasonable (77.3%). Intake of fruit and vegetables tended to be lower for smokers than for snuff users and non-tobacco users.
Persson *et al.*, 2000 [55] ORAL SNUFF	Stockholm–men born during 1938–1957 (aged 35–56 years), 50% had strong family history of diabetes.	3162 men 376 former snuff users, 492 current users	Snuff use clearly defined and some attempt to measure quantity used per week. Outcome–glucose intolerance and type II diabetes clearly defined. Confounders considered include age, alcohol consumption, BMI, family history of diabetes, physical activity, cigarette smoking.	No statistically significantly raised OR for glucose intolerance associated with oral snuff use or cigarette smoking. The OR of type II diabetes was raised, but not statistically significant for both current cigarette smokers and current snuff users (OR=1.5, 95% CI 0.8–3.0 for current snuff users, OR=1.3, 95% CI 0.6–2.7 for current smokers). However, statistically significant OR were found among those who consumed the most cigarettes or snuff, (OR=2.7, 95% CI 1.3–5.5 for snuff users consuming three or more boxes per week, OR=2.6 95% CI 1.1–5.8 for smokers consuming 25 or more cigarettes per day).	Well-designed cross-sectional study with large sample size. Most important confounders were considered. Exposure and outcomes clearly described. Representativeness of sample may be an issue; 79% responded to initial 'screening' questionnaire, but then a further 27.4% were excluded due to incomplete answers, and only 70% of those selected to take part agreed to do so.

ST, smokeless tobacco; RR, relative risk; CI, confidence interval; IHD, ischaemic heart disease; BMI, body mass index; CVD, cardiovascular disease; MI, myocardial infarction; BP, blood pressure; WHR, waist-to-hip ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HR, heart rate; ECG, electrocardiogram; M–H, Mantel–Haenzel; tPA, tissue plasminogen activator; PAI, plasminogen activator inhibitor.

Table 2 **Cardiovascular disease (CVD) deaths attributed to smokeless tobacco (ST) use and smoking in men aged 35 and over, in Sweden 1999**

	Cardiovascular disease mortality PAR % (95% CI)	Number of CVD deaths attributed (95% CI)
Smokeless tobacco use	7% (4–11%)	1597 (829–2309)
Smoking		
<15 cigarettes a day	7% (6–9%)	1597 (1220–1960)
>15 cigarettes a day	8% (7–11%)	1780 (1410–2309)
Total cigarette smoking	15% (13–20%)	3376 (2630–4269)

Approximately 21 555 deaths from CVD among men over 35 in Sweden in 1999 [40]. Estimated Swedish prevalence of ST use and cigarette smoking both about 20% in men [40]. Approximately half of these are light smokers (<15 cigarette per day, and half heavy smokers ≥ 15 cigarettes per day) [Sylwan Lisen. Swedish Cancer Society, 2003. (Personal Communication)]. PAR, population attributable risks; CI, confidence interval.

shown between snuff use and MI. In a logistic regression model for MI (including smoking, low levels of education, and age), snuff use was not a significant risk factor for MI. Blood pressure, cholesterol, and diabetes prevalence were similar in cases and controls so not included in the multivariate model.

In the second paper by Huhtasaari *et al.* [42], (Table 1) more detailed information about ST (present use, previous use, amount, type of preparation, age of onset and whether or not snuffing was associated with quitting smoking) was obtained from MI patients, or if cases had died, from next of kin. Median consumption of snuff was two boxes per week in both cases and controls. Median age of starting snuff use was 31.5 years, which may be explained by the fact that many had started snuff in conjunction with quitting smoking. Regular use of snuff was adjusted to control for confounding by hypertension, low levels of education, not being married or cohabiting, diabetes, known high cholesterol and heredity in conditional logistic regression. Odds ratios (OR) for all and fatal MI remained statistically insignificant after this adjustment.

Explanations for the differences between the prospective cohort and case–control studies

It is difficult to assess why these studies should have obtained such discrepant results. Bolinder's study [39] was carried out 10 years earlier, and it is possible that types of snuff in use may have changed during this time period [20]. All three studies have some non-response bias—in Bolinder's around 25% of employees did not attend the baseline assessment, and in Huhtassari's around 20% of the case-series did not take part. Bolinder's study is prospective, large, and well designed, and its 40% excess mortality risk should not be dismissed. Misclassification of tobacco users is possible, as smoking was not re-measured after baseline in this survey. However, at a population level a higher proportion of cigarette smokers have quit to use snuff than vice versa [43]. This could result in an underestimate of the risk associated with cigarette use, making it appear more similar to that of snuff use, but should not greatly affect the risk associated with snuff use. Adjustment for confounders in each study might have played a role. Unlike Bolinder's cohort, Huhtasaari's studies [41,42] adjusted for low levels of education and marital status along with other factors. However, this is not likely to explain all the association as the cohort was relatively uniform socio-economically (construction workers), and Swedish surveys during the 1980s show little differences in snus use by socio-economic status [40]. Huhtasaari's studies are well designed, but are not prospective, and may dilute risk estimates slightly because of inclusion of occasional and former smokers in the reference group, or recall biases.

Studies considering 'intermediate outcomes' (CHD risk factors)

Studies of multiple risk factors

A number of cross-sectional studies have evaluated the relationship between ST use and CVD risk factors. These studies can be hard to interpret, as the time relationship between ST use and CHD risk factors is uncertain (previous exposure to ST use may be more relevant than exposure at the time of the study).

Bolinder's large study of mortality among construction workers also considered receipt of disability pensions, and symptoms among exclusive snuff users compared with non-tobacco users at baseline [11]. Among 46–55 year olds, snuff users were more likely to have a CHD diagnosis or hypertension (OR = 1.6, 95% CI 0.7–3.5 and OR 3.0, 95% CI 1.9–4.9, respectively).

One Swedish study reassuringly found little evidence of increased risk factors among young male ST users, except for elevated serum insulin and higher fibrinogen levels [44]. However, this study was very small ($n = 60$), used 'convenience' volunteer samples, and was limited to young men under the age of 30. Evidence was found of differences in other CHD risk factors (such as increases in alcohol and coffee consumption and lower exercise levels compared with non-tobacco users), and there were differences in educational levels between cigarette smokers, snus users, and non-tobacco users. As no multivariate analyses were performed, it is difficult to attribute any differences observed to snuff use or other lifestyle factors. It is also possible that further changes in risk factors may occur with longer-term snuff use among older men.

A further North Swedish study, (part of MONICA) found no associations between ST use, plasma fibrinogen, serum insulin and fibrinolytic variables [45], despite high plasma nicotine, and higher plasma cotinine levels among snuff users compared with cigarette smokers. Cigarette smokers, however, had significantly raised plasma fibrinogen.

These findings were supported by a further large cross-sectional study ($n = 1061$) of young male baseball players in the USA [46]. All participants were well educated and there were no significant differences between users and non-users. After adjustments, no associations were found between ST use with systolic or diastolic blood pressure, pulse, and total or high-density lipoprotein cholesterol. Again, these are relatively young men, and also light, often seasonal users of ST [46]. Whether risk factor profiles would be altered among older men or women, with higher use remains unexplored.

Hypercholesterolaemia

Two studies considered the relationship between ST use and cholesterol levels. One large cross-sectional study ($n = 2840$) from the USA found a 2.5-fold increased risk of hypercholesterolaemia among ST users compared with non-tobacco users (RR = 2.51, 95% CI 1.47–4.29) [8]. The risk among cigarette smokers was also raised, (RR = 1.51, 95% CI 1.14–2.0). Possible confounding with dietary factors, however, was not considered. Smokeless tobacco use was more common in younger and less educated subjects. The types of ST used were not stated or described.

One further small study from Jaipur, India, compared lipid levels among 30 smokers, tobacco chewers, and non-tobacco users [47]. It is not very clear how the participants were selected, and the type of tobacco used is not stated. It is also unlikely that major confounders (such as diet) were considered; the sex distribution of the participants is not even given. However, statistically significantly higher levels of low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglycerides, and lower levels of high-density lipoprotein cholesterol were found among both the smokers and chewers compared with non-smokers. No statistically significant differences were found between the smokers and chewers.

Atherosclerosis and other risk factors

One Swedish study of carotid artery ultrasonography among 143 middle-aged firemen found no evidence of increased wall thickness of the artery or carotid bulb among ST users (significant increases among cigarette smokers were observed) [48]. No statistically significant increases were found in atherosclerotic plaques, or other cardiovascular risk factors (lipid fractions, blood pressure) among ST users though these tended to be slightly higher than among those who had never used tobacco. Exposure to nicotine, however, was 37% higher among the ST users than cigarette smokers.

Physical capacity

Low levels of fitness are independently predictive of cardiovascular mortality [49,50]. A further study of physical performance from the same population of firemen [48,52] found that long-term use of ST did not significantly influence exercise capacity (no significant differences in maximal work performed or oxygen uptake between snuff dippers and non-tobacco users, cigarette smokers however, performed significantly worse) [52].

Hypertension

A number of studies have considered the effects of ST use on blood pressure, although the majority of these have considered the 'acute' effects rather than possible chronic influences. Bolinder's study (described above) found associations between ST use and blood pressure [11]. In a cross-sectional study from the 1980s, Schroeder and Chen [52] found a relationship between ST use and higher blood pressure among 710 young men volunteers aged 18–25. The mean blood pressure of 19 ST users was 143.7/80.7 mmHg compared with 131.6/72.8 among non-tobacco users. This report was in the form of a letter, and no other details of the participants, selection, and possible confounding factors were provided.

A further cross-sectional study of ST use and hypertension in the USA reported that mean systolic blood pressure was significantly higher among 'heavy' tobacco chewers compared with non-tobacco users (139.3 ± 25.1 versus 124.2 ± 13.5). Diastolic blood pressure was also slightly but not significantly raised [53]. Snuff use was not associated with higher blood pressure. The authors attribute this to the high liquorice content of chewing tobacco, but not of snuff. However, the study was reported as a letter, sample size was small, and selection unclear, and other potential lifestyle factors (such as physical activity or BMI) were not controlled for. Indeed, 'heavy tobacco chewers' were 10 years older than non-chewers, and this alone could account for much of the increase in blood pressure (snuff users were slightly younger than non-tobacco users).

Anti-oxidant nutrients

A further study from the MONICA project in Northern Sweden considered the effects of ST use on plasma levels of anti-oxidant vitamins in a small sample of 40–49 year old males (ascorbate, tocopherols, carotenoids) [54]. Regular smokers had significantly lower levels of ascorbate, lipid-standardized α-tocopherol, α-carotene and β-carotene than non-tobacco users. Levels among snuff users were generally similar to non-tobacco users, except that slightly lower α- and β-carotene were observed. However, consumption of fruit and vegetables tended to be lower for smokers than the other two groups, though these differences were not statistically significant. The authors suggest that high turnover of these vitamins in cigarette smokers may therefore be caused by components of tobacco smoke other than nicotine, though the sample size is small ($n = 97$).

Glucose intolerance and diabetes

One Swedish study has examined the relationship between use of oral moist snuff, cigarette smoking, and glucose intolerance in men [55]. This was a large, well-designed cross-sectional study. A raised but not statistically significant relationship between both current snuff use and cigarette smoking was found with type II diabetes (OR 1.5, 95% CI 0.8–3.0 for current snuff use, OR = 1.3, 95% CI 0.6–2.7 for current cigarette smoking), but not with glucose intolerance or insulin resistance. A dose–response relationship was also found; both snuff users and cigarette smokers consuming the most tobacco had the highest odds ratio for diabetes (OR = 2.7, 95% CI 1.3–5.5 for snuff users consuming three or more boxes per week, OR = 2.6, 95% CI 1.1–5.8 for smoking 25 or more cigarettes per day).

Discussion

Numerous studies have explored the possible influence of ST use on cancers, especially oral cancers. Most of these cancers are relatively rare. For example, in the UK the incidence of oral cancers (ICD 9, 140–149) was 9.3 per 100 000 in men, 5.0 in women in 1994 [22]. Conversely, estimates of the MI (ICD 9, 410–414) incidence in men are 100-fold greater, at 950 per 100 000 in the UK [56]. Estimates for women vary from 94–265 per 100 000. Studies investigating oral and other cancer outcomes must have had sufficient power to report on much more common cardiovascular outcomes; however, these results are generally not reported in the published literature. The potential cardiovascular effects of ST use have thus been largely overlooked.

The evidence for an effect of cigarette smoking on CVD risk is clear-cut, but an area of contention is how exactly these effects are mediated. Most studies have found very low cardiovascular risks associated with medicinal nicotine products (nicotine replacement therapies such as patches and gum) [57–59]. In conjunction with several studies showing little increased CVD risk factors or risk of CHD associated with ST, this suggests that nicotine *per se* may not be a major factor promoting atherosclerosis or thrombolysis, and other components of smoked tobacco may be responsible [45].

One well-designed and very large prospective cohort study found an increased risk of CHD deaths in Sweden [39]. Based on this study, it seems possible that there is a modest risk of cardiovascular disease associated with snus use in Sweden. Calculation of PARs for snus use and cigarette smoking from the estimates of RR in this study, and estimates of prevalence of cigarette smoking and snus use among men in Sweden, suggest that roughly half the number of CHD deaths could be attributed to snus use compared with cigarette smoking. Several other, smaller, cross-sectional studies have suggested possible increased risks [8,55]. Many of the studies reviewed are relatively poor in determining causality; they are cross-sectional in design, sometimes small, use convenience samples and do not necessarily adjust for important confounders. In particular, socio-economic status is not always measured and controlled for [44,47,52,53]. Most of the studies come from Sweden, and it cannot be assumed that the results would be generalizable to the types of ST used elsewhere. Most ST products are probably considerably lower risk than cigarette smoking (taking all the potential health effects, particularly cancers, into account). Switching to ST may reduce risks of major death and illness for *some* nicotine-addicted cigarette smokers. However, any 'tobacco harm reduction' strategy will need to acknowledge the lack of evidence and uncertainties (particularly for cardiovascular disease) and determine how best to communicate these reservations to the general public [60].

As with any review, it is possible that some published or unpublished studies may have been overlooked. Studies considering acute effects of cardiovascular disease were also excluded. However, the search strategy was comprehensive, involving extensive database searching carried out by two researchers independently, as well as contact with a number of experts in the field. It is therefore unlikely that important studies have been missed. Further, large, well-designed epidemiological studies of ST use and cardiovascular diseases and mortality are required in a variety of regions to clarify the potential risks.

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RESEARCH

Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis

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ABSTRACT

Objective To assess whether people who use smokeless tobacco products are at increased risk of myocardial infarction and stroke.

Design Meta-analysis of observational studies from Sweden and the United States.

Data sources Electronic databases and reference lists.

Data extraction Quantitative estimates of the association between use of smokeless tobacco products and risk of myocardial infarction and stroke among never smokers.

Review methods Both authors independently abstracted risk estimates and study characteristics. Summary relative risks were estimated on the basis of random effects models.

Results 11 studies, mainly in men, were included. Eight risk estimates were available for fatal myocardial infarction: the relative risk for ever use of smokeless tobacco products was 1.13 (95% confidence 1.06 to 1.21) and the excess risk was restricted to current users. The relative risk of fatal stroke, on the basis of five risk estimates, was 1.40 (1.28 to 1.54). The studies from both the United States and Sweden showed an increased risk of death from myocardial infarction and stroke. The inclusion of non-fatal myocardial infarction and non-fatal stroke lowered the summary risk estimates. Data on dose-response were limited but did not suggest a strong relation between risk of dying from either disease and frequency or duration of use of smokeless tobacco products.

Conclusion An association was detected between use of smokeless tobacco products and risk of fatal myocardial infarction and stroke, which does not seem to be explained by chance.

INTRODUCTION

Oral and nasal smokeless tobacco products have been used in many countries for centuries. During most of the 20th century, use of these products declined in Europe and North America, but a reverse trend in prevalence of use has been reported in the past few decades, particularly among people younger than 40.[1] These products have been proposed as an alternative to cigarettes and other smoking products under the claim of a smaller, or negligible, risk to health.[2] Smokeless tobacco is a recognised carcinogen in humans[1]; other potential health effects include an increased risk of myocardial infarction, stroke, and adverse reproductive outcome.[1 3 4] Determining the role of smokeless tobacco in cardiovascular diseases is important, given the high incidence and mortality from these diseases.

We systematically reviewed studies that analysed the risk of myocardial infarction and stroke among users of smokeless tobacco products, with the aim of updating and expanding a previous review and meta-analysis on this topic.[5] Smokeless tobacco products consumed in Asia are different from those consumed in Europe and North America. We aimed to determine whether users of smokeless tobacco products in Sweden and North America are at an increased risk of death from myocardial infarction and from stroke compared with non-users.

METHODS

The MOOSE guidelines for meta-analysis of observational studies in epidemiology were followed.[6] We selected studies that provided a quantitative estimate of the association between ever use of smokeless tobacco products and occurrence (incidence or mortality) of myocardial infarction or stroke among never smokers. We carried out a search in PubMed using the terms ((("cardiovascular diseases"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR "cardiovascular diseases"[All Fields]) OR ("cerebrovascular disorders"[MeSH Terms] OR ("cerebrovascular"[All Fields] AND "disorders"[All Fields]) OR "cerebrovascular disorders"[All Fields] OR MORTALITY OR DEATH*)) AND ((((((snus)) OR ((snuff))) OR ((tobacco, smokeless[mesh]))) OR (("smokeless tobacco"))) OR ((("spit tobacco" OR "chewing tobacco"))) AND ((cohort studies[mesh] OR case control studies[mesh]) OR (cohort[TI] AND stud*[TI]) OR (case*[TI] AND control*[TI] OR prospective study)), which identified 118 potentially relevant references. We completed it with a second search in ISI Web of Science 1945-2009 (updated 15 January 2009) using the terms ((Snus OR snuff OR OR "spit* tobacco" OR "smokeless tobacco" OR "tobacco SAME smokeless" OR "chewing tobacco" OR "tobacco SAME chewing") AND (cardiovascular OR cerebrovascular OR "heart" OR "myocardial infarction" OR mortality OR death* OR ischaemic OR ischemic OR stroke OR coronary) AND (Cohort*

OR Case* OR control* OR prospective)), which resulted in an additional 75 references. After excluding irrelevant studies[w1-w175] we checked the reference lists of relevant studies and identified one additional publication.[w176] After further exclusion of studies done in Asia[w177-w181] (including one study carried out in 52 countries, predominantly Asian[w181]), reports in subsequent publications,[w176 w182 w183] and studies not reporting separate risk estimates for myocardial infarction and stroke,[w184] 10 publications were included for meta-analysis.[7-16]

Data extraction and quality assessment

Both authors independently abstracted the estimates of risk of cardiovascular diseases, ischaemic heart disease or myocardial infarction, and cerebrovascular disease or stroke (including separate estimates for the fatal forms of the diseases, if available) and the characteristics of the study. The abstracted data were compared and any inconsistencies resolved. When possible, risk estimates for current and former use of smokeless tobacco were abstracted separately.

If several risk estimates were available from one study (for example, separate results for men and women or for current and former use), we combined them by carrying out a meta-analysis based on a fixed effect model.

Data synthesis and analysis

We carried out a meta-analysis of the study specific results based on a random effects model.[17] We used the statistical package STATA to test for heterogeneity and to calculate summary relative risks and 95% confidence intervals.[18] Begg's test was used to determine the presence of publication bias.[19]

We classified studies on the basis of outcome (myocardial infarction, stroke), country (United States, Sweden), study design (cohort, including nested case-control, other case-control), and adjustment for potential confounders, in addition to age and sex. We repeated the meta-analysis after stratification by country (United States, Sweden). As is usual in main analyses of epidemiological studies,[20] we combined the results of cohort and case-control studies. The possible influence of study design was assessed by repeating the main analysis with cohort studies only. Three case-control studies were available: all were from Sweden and reported only results on myocardial infarction. To disentangle the effect of country from that of study design we carried out a further meta-analysis of myocardial infarction restricted to cohort studies from Sweden.

Calculation of attributable fraction

The attributable fraction is a measure of the burden of smokeless tobacco use on cardiovascular diseases. It can be estimated on the basis of the relative risk from use of smokeless tobacco and the proportion of the exposed population: proportion of exposed population×(relative risk−1) divided by [proportion of exposed population×(relative risk−1)]+1.

We used the country specific relative risk of fatal myocardial infarction and fatal stroke derived from the present meta-analysis, and data on proportion of smokeless tobacco users from surveys in the United States[21] and Sweden.[22]

RESULTS

Eleven studies reported in 10 publications were included in the meta-analysis (fig 1 and table 1).[7-16] Eight studies were from Sweden and three from the United States. Eight studies used a prospective cohort design (in two, only results based on nested case-control analyses were reported) and three used a population based case-control design. Nine studies were restricted to never tobacco smokers, whereas two also included former smokers.[7 8] Fixed effect meta-analyses of stratified results were done for four studies to obtain a summary relative risk.[9 11 12 15]

The nine independent risk estimates for myocardial infarction (table 1) resulted in a summary relative risk for ever use of smokeless tobacco products of 0.99 (95% confidence interval 0.89 to 1.10), with evidence of heterogeneity between studies (table 2; test for publication bias P=0.2). No evidence of an increased risk was present among current users (seven risk estimates, with heterogeneity) or former users (four risk estimates; table 2). Restricting the meta-analysis to cohort studies gave a summary relative risk of 1.04 (0.95 to 1.14, six risk estimates). As all studies but one were in men, the analyses stratified by sex were not informative.

No heterogeneity was found among the studies reporting fatal myocardial infarction, resulting in a summary relative risk for ever use of 1.13 (1.06 to 1.21), based on eight risk estimates (table 2, fig 2; test for publication bias P=0.4). The increase was present for current use of smokeless tobacco products but not

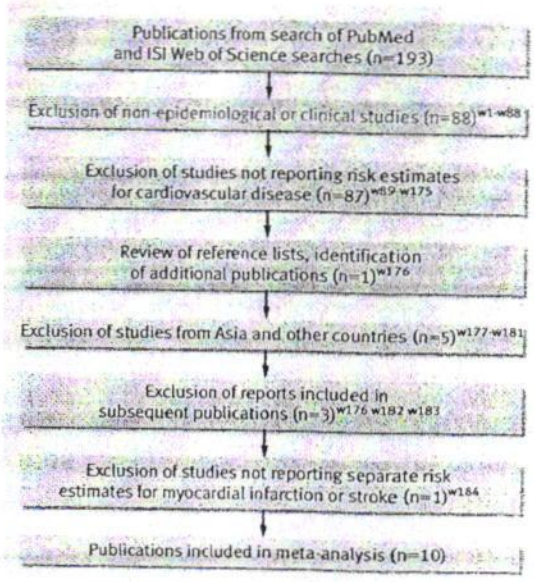

Fig 1 | Strategy for selection of studies in meta-analysis

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Table 1 | Epidemiological studies on use of smokeless tobacco and risk of cardiovascular disease included in meta-analysis

Reference	Country, sex, recruitment, follow-up	Study design	Adjustment factors	Exposure	Outcome	No of cases/ No of deaths	Relative risk (95% CI)	Comments
Huhtasaari et al 1992[7]	Sweden, men, 1989-91, NR	Population based case-control	Age, region of residence	Snuff	Myocardial infarction	177	0.89 (0.62 to 1.29)	Including former smokers; limited overlap with Wennberg et al 2007[15]
Huhtasaari et al 1999[8]	Sweden, men, 1991-3, NR	Population based case-control	Age, region of residence, "various cardiovascular risk factors"	Snuff	Fatal myocardial infarction	NA/NA	0.58 (0.35 to 0.94), 1.50 (0.45 to 5.03)	Including former smokers; limited overlap with Hergens et al 2005[12] and Wennberg et al 2007[15]
Accortt et al 2002[9]	United States, both sexes, 1971-5, 1971-92	Cohort	Age, sex, socioeconomic status, alcohol consumption, physical activity, fruit and vegetable intake, blood pressure, cholesterol, body mass index	Smokeless tobacco	Fatal myocardial infarction, fatal stroke	NA/NA	1.0 (0.7 to 1.6)*, 0.8 (0.4 to 1.8)*	Proxy interviews for many; meta-analysis of results reported in paper (sex)
Asplund et al 2003[10]	Sweden, men,1985-6, 1985-2000	Case-control analysis nested in cohort study	Age, region of residence, education, blood pressure, diabetes, cholesterol, marital status	Snuff	Stroke	NA	1.05 (0.37 to 2.94)	
Henley et al 2005[11]	United States, men, 1959, 1959-71	Cohort	Age, race, education, alcohol consumption, physical activity, aspirin intake, body mass index, fruit and vegetable intake	Spit tobacco	Fatal myocardial infarction, fatal stroke	799/460	1.12 (1.03 to 1.21), 1.46 (1.31 to 1.64)	
Henley et al 2005[11]	United States, men, 1982, 1982-8	Cohort	Age, race, education, alcohol consumption, physical activity, aspirin intake, body mass index, fruit and vegetable intake, occupation	Spit tobacco	Fatal myocardial infarction, fatal stroke	216/100	1.11 (0.97 to 1.28)*, 1.34 (1.09 to 1.65)*	Meta-analysis of results reported in paper (current or former use)
Hergens et al 2005[12]	Sweden, men, 1992-4, NR	Population based case-control	Age, region of residence	Snuff	Fatal myocardial infarction	310/49	0.88 (0.49 to 1.60*, 1.7 (0.59 to 4.9)*	Meta-analysis of results reported in paper (current or former use); limited overlap with Huhtasaari et al 1999[8]
Haglund et al 2007[13]	Sweden, men, 1988-9, 1988-2003	Cohort	Age, region of residence, socioeconomic status, physical activity, self reported health, number of chronic diseases	Snuff	Fatal myocardial infarction, fatal stroke	255/72; 145/33	0.77 (0.51 to 1.15), 1.15 (0.54 to 2.41); 1.07 (0.65 to 1.77), 1.01 (0.35 to 2.92)	
Hergens et al 2007[14]	Sweden, men, 1978-93, 1978-2004	Cohort	Age, place of residence, body mass index	Snuff	Fatal myocardial infarction	3651/841	0.99 (0.90 to 1.10), 1.28 (1.06 to 1.55)	Same cohort as for Hergens et al 2008[16]
Wennberg et al 2007[15]	Sweden, men, 1985-6, 1985-99	Case-control analysis nested in cohort study	Age, education, physical activity, body mass index, cholesterol	Snuff	Fatal myocardial infarction	843/39	0.75 (0.48 to 1.18)*, 0.94 (0.38 to 2.30)*	Meta-analysis of results reported in paper (current or former use); limited overlap with Huhtasaari et al 2007[7,8]
Hergens et al 2008[16]	Sweden, men, 1978-93, 1978-2003	Cohort	Age, place of residence, body mass index	Snuff	Stroke, fatal stroke	444/45	1.02 (0.92 to 1.13), 1.27 (0.92 to 1.76)	Same cohort as for Hergens et al 2007[14]

NA=not available; NR=not relevant.
*Results of meta-analysis.

for former use. An increased risk of fatal myocardial infarction was present in studies from both the United States and Sweden. In one study from the United States, which analysed chewing tobacco and snuff use separately, the results were similar.[11] Restricting the analysis to the three risk estimates from cohort studies in Sweden gave a summary relative risk of 1.26 (1.05 to 1.51). Dose-response analyses for fatal myocardial infarction were reported in two studies[11,14]: in neither was there a significant trend in risk by duration or frequency of use, but in one study the relative risk of fatal myocardial infarction was highest in the group that used smokeless tobacco most often.[14]

On the basis of six risk estimates the overall relative risk of stroke was 1.19 (0.97 to 1.47; test for publication bias P=1.0; table 2). The results were heterogeneous.

Table 2 | Results of meta-analysis on risk of myocardial infarction and stroke* and use of smokeless tobacco products

Outcome and subgroups	No of risk estimates	P for heterogeneity	Relative risk (95% CI)
Any myocardial infarction:			
Overall	9	0.05	0.99 (0.89 to 1.10)
Current use of smokeless tobacco	7	0.02	1.03 (0.91 to 1.17)
Former use of smokeless tobacco	4	0.7	0.74 (0.60 to 0.91)
Cohort studies	6	0.1	1.04 (0.95 to 1.14)
United States	3	0.9	1.11 (1.04 to 1.19)
Sweden	6	0.01	0.87 (0.75 to 1.02)
Sweden—cohort studies	3	0.3	0.92 (0.77 to 1.09)
Fatal myocardial infarction:			
Overall	8	0.9	1.13 (1.06 to 1.21)
Current use of smokeless tobacco	6	0.6	1.17 (1.09 to 1.25)
Former use of smokeless tobacco	4	0.6	0.76 (0.58 to 0.99)
Cohort studies	6	0.8	1.13 (1.06 to 1.21)
United States	3	0.9	1.11 (1.04 to 1.19)
Sweden	5	0.9	1.27 (1.07 to 1.52)
Sweden—cohort studies	3	0.8	1.26 (1.05 to 1.51)
Any stroke:			
Overall	6	<0.001	1.19 (0.97 to 1.47)
Current use of smokeless tobacco	3	<0.001	1.28 (1.00 to 1.64)
Former use of smokeless tobacco	2	0.05	0.93 (0.56 to 1.55)
United States	3	0.3	1.39 (1.22 to 1.60)
Sweden	3	1.0	1.02 (0.93 to 1.13)
Fatal stroke:			
Overall	5	0.5	1.40 (1.28 to 1.54)
Current use of smokeless tobacco	3	0.9	1.44 (1.31 to 1.59)
Former use of smokeless tobacco	2	0.2	0.86 (0.26 to 2.79)
United States	3	0.3	1.39 (1.22 to 1.60)
Sweden	2	0.7	1.25 (0.91 to 1.70)

*All studies included in meta-analysis were of cohort design.

As was the case with myocardial infarction, all studies but one included only men and therefore stratification of the meta-analysis by sex was not informative. Only three estimates were available for current use of smokeless tobacco products and two estimated for former use: an increased risk was present only for current exposure. Studies from Sweden (three risk estimates) showed no increased risk of stroke. The results on fatal stroke were not heterogeneous. The overall relative risk on the basis of five risk estimates was 1.40 (1.28 to 1.54, table 2 and fig 3; test for publication bias P=0.2). Results were comparable between studies from the United States and Sweden (three risk estimates compared with two risk estimates, respectively). In the only study that reported results according to frequency or duration of use, no significant trend in the risk of fatal stroke was detected for either dimension of use, but the relative risk was highest in the group with longest duration of use.[11] Only one of the studies reported results by type of stroke among snuff users: the relative risk for fatal ischaemic stroke (1.63, 1.02 to 2.62) was higher than that for haemorrhagic stroke (1.05, 0.61 to 1.80; test for heterogeneity P=0.2).[16]

The results of the calculation of attributable fraction are presented in table 3. The proportion of deaths from

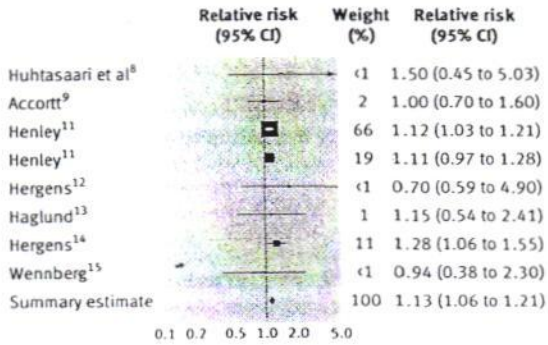

Fig 2 | Forest plot of risk estimates for fatal myocardial infarction among users of smokeless tobacco products

myocardial infarction attributable to use of smokeless tobacco products was 0.5% in the United States and 5.6% in Sweden. The corresponding figures for deaths from stroke were 1.7% and 5.4%: the latter result was based on a summary relative risk that was not statistically significant.

DISCUSSION

This meta-analysis showed an increased risk of fatal myocardial infarction and fatal stroke among users of smokeless tobacco products compared with non-users. Although the magnitude of the excess risk, particularly for fatal myocardial infarction, was small, the consistency of the results among studies and their robustness for study design and quality added to their credibility. The meta-analyses including the results on non-fatal cardiovascular diseases, however, showed heterogeneity between studies, which limits their interpretation. All the studies on risk of non-fatal myocardial infarction and stroke were done in Sweden. Several possible explanations may be given for the discrepancies in results between fatal and non-fatal cardiovascular diseases. Outcomes are less likely to be misclassified in studies of incident cases recruited in hospital shortly after diagnosis. It is unclear, however, how misclassification of fatal cardiovascular diseases could generate a false positive result in prospective studies, as misclassification would most likely be non-differential for use of smokeless tobacco.[24] The difference in results might, however, reflect a true phenomenon.

Animal experiments and studies in humans indicate that smokeless tobacco has mainly short term effects

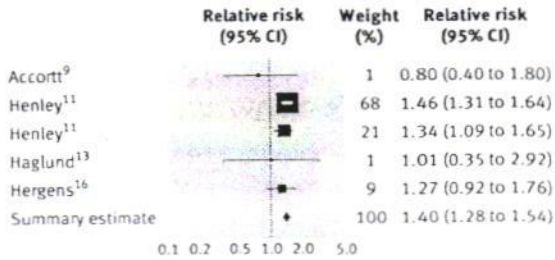

Fig 3 | Forest plot of risk estimates for fatal stroke among users of smokeless tobacco products

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Table 3 | Attributable fraction and attributable number of deaths from myocardial infarction and stroke among men in United States and Sweden

Country (year) and outcome	Attributable fraction (%)	No of deaths
United States (2000):		
Fatal myocardial infarction	0.5	483
Fatal stroke	1.7	1093
Sweden (2001):		
Fatal myocardial infarction	5.6	346
Fatal stroke	5.4	220

Based on mortality data from WHO database,[23] 4.4% prevalence of use in United States,[21] and 23% prevalence of use in Sweden,[22] and country specific relative risks from table 2.

resulting in increased blood pressure and heart rate that are presumably due to nicotine, whereas data on long term use and hypertension are inconclusive.[3 4] Several studies suggest that increased levels of triglycerides, diabetes, obesity, and metabolic syndrome might be associated with use of smokeless tobacco.[1 4] Experimental findings of increased damage to the cardiac muscle and poorer myocardial healing in dogs exposed to nicotine may provide a pathophysiological rationale for the increased mortality from myocardial infarction. Furthermore, nicotine induced cardiac arrhythmias in dogs and increased the sensitivity towards arrhythmias and induced ventricular fibrillation in canine hearts that survived myocardial infarction.[4]

Previous reviews on the risk of cardiovascular diseases among users of smokeless tobacco emphasised the differences in exposure and results and concluded that the evidence did not suggest an association.[3 5 25] Our meta-analysis, however, is based on explicit criteria for inclusion of studies, and abstraction and pooling of results. Compared with the most recent published meta-analysis,[5] our review excluded two studies that have been included in subsequent publications[w17b w18] and one study with no risk estimate for never smokers,[w23] and included four studies published in the past two years.[13-16] Our meta-analysis provides consistent evidence of a moderate increase in risk of fatal myocardial infarction and fatal stroke, whereas it does not provide evidence of a difference in effect of products consumed in North America compared with northern Europe. The different conclusions reached by previous authors might be explained by the combination of results on incident and fatal cardiovascular diseases, the lack of inclusion of several recent studies, and the lack of a formal meta-analysis.[3 5 25]

The results on fatal myocardial infarction did not depend on the inclusion of case-control studies, and all risk estimates for fatal stroke were based on prospective studies. Cohort studies might be prone to bias if the members change their use of smokeless tobacco products during follow-up. This would, however, generate a positive result for smokeless tobacco only if users switched to smoking products. Some evidence from the United States shows that use of smokeless tobacco may lead to subsequent cigarette smoking.[26] The Swedish data do not support the hypothesis that smokeless tobacco is a precursor to future smoking.[27 28] Other sources of bias (for example, misclassification of outcomes) in cohort studies are unlikely to result in a false positive result. This is not the case for case-control studies, in which information bias remains a potential problem.[24] The consistency of results in prospective and retrospective studies, however, argues against such bias playing an important part.

Confounding by active smoking is a potential source of bias in the studies included in the meta-analysis. We aimed to control for this by restricting the meta-analysis to studies of never smokers. Only two relatively small case-control studies included former smokers in their category of non-smokers.[7 8] It is plausible, however, that some current or former smokers might have been misclassified as never smokers. If this happened, irrespective of smokeless tobacco use, it would have resulted in bias towards the null. However, the possibility remains that confounding owing to misclassification of smoking status might have been differential for smokeless tobacco use (that is, smokeless tobacco users might have comprised more misclassified smokers than non-users), thus resulting in an inflation of the risk associated with smokeless tobacco use. A sensitivity analysis carried out by us showed that to explain a relative risk of 1.40 for fatal stroke reported in this study 25% of smokeless tobacco users should actually be misclassified as smokers (assuming no effect of smokeless tobacco, relative risk equal to 2.5 for tobacco smoking, and no misclassification among non-users). Such a degree of misclassification is unlikely. The results included in the meta-analysis were adjusted for sex, age, race (if appropriate), and (in cohort studies) for other known risk factors of cardiovascular disease, such as body mass index and hypertension.

In conclusion, in studies carried out in the United States and Sweden we detected an association between use of smokeless tobacco products and risk of fatal myocardial infarction and fatal stroke, which is not readily explained by chance. Confounding and other sources of bias, however, cannot be completely excluded on the basis of available data, although we found no strong evidence for their effect. If the association is real, its public health and clinical implications might be substantial, despite the fact that the

WHAT IS ALREADY KNOWN ON THIS TOPIC

Smokeless tobacco products are widely used in many populations

An association with risk of cardiovascular disease is plausible

WHAT THIS STUDY ADDS

This systematic review and meta-analysis provided evidence for an association between use of smokeless products and risk of fatal myocardial infarction and stroke

magnitude of the excess risk is small. Future research should aim to clarify the mechanisms of effect of smokeless tobacco products on deaths from cardiovascular disease and to elucidate whether a similar effect is present for non-fatal myocardial infarction and non-fatal stroke.

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Competing interests: None declared.

Ethical approval: Not required.

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RESEARCH

Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis

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ABSTRACT

Objective To assess whether people who use smokeless tobacco products are at increased risk of myocardial infarction and stroke.

Design Meta-analysis of observational studies from Sweden and the United States.

Data sources Electronic databases and reference lists.

Data extraction Quantitative estimates of the association between use of smokeless tobacco products and risk of myocardial infarction and stroke among never smokers.

Review methods Both authors independently abstracted risk estimates and study characteristics. Summary relative risks were estimated on the basis of random effects models.

Results 11 studies, mainly in men, were included. Eight risk estimates were available for fatal myocardial infarction: the relative risk for ever use of smokeless tobacco products was 1.13 (95% confidence 1.06 to 1.21) and the excess risk was restricted to current users. The relative risk of fatal stroke, on the basis of five risk estimates, was 1.40 (1.28 to 1.54). The studies from both the United States and Sweden showed an increased risk of death from myocardial infarction and stroke. The inclusion of non-fatal myocardial infarction and non-fatal stroke lowered the summary risk estimates. Data on dose-response were limited but did not suggest a strong relation between risk of dying from either disease and frequency or duration of use of smokeless tobacco products.

Conclusion An association was detected between use of smokeless tobacco products and risk of fatal myocardial infarction and stroke, which does not seem to be explained by chance.

INTRODUCTION

Oral and nasal smokeless tobacco products have been used in many countries for centuries. During most of the 20th century, use of these products declined in Europe and North America, but a reverse trend in prevalence of use has been reported in the past few decades, particularly among people younger than 40.[1] These products have been proposed as an alternative to cigarettes and other smoking products under the claim of a smaller, or negligible, risk to health.[2] Smokeless tobacco is a recognised carcinogen in humans[1]; other potential health effects include an increased risk of myocardial infarction, stroke, and adverse reproductive outcome.[1 3 4] Determining the role of smokeless tobacco in cardiovascular diseases is important, given the high incidence and mortality from these diseases.

We systematically reviewed studies that analysed the risk of myocardial infarction and stroke among users of smokeless tobacco products, with the aim of updating and expanding a previous review and meta-analysis on this topic.[5] Smokeless tobacco products consumed in Asia are different from those consumed in Europe and North America. We aimed to determine whether users of smokeless tobacco products in Sweden and North America are at an increased risk of death from myocardial infarction and from stroke compared with non-users.

METHODS

The MOOSE guidelines for meta-analysis of observational studies in epidemiology were followed.[6] We selected studies that provided a quantitative estimate of the association between ever use of smokeless tobacco products and occurrence (incidence or mortality) of myocardial infarction or stroke among never smokers. We carried out a search in PubMed using the terms ((“cardiovascular diseases”[MeSH Terms] OR (“cardiovascular”[All Fields] AND “diseases”[All Fields]) OR “cardiovascular diseases”[All Fields]) OR (“cerebrovascular disorders”[MeSH Terms] OR (“cerebrovascular”[All Fields] AND “disorders”[All Fields]) OR “cerebrovascular disorders”[All Fields] OR MORTALITY OR DEATH*)) AND ((((((snus)) OR ((snuff))) OR ((tobacco, smokeless[mesh])))) OR ((“smokeless tobacco”))) OR ((“spit tobacco” OR “chewing tobacco”))) AND ((cohort studies[mesh] OR case control studies[mesh]) OR (cohort[TI] AND stud*[TI]) OR (case*[TI] AND control*[TI] OR prospective study)), which identified 118 potentially relevant references. We completed it with a second search in ISI Web of Science 1945-2009 (updated 15 January 2009) using the terms ((Snus OR snuff OR OR “spit* tobacco” OR “smokeless tobacco” OR “tobacco SAME smokeless” OR “chewing tobacco” OR “tobacco SAME chewing”) AND (cardiovascular OR cerebrovascular OR “heart” OR “myocardial infarction” OR mortality OR death* OR ischaemic OR ischemic OR stroke OR coronary) AND (Cohort*

OR Case* OR control* OR prospective)), which resulted in an additional 75 references. After excluding irrelevant studies[w1-w175] we checked the reference lists of relevant studies and identified one additional publication.[w176] After further exclusion of studies done in Asia[w177-w181] (including one study carried out in 52 countries, predominantly Asian[w181]), reports in subsequent publications,[w176 w182 w183] and studies not reporting separate risk estimates for myocardial infarction and stroke,[w184] 10 publications were included for meta-analysis.[7-16]

Data extraction and quality assessment

Both authors independently abstracted the estimates of risk of cardiovascular diseases, ischaemic heart disease or myocardial infarction, and cerebrovascular disease or stroke (including separate estimates for the fatal forms of the diseases, if available) and the characteristics of the study. The abstracted data were compared and any inconsistencies resolved. When possible, risk estimates for current and former use of smokeless tobacco were abstracted separately.

If several risk estimates were available from one study (for example, separate results for men and women or for current and former use), we combined them by carrying out a meta-analysis based on a fixed effect model.

Data synthesis and analysis

We carried out a meta-analysis of the study specific results based on a random effects model.[17] We used the statistical package STATA to test for heterogeneity and to calculate summary relative risks and 95% confidence intervals.[18] Begg's test was used to determine the presence of publication bias.[19]

We classified studies on the basis of outcome (myocardial infarction, stroke), country (United States, Sweden), study design (cohort, including nested case-control, other case-control), and adjustment for potential confounders, in addition to age and sex. We repeated the meta-analysis after stratification by country (United States, Sweden). As is usual in main analyses of epidemiological studies,[20] we combined the results of cohort and case-control studies. The possible influence of study design was assessed by repeating the main analysis with cohort studies only. Three case-control studies were available: all were from Sweden and reported only results on myocardial infarction. To disentangle the effect of country from that of study design we carried out a further meta-analysis of myocardial infarction restricted to cohort studies from Sweden.

Calculation of attributable fraction

The attributable fraction is a measure of the burden of smokeless tobacco use on cardiovascular diseases. It can be estimated on the basis of the relative risk from use of smokeless tobacco and the proportion of the exposed population: proportion of exposed population×(relative risk−1) divided by [proportion of exposed population×(relative risk−1)]+1.

We used the country specific relative risk of fatal myocardial infarction and fatal stroke derived from the present meta-analysis, and data on proportion of smokeless tobacco users from surveys in the United States[21] and Sweden.[22]

RESULTS

Eleven studies reported in 10 publications were included in the meta-analysis (fig 1 and table 1).[7-16] Eight studies were from Sweden and three from the United States. Eight studies used a prospective cohort design (in two, only results based on nested case-control analyses were reported) and three used a population based case-control design. Nine studies were restricted to never tobacco smokers, whereas two also included former smokers.[7 8] Fixed effect meta-analyses of stratified results were done for four studies to obtain a summary relative risk.[9 11 12 15]

The nine independent risk estimates for myocardial infarction (table 1) resulted in a summary relative risk for ever use of smokeless tobacco products of 0.99 (95% confidence interval 0.89 to 1.10), with evidence of heterogeneity between studies (table 2; test for publication bias P=0.2). No evidence of an increased risk was present among current users (seven risk estimates, with heterogeneity) or former users (four risk estimates; table 2). Restricting the meta-analysis to cohort studies gave a summary relative risk of 1.04 (0.95 to 1.14, six risk estimates). As all studies but one were in men, the analyses stratified by sex were not informative.

No heterogeneity was found among the studies reporting fatal myocardial infarction, resulting in a summary relative risk for ever use of 1.13 (1.06 to 1.21), based on eight risk estimates (table 2, fig 2; test for publication bias P=0.4). The increase was present for current use of smokeless tobacco products but not

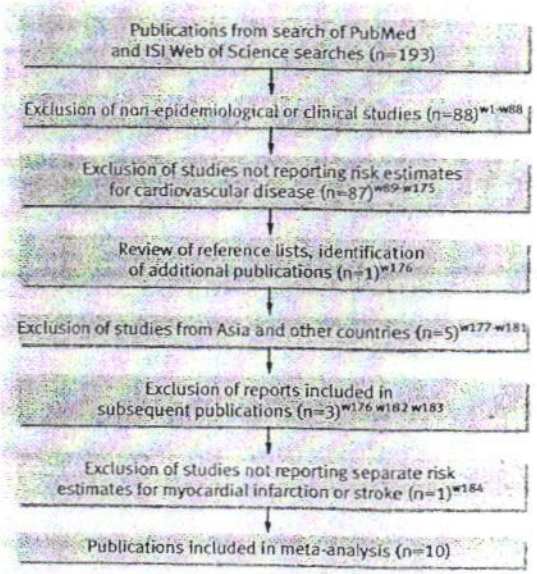

Fig 1| Strategy for selection of studies in meta-analysis

Table 1 | Epidemiological studies on use of smokeless tobacco and risk of cardiovascular disease included in meta-analysis

Reference	Country, sex, recruitment, follow-up	Study design	Adjustment factors	Exposure	Outcome	No of cases/ No of deaths	Relative risk (95% CI)	Comments
Huhtasaari et al 1992[7]	Sweden, men, 1989-91, NR	Population based case-control	Age, region of residence	Snuff	Myocardial infarction	177	0.89 (0.62 to 1.29)	Including former smokers; limited overlap with Wennberg et al 2007[15]
Huhtasaari et al 1999[8]	Sweden, men, 1991-3, NR	Population based case-control	Age, region of residence, "various cardiovascular risk factors"	Snuff	Fatal myocardial infarction	NA/NA	0.58 (0.35 to 0.94), 1.50 (0.45 to 5.03)	Including former smokers; limited overlap with Hergens et al 2005[12] and Wennberg et al 2007[15]
Accortt et al 2002[9]	United States, both sexes, 1971-5, 1971-92	Cohort	Age, sex, socioeconomic status, alcohol consumption, physical activity, fruit and vegetable intake, blood pressure, cholesterol, body mass index	Smokeless tobacco	Fatal myocardial infarction, fatal stroke	NA/NA	1.0 (0.7 to 1.6)*, 0.8 (0.4 to 1.8)*	Proxy interviews for many; meta-analysis of results reported in paper (sex)
Asplund et al 2003[10]	Sweden, men, 1985-6, 1985-2000	Case-control analysis nested in cohort study	Age, region of residence, education, blood pressure, diabetes, cholesterol, marital status	Snuff	Stroke	NA	1.05 (0.37 to 2.94)	
Henley et al 2005[11]	United States, men, 1959, 1959-71	Cohort	Age, race, education, alcohol consumption, physical activity, aspirin intake, body mass index, fruit and vegetable intake	Spit tobacco	Fatal myocardial infarction, fatal stroke	799/460	1.12 (1.03 to 1.21), 1.46 (1.31 to 1.64)	
Henley et al 2005[11]	United States, men, 1982, 1982-8	Cohort	Age, race, education, alcohol consumption, physical activity, aspirin intake, body mass index, fruit and vegetable intake, occupation	Spit tobacco	Fatal myocardial infarction, fatal stroke	216/100	1.11 (0.97 to 1.28)*, 1.34 (1.09 to 1.65)*	Meta-analysis of results reported in paper (current or former use)
Hergens et al 2005[12]	Sweden, men, 1992-4, NR	Population based case-control	Age, region of residence	Snuff	Fatal myocardial infarction	310/49	0.88 (0.49 to 1.60*, 1.7 (0.59 to 4.9)*	Meta-analysis of results reported in paper (current or former use); limited overlap with Huhtasaari et al 1999[8]
Haglund et al 2007[13]	Sweden, men, 1988-9, 1988-2003	Cohort	Age, region of residence, socioeconomic status, physical activity, self reported health, number of chronic diseases	Snuff	Fatal myocardial infarction, fatal stroke	255/72; 145/33	0.77 (0.51 to 1.15), 1.15 (0.54 to 2.41); 1.07 (0.65 to 1.77), 1.01 (0.35 to 2.92)	
Hergens et al 2007[14]	Sweden, men, 1978-93, 1978-2004	Cohort	Age, place of residence, body mass index	Snuff	Fatal myocardial infarction	3651/841	0.99 (0.90 to 1.10), 1.28 (1.06 to 1.55)	Same cohort as for Hergens et al 2008[16]
Wennberg et al 2007[15]	Sweden, men, 1985-6, 1985-99	Case-control analysis nested in cohort study	Age, education, physical activity, body mass index, cholesterol	Snuff	Fatal myocardial infarction	843/39	0.75 (0.48 to 1.18)*, 0.94 (0.38 to 2.30)*	Meta-analysis of results reported in paper (current or former use); limited overlap with Huhtasaari et al 2002[7,8]
Hergens et al 2008[16]	Sweden, men, 1978-93, 1978-2003	Cohort	Age, place of residence, body mass index	Snuff	Stroke, fatal stroke	444/45	1.02 (0.92 to 1.13), 1.27 (0.92 to 1.76)	Same cohort as for Hergens et al 2007[14]

NA=not available; NR=not relevant.
*Results of meta-analysis.

for former use. An increased risk of fatal myocardial infarction was present in studies from both the United States and Sweden. In one study from the United States, which analysed chewing tobacco and snuff use separately, the results were similar.[11] Restricting the analysis to the three risk estimates from cohort studies in Sweden gave a summary relative risk of 1.26 (1.05 to 1.51). Dose-response analyses for fatal myocardial infarction were reported in two studies[11,14]: in neither was there a significant trend in risk by duration or frequency of use, but in one study the relative risk of fatal myocardial infarction was highest in the group that used smokeless tobacco most often.[11]

On the basis of six risk estimates the overall relative risk of stroke was 1.19 (0.97 to 1.47; test for publication bias P=1.0; table 2). The results were heterogeneous.

Table 2 | Results of meta-analysis on risk of myocardial infarction and stroke* and use of smokeless tobacco products

Outcome and subgroups	No of risk estimates	P for heterogeneity	Relative risk (95% CI)
Any myocardial infarction:			
Overall	9	0.05	0.99 (0.89 to 1.10)
Current use of smokeless tobacco	7	0.02	1.03 (0.91 to 1.17)
Former use of smokeless tobacco	4	0.7	0.74 (0.60 to 0.91)
Cohort studies	6	0.1	1.04 (0.95 to 1.14)
United States	3	0.9	1.11 (1.04 to 1.19)
Sweden	6	0.01	0.87 (0.75 to 1.02)
Sweden—cohort studies	3	0.3	0.92 (0.77 to 1.09)
Fatal myocardial infarction:			
Overall	8	0.9	1.13 (1.06 to 1.21)
Current use of smokeless tobacco	6	0.6	1.17 (1.09 to 1.25)
Former use of smokeless tobacco	4	0.6	0.76 (0.58 to 0.99)
Cohort studies	6	0.8	1.13 (1.06 to 1.21)
United States	3	0.9	1.11 (1.04 to 1.19)
Sweden	5	0.9	1.27 (1.07 to 1.52)
Sweden—cohort studies	3	0.8	1.26 (1.05 to 1.51)
Any stroke:			
Overall	6	<0.001	1.19 (0.97 to 1.47)
Current use of smokeless tobacco	3	<0.001	1.28 (1.00 to 1.64)
Former use of smokeless tobacco	2	0.05	0.93 (0.56 to 1.55)
United States	3	0.3	1.39 (1.22 to 1.60)
Sweden	3	1.0	1.02 (0.93 to 1.13)
Fatal stroke:			
Overall	5	0.5	1.40 (1.28 to 1.54)
Current use of smokeless tobacco	3	0.9	1.44 (1.31 to 1.59)
Former use of smokeless tobacco	2	0.2	0.86 (0.26 to 2.79)
United States	3	0.3	1.39 (1.22 to 1.60)
Sweden	2	0.7	1.25 (0.91 to 1.70)

*All studies included in meta-analysis were of cohort design.

As was the case with myocardial infarction, all studies but one included only men and therefore stratification of the meta-analysis by sex was not informative. Only three estimates were available for current use of smokeless tobacco products and two estimated for former use: an increased risk was present only for current exposure. Studies from Sweden (three risk estimates) showed no increased risk of stroke. The results on fatal stroke were not heterogeneous. The overall relative risk on the basis of five risk estimates was 1.40 (1.28 to 1.54, table 2 and fig 3; test for publication bias P=0.2). Results were comparable between studies from the United States and Sweden (three risk estimates compared with two risk estimates, respectively). In the only study that reported results according to frequency or duration of use, no significant trend in the risk of fatal stroke was detected for either dimension of use, but the relative risk was highest in the group with longest duration of use.[11] Only one of the studies reported results by type of stroke among snuff users: the relative risk for fatal ischaemic stroke (1.63, 1.02 to 2.62) was higher than that for haemorrhagic stroke (1.05, 0.61 to 1.80; test for heterogeneity P=0.2).[16]

The results of the calculation of attributable fraction are presented in table 3. The proportion of deaths from myocardial infarction attributable to use of smokeless tobacco products was 0.5% in the United States and 5.6% in Sweden. The corresponding figures for deaths from stroke were 1.7% and 5.4%: the latter result was based on a summary relative risk that was not statistically significant.

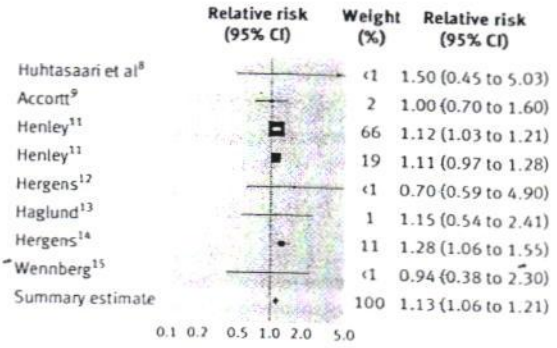

Fig 2 | Forest plot of risk estimates for fatal myocardial infarction among users of smokeless tobacco products

DISCUSSION

This meta-analysis showed an increased risk of fatal myocardial infarction and fatal stroke among users of smokeless tobacco products compared with non-users. Although the magnitude of the excess risk, particularly for fatal myocardial infarction, was small, the consistency of the results among studies and their robustness for study design and quality added to their credibility. The meta-analyses including the results on non-fatal cardiovascular diseases, however, showed heterogeneity between studies, which limits their interpretation. All the studies on risk of non-fatal myocardial infarction and stroke were done in Sweden. Several possible explanations may be given for the discrepancies in results between fatal and non-fatal cardiovascular diseases. Outcomes are less likely to be misclassified in studies of incident cases recruited in hospital shortly after diagnosis. It is unclear, however, how misclassification of fatal cardiovascular diseases could generate a false positive result in prospective studies, as misclassification would most likely be non-differential for use of smokeless tobacco.[24] The difference in results might, however, reflect a true phenomenon.

Animal experiments and studies in humans indicate that smokeless tobacco has mainly short term effects

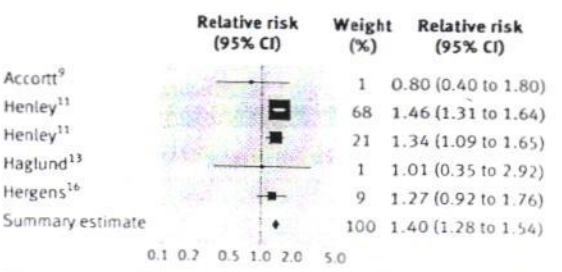

Fig 3 | Forest plot of risk estimates for fatal stroke among users of smokeless tobacco products

Table 3 | Attributable fraction and attributable number of deaths from myocardial infarction and stroke among men in United States and Sweden

Country (year) and outcome	Attributable fraction (%)	No of deaths
United States (2000):		
Fatal myocardial infarction	0.5	483
Fatal stroke	1.7	1093
Sweden (2001):		
Fatal myocardial infarction	5.6	346
Fatal stroke	5.4	220

Based on mortality data from WHO database,[23] 4.4% prevalence of use in United States,[21] and 23% prevalence of use in Sweden,[22] and country specific relative risks from table 2.

resulting in increased blood pressure and heart rate that are presumably due to nicotine, whereas data on long term use and hypertension are inconclusive.[3 4] Several studies suggest that increased levels of triglycerides, diabetes, obesity, and metabolic syndrome might be associated with use of smokeless tobacco.[1 4] Experimental findings of increased damage to the cardiac muscle and poorer myocardial healing in dogs exposed to nicotine may provide a pathophysiological rationale for the increased mortality from myocardial infarction. Furthermore, nicotine induced cardiac arrhythmias in dogs and increased the sensitivity towards arrhythmias and induced ventricular fibrillation in canine hearts that survived myocardial infarction.[4]

Previous reviews on the risk of cardiovascular diseases among users of smokeless tobacco emphasised the differences in exposure and results and concluded that the evidence did not suggest an association.[3 5 25] Our meta-analysis, however, is based on explicit criteria for inclusion of studies, and abstraction and pooling of results. Compared with the most recent published meta-analysis,[3] our review excluded two studies that have been included in subsequent publications[w12b w18a] and one study with no risk estimate for never smokers,[w7a] and included four studies published in the past two years.[13 16] Our meta-analysis provides consistent evidence of a moderate increase in risk of fatal myocardial infarction and fatal stroke, whereas it does not provide evidence of a difference in effect of products consumed in North America compared with northern Europe. The different conclusions reached by previous authors might be explained by the combination of results on incident and fatal cardiovascular diseases, the lack of inclusion of several recent studies, and the lack of a formal meta-analysis.[3 5 25]

The results on fatal myocardial infarction did not depend on the inclusion of case-control studies, and all risk estimates for fatal stroke were based on prospective studies. Cohort studies might be prone to bias if the members change their use of smokeless tobacco products during follow-up. This would, however, generate a positive result for smokeless tobacco only if users switched to smoking products. Some evidence from the United States shows that use of smokeless tobacco may lead to subsequent cigarette smoking.[26] The Swedish data do not support the hypothesis that smokeless tobacco is a precursor to future smoking.[27 28] Other sources of bias (for example, misclassification of outcomes) in cohort studies are unlikely to result in a false positive result. This is not the case for case-control studies, in which information bias remains a potential problem.[24] The consistency of results in prospective and retrospective studies, however, argues against such bias playing an important part.

Confounding by active smoking is a potential source of bias in the studies included in the meta-analysis. We aimed to control for this by restricting the meta-analysis to studies of never smokers. Only two relatively small case-control studies included former smokers in their category of non-smokers.[7 8] It is plausible, however, that some current or former smokers might have been misclassified as never smokers. If this happened, irrespective of smokeless tobacco use, it would have resulted in bias towards the null. However, the possibility remains that confounding owing to misclassification of smoking status might have been differential for smokeless tobacco use (that is, smokeless tobacco users might have comprised more misclassified smokers than non-users), thus resulting in an inflation of the risk associated with smokeless tobacco use. A sensitivity analysis carried out by us showed that to explain a relative risk of 1.40 for fatal stroke reported in this study 25% of smokeless tobacco users should actually be misclassified as smokers (assuming no effect of smokeless tobacco, relative risk equal to 2.5 for tobacco smoking, and no misclassification among non-users). Such a degree of misclassification is unlikely. The results included in the meta-analysis were adjusted for sex, age, race (if appropriate), and (in cohort studies) for other known risk factors of cardiovascular disease, such as body mass index and hypertension.

In conclusion, in studies carried out in the United States and Sweden we detected an association between use of smokeless tobacco products and risk of fatal myocardial infarction and fatal stroke, which is not readily explained by chance. Confounding and other sources of bias, however, cannot be completely excluded on the basis of available data, although we found no strong evidence for their effect. If the association is real, its public health and clinical implications might be substantial, despite the fact that the

WHAT IS ALREADY KNOWN ON THIS TOPIC

Smokeless tobacco products are widely used in many populations

An association with risk of cardiovascular disease is plausible

WHAT THIS STUDY ADDS

This systematic review and meta-analysis provided evidence for an association between use of smokeless products and risk of fatal myocardial infarction and stroke

magnitude of the excess risk is small. Future research should aim to clarify the mechanisms of effect of smokeless tobacco products on deaths from cardiovascular disease and to elucidate whether a similar effect is present for non-fatal myocardial infarction and non-fatal stroke.

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Annexe 90

Smokeless Tobacco and the Risk of Stroke

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Background: In Sweden, use of smokeless tobacco (oral moist snuff) is common among adult men. Research on cerebrovascular effects associated with long-term use of snuff is limited and inconclusive. We aimed to study whether long-term use of snuff affects the risk of stroke.

Methods: Information on tobacco use was collected by questionnaire among Swedish construction workers attending health check-ups between 1978 and 1993. In total, 118,465 never-smoking men without a history of stroke were followed through 2003. We used the Inpatient Register and Causes of Death Register to identify subsequent morbidity and mortality from stroke and its subtypes (ischemic, hemorrhagic, and unspecified stroke). Relative risk estimates were derived from Cox proportional hazards regression model.

Results: Almost 30% of the nonsmoking men had ever used snuff. Overall, 3248 cases of stroke were identified during follow-up. Compared with nonusers of tobacco, the multivariable-adjusted relative risks for ever-users of snuff were 1.02 (95% confidence interval; 0.92–1.13) for all cases and 1.27 (0.92–1.76) for fatal cases. Further analyses on subtypes of stroke revealed an increased risk of fatal ischemic stroke associated with current snuff use (1.72; 1.06–2.78), whereas no increased risk was noted for hemorrhagic stroke.

Conclusion: Snuff use may elevate the risk of fatal stroke, and particularly of fatal ischemic stroke.

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Oral moist snuff ("snus") is a type of smokeless tobacco widely used in Sweden. In 2004, 22% of men were daily snuff users, and the prevalence is steadily increasing.[1] Stroke is one of the leading causes of disability and death in Western countries, with tobacco smoking being a well-known risk factor.[2,3] Possible associations between snuff use and stroke have been investigated only to a limited extent.

Snuff consists of ground tobacco leaves that are pasteurized through a heating process. One of the constituents of snuff, nicotine, has direct cardiovascular effects through sympathicoadrenal activation.[4] The effects include increases in heart rate, systolic blood pressure, cardiac stroke volume, and coronary blood flow. Nicotine also induces vasoconstriction.[5,6] Animal studies show that nicotine may induce arrhythmias.[7] Results from the few epidemiologic studies on long-term use of snuff and the risk of stroke seem inconsistent.[8–11] One Swedish study found evidence of an increased risk of cerebrovascular mortality among snuff users,[10] whereas no such increase in risk was found in 2 later studies; 1 nested case-control study from northern Sweden[9] and 1 Swedish cohort study.[12] One American cohort study found no association between snuff use and risk of stroke,[8] whereas a subsequent US-based cohort study showed an increased risk of stroke among smokeless tobacco users but not among exclusive users of snuff.[11] None of these studies divided stroke into subtypes. Such a subdivision could be of importance, considering the different etiologies of hemorrhagic stroke and ischemic stroke.

We performed a prospective cohort study to assess the association between snuff use and the risk of stroke, with an emphasis on different types of stroke.

METHODS

Setting

This cohort has previously been described in detail.[13] In brief, the Swedish Construction Industry's Organization provided outpatient medical services to construction workers in Sweden from 1969 through 1993. This included preventive health service to all workers in the industry at stationary or mobile clinics staffed by nurses and doctors. About 80% of the construction workers attended at least 1 health check-up.[14] Information on medical history and working environment, and detailed smoking (from 1971) and snuff dipping history (from 1978), was obtained by questionnaires.

The Cohort

Exposure information was drawn from first visits starting in 1978 because data on tobacco use were incomplete before 1978. To minimize misclassification we used information on smoking (cigarettes, pipes, or cigars) from all check-ups between 1971 and 1993 to exclude participants who reported smoking daily at any time during this period. In all, 122,346 male workers who had never smoked daily were registered between 1978 and 1993. Using the unique national

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registration number, all subjects could be followed through record linkage to the nationwide Causes of Death Register, the Inpatient Register, and the Migration Register. We excluded 3881 men for the following reasons: inconsistent birth dates or personal identifiers (134); insufficient exposure data on snuff consumption (35); a history of stroke before entry (131); missing information on area of domicile, weight, or height (1830); and other inconsistencies (1751). The final study population comprised 118,465 men.

Follow-Up

The National Board of Health and Welfare has collected data since 1965 on individual hospital discharges in the Inpatient Register, described in detail elsewhere.[15] The proportion of the Swedish population covered by this register increased from 60% in 1969 to 85% in 1983, and to 100% in 1987, and thereafter. Each record contains up to 8 discharge diagnoses. The Causes of Death Register, which is also held by the National Board of Health and Welfare, includes information on date of death and underlying and contributory causes of death. Discharge diagnoses and death causes are coded according to the Swedish revision of 7th International Classification of Diseases (ICD-7) before 1969, ICD-8 from 1969 through 1986, ICD-9 from 1987 through 1996, and ICD-10 since 1997. We identified incident cases and subjects dying from ischemic, hemorrhagic and unspecified stroke using the Inpatient Register (as main diagnosis) and Causes of Death Register (as underlying cause). Stroke patients who survived fewer than 28 days after first admission were considered fatal cases. Stroke and its subtypes were derived in accordance with methods used in a previous study[16] (for details, see eTable, available with the online version of this article). Hemorrhagic stroke included both nontraumatic intracranial hemorrhage, and subarachnoid hemorrhage. Ischemic stroke included occlusion in both precerebral and cerebral arteries, cerebral thrombosis, and cerebral embolism, as well as transient cerebral ischemia. Ill-defined cerebrovascular diseases were categorized as unspecified stroke.

Information on Snuff Dipping and Other Risk Factors

Questionnaires provided information on amount of snuff used (g/wk), duration of snuff dipping, and time since cessation of snuff dipping. Regular snuff use was defined as consumption of at least 1 g/d for at least 1 year. Former snuff users were defined as those who had stopped using snuff more than 1 year before enrollment. The mean consumption among current snuff users was 23 g/d. We used snuff information only from the first registered visit. (Later visits varied in number and timing and were subject to self-selection; also, the number of repeated visits was age dependent.) Current users were divided into 4 groups according to amount of daily snuff intake in g/d; <12.5 g/d, 12.5–24.9 g/d, 25.0–49.9 g/d and 50 or more g/d.

Body mass index ([BMI]; weight [kg]/height [m]^2) was calculated using information from the first health check-up in 1978. Area of domicile at baseline was determined by linkage to the Total Population Register and the Register of Domestic Migration. We grouped the residence areas of participants into the northern, middle, and southern parts of Sweden. No information was available on other possible confounders, such as alcohol use and physical activity.

Statistical Analysis

Coverage of the Inpatient Register differed among counties over time. For subjects who lived in a county without coverage (or with incomplete coverage) before 1987, cohort entry was reset to the date at which the Inpatient Register had full coverage. Also, to exclude prevalent cases of stroke, we defined the date of complete coverage by the Inpatient Register as 2 years after the Register had actually achieved complete coverage. Each cohort member contributed person-years from the entry date until the date of first stroke diagnosis, death, emigration out of Sweden, the date for moving into a county without (or with incomplete) coverage by the Inpatient Register, or the end of year 2003, whichever occurred first. The incidence rate was standardized to the total person-years experienced by all participants, using 5-year age categories.

The associations between snuff dipping and risk of stroke were estimated by hazard ratios (presented as relative risks [RRs] with 95% confidence intervals [CIs]) derived from the Cox proportional hazards regression model with adjustment for attained age (as time scale),[17] BMI, and region of residence. Assumption of proportional hazards for snuff dipping and covariates was examined by the method of Shoenfeld's partial residuals; there was no indication of violation of the assumption for any of the variables checked in regression models.[18] To assess potential influence of selection bias, a sensitivity analysis was performed by excluding the first 5 years of follow-up.

Kaplan–Meier cumulative survival curves (all causes of death or deaths due to stroke) among those who had experienced a nonfatal ischemic stroke were plotted for ever-users of snuff and never-users, with follow-up through 2003. The log-rank test was used to examine the difference of survival curves between the 2 groups. The relative risks of mortality from all causes or stroke were similarly derived from the Cox proportional hazards regression model described above.

All analyses were conducted in SAS statistical software, version 9.1 (Cary, NC). This study was approved by the Regional Ethics Committee of Umeå University.

RESULTS

Twenty-nine percent of these never-smoking men had used snuff, with the highest proportion in the youngest group

TABLE 1. Baseline Characteristics of 118,465 Never-Smoking Male Workers in the Swedish Construction Workers Cohort, Registered From 1978–1993

Characteristics	N	(%)	Snuff Use (%)		
			Never	Former	Current
Total	118,465	(100)	71	2	27
Age at entry (y)					
<35	80,667	(68)	64	2	34
35–44	17,628	(15)	82	3	16
45–55	11,184	(10)	89	1	10
55+	8986	(8)	88	1	11
BMI[a] (weight/height^2)					
<20	7610	(6)	71	1	28
20–24	71,647	(61)	72	2	26
25–30	34,148	(29)	69	2	28
30+	5060	(4)	68	1	31
Region					
North	32,815	(28)	68	2	29
Middle	61,682	(52)	71	2	27
South	23,968	(20)	74	2	25

[a]Adjusted to age distribution at entry.

(<35 years). Snuff users in general had a higher BMI than nonusers, and snuff prevalence was highest in northern Sweden (Table 1).

During an average of 18 years (>2 million person-years) of follow-up, 3248 subjects had ischemic, hemorrhagic, or unspecified stroke as a primary cause of death or primary discharge diagnosis. Among them, 2283 (70%) had ischemic stroke, 550 (17%) hemorrhagic stroke, and 415 (13%) stroke of unspecified type. The proportion of unspecified stroke decreased during the follow-up, from 16% in 1987 to 8% in 2003. This may have been the result of introduction of new diagnostic tools, such as computed tomography scanning. The average age at diagnosis was 66, 59, and 66 years among patients with ischemic, hemorrhagic, and unspecified stroke, respectively.

Table 2 provides relative risks of all types of stroke taken together, as well as stroke subtypes, for categories of snuff use. The overall relative risk of stroke among ever-users of snuff was 1.02 (95% CI = 0.92–1.13). There was an indication of an elevated risk for fatal stroke (1.27 [0.92–1.76]), which was mainly driven by an excess risk among current snuff users (1.38 [0.99–1.91]). Further analyses on subtypes of stroke showed that the excess risk was primarily confined to ischemic stroke among ever-users of snuff (1.63 [1.02–2.62]). Among former snuff users, a tendency toward decreased risk was observed for all subtypes of stroke. Further analyses among current snuff users showed no clear evidence of a dose response effect (Table 3). Sensitivity analyses excluding the first 5 years of follow-up confirmed

TABLE 2. Standardized Incidence Rates and Relative Risks of Stroke (Hemorrhagic, Ischemic, Unspecified Stroke, and All Cerebrovascular Diseases) for Snuff Users Compared With Nonusers of Tobacco Among 118,465 Never-Smoking Swedish Construction Workers

	Never-Users[a]			Ever-Use			Former Use			Current Use		
	No. Cases	SIR	RR	No. Cases	SIR	RR (95% CI)	No. Cases	SIR	RR (95% CI)	No. Cases	SIR	RR (95% CI)
All types of stroke												
All	2805	152	1.00	443	173	1.02 (0.92–1.13)	31	104	0.72 (0.50–1.02)	412	182	1.05 (0.95–1.17)
Nonfatal	2569	139	1.00	398	154	1.00 (0.89–1.11)	30	100	0.75 (0.53–1.08)	368	161	1.02 (0.91–1.14)
Fatal	236	13	1.00	45	19	1.27 (0.92–1.76)	1	5	0.30 (0.04–2.11)	44	21	1.38 (0.99–1.91)
Ischemic stroke												
All	1979	106	1.00	304	122	1.03 (0.91–1.16)	20	72	0.68 (0.44–1.06)	284	129	1.07 (0.94–1.22)
Nonfatal	1887	101	1.00	282	112	1.00 (0.88–1.13)	19	67	0.67 (0.43–1.06)	263	118	1.04 (0.91–1.18)
Fatal	92	5	1.00	22	10	1.63 (1.02–2.62)	1	5	0.82 (0.12–5.93)	21	11	1.72 (1.06–2.78)
Hemorrhagic stroke												
All	474	26	1.00	76	25	0.86 (0.67–1.10)	8	21	0.90 (0.45–1.82)	68	26	0.85 (0.65–1.10)
Nonfatal	378	21	1.00	60	19	0.82 (0.62–1.08)	8	21	1.10 (0.54–2.21)	52	19	0.77 (0.57–1.04)
Fatal	96	5	1.00	16	6	1.05 (0.61–1.80)	0	—	—	16	7	1.17 (0.68–2.01)
Unspecified stroke												
All	352	19	1.00	63	26	1.22 (0.93–1.61)	3	11	0.66 (0.21–2.06)	60	28	1.35 (1.02–1.80)
Nonfatal	304	16	1.00	56	22	1.25 (0.93–1.67)	3	11	0.69 (0.22–2.14)	53	24	1.31 (0.98–1.77)
Fatal	48	3	1.00	7	3	1.03 (0.47–2.31)	0	—	—	7	4	1.14 (0.51–2.54)

Number of person-years was 1,524,553 for never-users, 590,925 for ever-users; 43,474 for former users, and 547,452 for current users.
[a]Reference category.
SIR indicates incidence rate (per 100,000 person-years), standardized to the age distribution of person-years experienced by all study participants using 5-year age categories; RR, relative risk derived from Cox proportional hazards regression model; adjusted for age (age at follow-up was used as time scale), BMI (weight [kg]/height [m]^2, categorized into <20, 20–24.9, 25–29.9, and ≥30) and region of residence (north, middle, and south part of Sweden).

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TABLE 3. Standardized Incidence Rates and Relative Risks of Stroke (Hemorrhagic, Ischemic, Unspecified Stroke, and All Cerebrovascular Diseases) for Current Snuff Users by Amount Used, Compared With Nonusers of tobacco Among 118,465 Never-Smoking Swedish Construction Workers

	Snuff Use (g/d)											
	<12.5			12.5–29.9			25–49.9			≥50		
	No. Cases	SIR	RR (95% CI)	No. Cases	SIR	RR (95% CI)	No. Cases	SIR	RR (95% CI)	No. Cases	SIR	RR (95% CI)
All types of stroke												
All	150	182	1.08 (0.92–1.27)	175	185	1.11 (0.95–1.29)	58	164	1.06 (0.82–1.38)	29	174	1.13 (0.78–1.64)
Nonfatal	133	161	1.05 (0.88–1.25)	155	162	1.07 (0.91–1.26)	53	150	1.05 (0.80–1.38)	27	161	1.13 (0.77–1.66)
Fatal	17	21	1.42 (0.86–2.32)	20	24	1.57 (0.99–2.49)	5	14	1.24 (0.51–3.03)	2	12	1.16 (0.29–4.69)
Ischemic stroke												
All	106	129	2.11 (1.10–4.07)	117	128	1.66 (0.80–3.44)	40	120	0.66 (0.09–4.76)	21	130	3.28 (0.79–13.6)
Nonfatal	96	117	1.05 (0.85–1.28)	109	118	1.08 (0.89–1.31)	39	116	1.15 (0.83–1.58)	19	118	1.19 (0.76–1.88)
Fatal	10	13	2.11 (1.10–4.07)	8	10	1.99 (0.80–3.44)	1	5	0.66 (0.09–4.76)	2	12	3.28 (0.79–13.6)
Hemorrhagic stroke												
All	20	23	0.79 (0.51–1.24)	31	26	0.92 (0.64–1.33)	11	22	0.83 (0.45–1.52)	6	24	0.91 (0.40–2.05)
Nonfatal	15	17	0.73 (0.44–1.23)	23	18	0.82 (0.53–1.25)	8	17	0.70 (0.35–1.42)	6	24	1.05 (0.47–2.37)
Fatal	5	6	1.05 (0.43–2.59)	8	8	1.43 (0.69–2.96)	3	5	1.56 (0.46–4.99)	0		—
Unspecified stroke												
All	24	30	1.39 (0.92–2.10)	27	30	1.46 (0.98–2.17)	7	21	1.16 (0.55–2.47)	2	20	0.75 (0.19–3.03)
Nonfatal	22	27	1.49 (0.97–2.30)	23	25	1.42 (0.93–2.18)	6	17	1.11 (0.49–2.50)	2	20	0.81 (0.20–3.27)
Fatal	2	3	0.78 (0.19–3.21)	4	5	1.71 (0.62–4.76)	1	5	1.65 (0.22–12.06)			—

these results, and showed a relative risk of 1.71 (1.06–2.77) for fatal ischemic stroke among ever-users of snuff.

Kaplan–Meier survival curves among those who experienced a nonfatal ischemic stroke during follow-up, either from any cause or from stroke, are shown in Figures 1 and 2. Compared with nonusers, snuff users had a higher probability of dying from either all causes (P value from log-rank test = 0.08) or stroke (P value from log-rank test = 0.02). With multivariable analyses, the relative risk for mortality from all causes was 1.32 (1.07–1.65) for ever-users of snuff compared

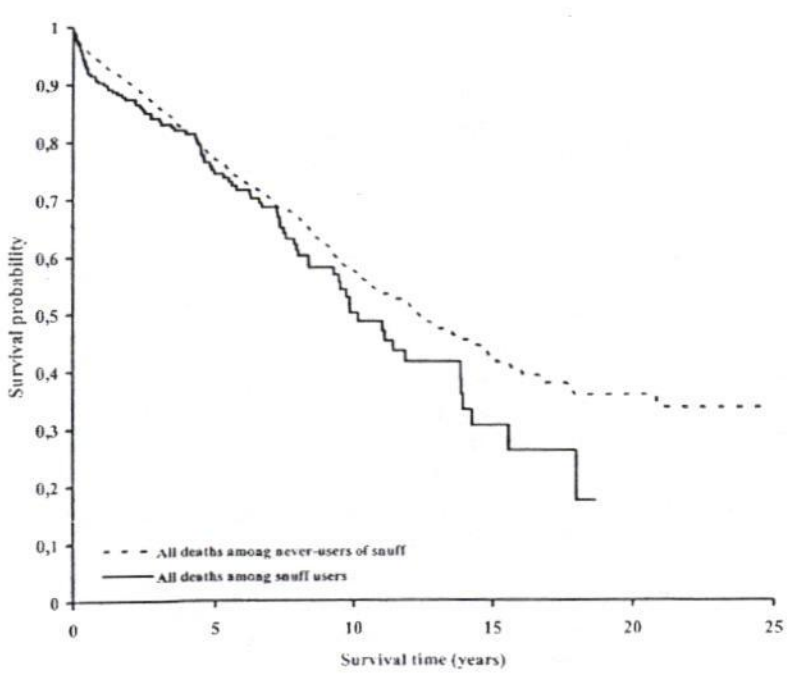

FIGURE 1. Kaplan–Meier survival curves for all deaths among male never-smoking Swedish construction workers with prior nonfatal ischemic stroke, stratified by snuff use at baseline.

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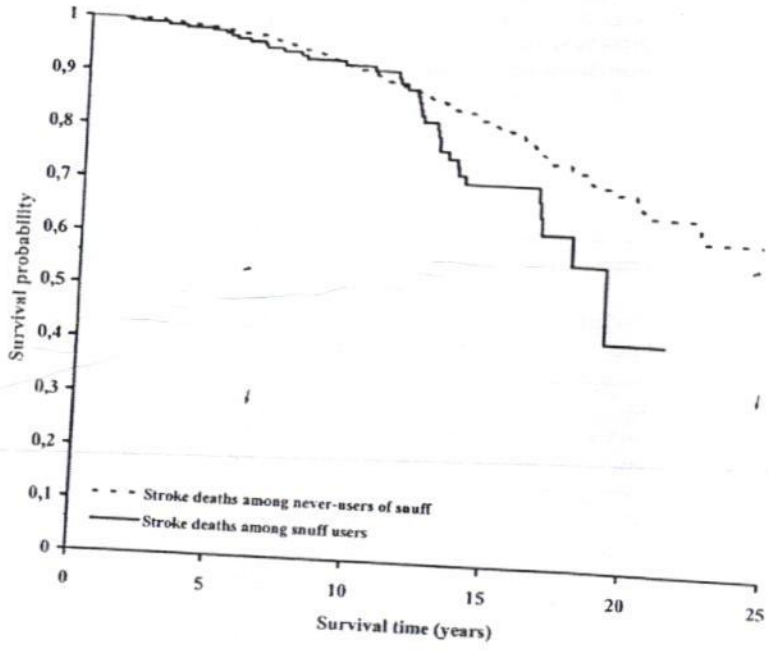

FIGURE 2. Kaplan–Meier survival curves for stroke deaths among male never-smoking Swedish construction workers with prior nonfatal ischemic stroke, stratified by snuff use at baseline.

with nonusers of tobacco. The corresponding relative risk for mortality from stroke was 1.52 (1.01–2.29).

DISCUSSION

We found no evidence of an overall elevated risk of stroke or nonfatal stroke among snuff users. However, there was an increased risk for fatal ischemic and unspecified stroke among snuff users. Our finding of no overall excess risk of stroke among snuff users is in line with 2 previous studies in Sweden.[9,12] We observed an elevated risk for fatal stroke among snuff users and also found evidence that the effect was strongest for fatal ischemic stroke among current snuff users. Results from previous studies of the association of snuff use with cerebrovascular death are inconclusive; 2 studies showed an increased risk,[11,19] whereas 2 did not.[8,12] Only 1 previous study looked separately at former and current snuff users,[11] with stronger effects among current users. None of the previous studies has subdivided stroke into subtypes. Our results did not indicate an increased risk of hemorrhagic stroke among snuff users, corroborating negative findings from a recently published Swedish study on snuff use and subarachnoid hemorrhage.[20]

Differences in etiology between hemorrhagic and ischemic stroke could help explain our results. Smoking is a well-known risk factor for stroke, and this effect seems more consistent for ischemic stroke.[3,21] A rapid decline in excess risk following cessation of smoking has suggested an acute effect from tobacco. This is supported by our data, in which the increased risk was confined to current users of snuff. We found some evidence of decreased risk for stroke among former snuff users. This may reflect negative confounding if more health cautious men quit snuff use.

Biologic mechanisms by which snuff might cause fatal ischemic stroke are not implausible. Results from animal studies show that nicotine can induce cardiac arrhythmias.[7] About 20% of all strokes are cardioembolic strokes, and atrial fibrillation is a risk factor for this type of ischemic stroke.[22,23] Cardiac embolization may explain the observed differences of risk between ischemic and hemorrhagic stroke. Also, results from in vitro studies suggest that nicotine opens the blood brain barrier, which could increase the severity of the stroke by allowing postischemic brain edema.[24] A previous study on snuff use and myocardial infarction also found an increased risk of fatal myocardial infarction, but not nonfatal cases.[25]

This study is the largest study to date on the possible association between snuff use and stroke risk. Disease-related misclassification of exposure was not an issue because data on exposure and outcome were collected from independent sources in a prospective manner. Follow-up was virtually complete, which diminishes the influence of selection bias, and the restriction of our study subjects to never-smokers minimized the risk of confounding by smoking.

Some weaknesses of our study should also be pointed out. Although use of the Inpatient Register in combination with the Causes of Death Register is an efficient way to identify cases of stroke,[26] this may lead to inclusion of nondefinite events, ie, false positives.[27] However, there is no reason to believe that misclassification of disease would differ between exposure groups (snuff users and nonusers). If anything, misclassifica-

tion would lead to a dilution of associations. Studies of stroke subtypes can be difficult due to misclassification.[27] By using only first events of stroke we decreased this problem. Further, our data suggested differential effects of snuff on risks of hemorrhagic and ischemic stroke, which allayed such a concern. Our analyses were based on the baseline information, because health status (eg, early symptoms of stroke) and exposure status (eg, snuff use) might correlate with the likelihood of obtaining later check-ups.

During extended follow-up, misclassification of exposure is a concern; tobacco use can change. Snuff users who had never smoked could be more inclined than never-users of tobacco to take up smoking during follow-up. However, previous sensitivity analysis suggests this concern is of limited influence.[28] We had information only on daily smoking; snuff users may be occasional smokers to a larger extent than never-users of tobacco. However, the observed differential associations between snuff use and risk of stroke subtypes (ischemic vs. hemorrhagic or nonfatal vs. fatal) allayed this concern, in that smoking is a risk factor for all types of stroke. Further, no excess risk of lung cancer was observed among never-smoking snuff users, as compared with nonusers of tobacco.[29] Alcohol is an important risk factor for stroke, especially hemorrhagic stroke.[30] The lack of association between snuff use and hemorrhagic stroke suggests that confounding from alcohol is unlikely to have had an important influence. Our study base consisted of male construction workers, which reduced the risk of confounding by sex, socioeconomic status, or education. Confounding by dietary and other life style factors is possible, but this would have to affect mainly fatal ischemic stroke to explain our results.

In conclusion, our results suggest that use of Swedish moist snuff is associated with an increased risk of fatal ischemic stroke. Considering the increasing prevalence of snuff use in Sweden, this association deserves to be pursued further.

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Annexe 91

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ORIGINAL ARTICLE

Contribution of Swedish moist snuff to the metabolic syndrome: A wolf in sheep's clothing?

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Abstract

Aim: Combined effects of genetic and environmental factors underlie the clustering of cardiovascular risk factors in the metabolic syndrome (MetSy). The aim was to investigate associations between several lifestyle factors and MetSy, with a focus on the possible role of smokeless tobacco in the form of Swedish moist snuff (snus). *Methods:* A population-based longitudinal cohort study within the Västerbotten Intervention Programme in Northern Sweden. All inhabitants at the ages of 30, 40, 50, and 60 are invited to participate in a health survey that includes a questionnaire on psychosocial conditions and lifestyle and measurement of biological variables. Individuals examined in 1990–94 (n=24,230) and who also returned for follow-up after 10 years were included (total of 16,492 individuals: 46.6% men and 53.4% women). Regression analyses were performed. MetSy was the outcome and analyses were adjusted for age, sex, alcohol abuse, and family history of CVD and diabetes. *Results:* Ten-year development of MetSy was associated with high-dose consumption of snus at baseline (OR 1.6 [95% CI 1.26–2.15]), low education (2.2 [1.92–2.63]), physical inactivity (1.5 [1.22–1.73]) and former smoking (1.2 [1.06–1.38]). Snus was associated with separate components of MetSy, including triglycerides (1.6, 1.30–1.95), obesity (1.7 [1.36–2.18]) but not hypertension, dysglycemia and low HDL cholesterol. *Conclusions:* MetSy is independently associated with high consumption of snus, even when controlling for smoking status. The finding is of public health interest in societies with widespread use of snus. More research is needed to better understand the mechanisms underlying this effect.

Key Words: *Lifestyle, metabolic syndrome, smokeless tobacco, risk factors, public health*

Introduction

The metabolic syndrome (MetSy) is a worldwide time bomb, fuelled by increasing obesity [1] and signified clinically and epidemiologically by its association with cardiovascular disease (CVD) [2]. There are several working definitions of MetSy with varying constellations and criteria of the principal components: obesity, impaired glucose regulation, dyslipidemia, and hypertension [3–5]. MetSy is currently debated primarily because an underlying pathophysiologial cause (or causes) has not been clearly elucidated and no specific treatment is available that targets the syndrome beyond the usual treatments of its individual components [6,7]. However, MetSy is thought to facilitate the clinical focus on individuals at high risk of CVD and diabetes [5].

Interacting effects of genetic and environmental factors underlie the clustering of MetSy components [4]. Although genes determine the individual susceptibility to obesity and MetSy, the main reasons for the obesity epidemic are societal changes with increased consumption of energy-dense food and

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decreased physical activity [1]. Psychosocial and sociodemographic factors [8], as well as heavy use of alcohol and cigarette smoking, also contribute to MetSy [9].

In Northern Sweden, rapid shifts in lifestyle habits are occurring with a substantial decrease in smoking, especially among men, paralleled with increased use of Swedish moist snuff (snus) in both men and women [10]. It has been proposed that the use of snus is contributing to the decline in smoking rates [11]. However, snus is not necessary for smoking cessation at the population level [12].

Numerous studies have shown a link between smoking and several components of MetSy [13]. Studies on the effect of smokeless tobacco are fewer and have conflicting results. While acute effects of exposure to smokeless tobacco such as increased heart rate and blood pressure have been reported [14], chronic effects on blood pressure and glucose and insulin levels have not been found [15,16]. However, associations between snus and overweight [17] and triglycerides [15] have been demonstrated. One study also showed ultrasound-measured subclinical atherosclerosis among smokers but not among snus users [15]. Another study demonstrated impaired endothelial function among snus users [18]. A large Swedish study found increased CVD mortality among construction workers using snus [19]. Other studies from Sweden have failed to prove an increased risk of myocardial infarction [20,21] or stroke [22]. Heavy consumers of snus (≥3 cans/week) have been reported to have an increased risk of type 2 diabetes [23]. Another study that did not stratify for different doses of snus failed to find any association with diabetes among snus users [24].

Several overview articles have concluded that although the tobacco-associated risk of disease undoubtedly is greater with smoking, most studies on smokeless tobacco have been too small to be conclusive. More research, with larger and longitudinal panel studies, is therefore needed on the impact of smokeless tobacco on disease outcomes [25–27]. In this study we use a prospective cohort design to investigate associations between lifestyle factors and MetSy, with a focus on the possible role of snus as one piece in the jigsaw puzzle of lifestyle patterns.

Material and methods

This is a prospective cohort study using a subset of the Västerbotten Intervention Programme (VIP), a community programme for prevention of CVD and diabetes. VIP started 1985 in the county of Västerbotten in northern Sweden and has been described in detail previously [28]. Briefly, at the ages of 30, 40, 50, and 60 years, all inhabitants are invited to their primary care centre for a health survey. Participants answer a comprehensive questionnaire on psychosocial conditions and lifestyle. An oral glucose tolerance test (OGTT) is performed. Body mass index (BMI), blood pressure, and blood lipids are measured. Central obesity, as measured by waist circumference, was not recorded until 2003. HDL cholesterol was measured only if the total cholesterol was > 6.5 mmol/L or if any of the other criteria of MetSy according to the WHO definition were present. At the end of the health survey information about the examination results and individual lifestyle counselling were given. When the programme was launched, reduction of hypertension, hypercholesterolemia, and smoking was targeted since these were established CVD risk factors. The participation rate has been 60% on average. No significant differences in socioeconomic status have been demonstrated between participants and non-participants [28]. The present study includes individuals aged 30, 40, or 50 years who first were examined in 1990–94 (n=24,230) and returned for follow-up 10 years later. This comprises a total of 16,492 individuals (46.6% men and 53.4% women).

Metabolic syndrome was identified at follow-up according to the new definition from the International Diabetes Federation (IDF). This definition assumes central obesity if the BMI is > 30 [5] (Table I). The National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) definition was not applied since waist circumference was not measured in the whole study population. The World Health Organization (WHO) definition was used in an additional analysis.

Subjects were grouped according to lifestyle habits and educational level at baseline. Smoking was stratified into non-smoking, ex-smoking, and daily smoking. The non-smoking group included never smokers, those who smoked occasionally, and former occasional smokers. Ex-smoking included only former daily smokers. Daily smoking included daily smokers of cigarettes (without grading due to number of cigarettes consumed), cigar, and pipe. The questionnaire encoded the use of snus as follows: never use, former use, consumption of < 2 cans of snus/week, 2–4 cans/week, 5–6 cans/week, or ≥7 cans/week. For simplicity this was categorized into no use (including never and former use), low dose use (≤ 4 cans/week), and high dose use (> 4 cans/week). The Cage questionnaire was used to

Table I. Criteria for the clinical diagnosis of Metabolic Syndrome according to the World Health Organization (WHO), National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) and the International Diabetes Federation (IDF).

WHO criteria	
Impaired glucose regulation identified by one of the following:	Plus any two of the following:
• Type 2 diabetes	• Blood pressure≥140/90 and/or antihypertensive medication
• Impaired fasting glucose	• Triglycerides≥1.7 mmol/L and/or HDL cholesterol<0.9 mmol/L in men, <1.0 mmol/L in women
• Impaired glucose tolerance	• BMI≥30 and/or waist–hip ratio>0.9 in men, >0.85 in women
• Lowest quartile glucose uptake under hyperinsulinemic euglycaemic conditions	• Urinary albumin≥20 μg/min or albumin:creatinine ratio≥30 mg/g
NCEP/ATP III criteria	
Any three of the following:	
• Fasting plasma glucose≥5.6 mmol/L	
• Blood pressure≥130/85 or antihypertensive medication	
• Triglycerides≥1.7 mmol/L or specific drug treatment	
• HDL cholesterol<1.0 mmol/L in men, <1.3 mmol/L in women or specific drug treatment	
• Waist circumference≥102 cm in men, ≥88 cm in women	
IDF criteria	
• Waist≥94 cm in men, ≥80 cm in women[1]	Plus any two of the following:
	• Blood pressure≥130/85 and/or antihypertensive medication
	• Triglycerides≥1.7 mmol/L or medication
	• HDL cholesterol<1.03 mmol/L in men, <1.29 mmol/L in women or medication
	• Fasting plasma glucose≥5.6 mmol/L[2] or previously known diabetes

[1]If BMI is>30, central obesity can be assumed and waist circumference need not be measured. [2]In clinical practice, impaired glucose tolerance (IGT) is also accepted. Prevalences including IGT can be added as supplementary findings.

evaluate for alcohol abuse and graded on the number of positive answers to the four questions (Cut down, Annoyance, Guilt, Eye-opener) [29]. Level of education was grouped into high (≥13 school years or university), medium (10–12 years), and low (9 years or less). Physical activity was assessed from a question on exercise in training clothes in leisure time, and stratified into four groups: at least twice/week, once/week, "now and then", and "never". Univariate and multivariate logistic regression analyses were performed using SPSS v11, with lifestyle variables at baseline as predictors and the presence of the metabolic syndrome at follow-up as outcome.

The protocol was approved by the Research Ethics Committee of Umeå University and all participants gave informed consent.

Results

Clinical characteristics for participants at baseline and follow-up are given in Table II. The frequency of missing data was 0–5% except for HDL cholesterol, which was missing in 87.9% of women and 86.2% of men at baseline and in 75.2 and 71.4%, respectively, at follow-up. There were 594 subjects with obesity and also one trait out of dysglycemia, hypertension, or hypertriglyceridemia. This could have added at maximum 3.6% to the MetSy prevalence, provided all of them also had low HDL cholesterol. The study subjects were in early middle age at baseline. We did not use the result of 2-h glucose testing in the case definition of MetSy according to IDF as this only added 9 women and 6 men with MetSy at follow-up. There were significant shifts in almost all metabolic variables from baseline to the re-examination at 10-year follow-up. Of note is the large increase in use of lipid-lowering and antihypertensive medications. There was a decrease in smoking rates with only 12.7% of men and 15.6% of women categorized as daily smokers at follow-up. The use of snus, mainly low-grade consumption, increased with a near doubling among women from 3.1% to 6.0%. Almost one out of four men used snus at baseline and there was a small but significant increase to 26.3% at follow-up. Physical activities in leisure time also changed: the number of those who reported never exercising increased, as well as the number reporting exercising at least twice a week. Women reported significantly more, and men significantly fewer alcohol problems at follow-up.

The results of bivariate and multivariate regression analyses are given in Table III. All evaluated lifestyle factors were significantly associated with the

Table II. Clinical characteristics for women and men at baseline and 10-year follow-up. Mean ± SD or numbers of observations and frequency are given.

	Women n=8,800			Men n=7,692		
	Baseline	Follow-up		Baseline	Follow-up	
Age, years	41.6 ± 7.6	51.1 ± 7.6		41.2 ± 7.7	51.2 ± 7.7	
Metabolic syndr IDF n (%)	311 (3.5)	940 (10.7)	<0.001	276 (3.6)	864 (11.2)	<0.001
Metabolic syndr WHO n (%)	158 (1.8)	768 (8.7)	<0.001	140 (1.8)	836 (10.9)	<0.001
Body mass index (kg/m^2)	24.4 ± 3.9	26.0 ± 4.6	<0.001	25.5 ± 3.1	26.6 ± 3.7	<0.001
Triglycerides (mmol/L)	1.2 ± 0.7	1.3 ± 0.8	<0.001	1.5 ± 1.0	1.5 ± 0.9	0.743
Cholesterol (mmol/L)	5.37 ± 1.12	5.42 ± 1.06	<0.001	5.62 ± 1.21	5.43 ± 1.06	<0.001
HDL cholesterol[1] (mmol/L)	1.5 ± 1.0	1.4 ± 0.6	0.152	1.5 ± 2.4	1.1 ± 0.5	0.001
Lipid-lowering drug n (%)	11 (0.1)	261 (3.0)	<0.001	32 (0.4)	374 (4.9)	<0.001
Systolic BP (mmHg)	120.5 ± 15.0	126.5 ± 18.7	<0.001	125.3 ± 13.8	128.9 ± 16.8	<0.001
Diastolic BP (mmHg)	75.6 ± 10.1	76.4 ± 10.5	<0.001	78.5 ± 10.0	79.6 ± 11.4	<0.001
Antihypertensive drug n (%)	417 (4.7)	1352 (15.4)	<0.001	261 (3.4)	1015 (13.2)	<0.001
Fasting P-glucose[1] (mmol/L)	5.1 ± 0.7	5.6 ± 0.9	<0.001	5.2 ± 0.8	5.8 ± 1.3	<0.001
2-hour P-glucose[2] (mmol/L)	6.6 ± 1.4	7.0 ± 1.6	<0.001	5.9 ± 1.4	6.6 ± 1.7	<0.001
Ex-smoker n (%)	1502 (17.1)	1933 (22.0)	<0.001	1709 (22.2)	1989 (25.9)	<0.001
Daily smoker n (%)	1957 (22.2)	1374 (15.6)	<0.001	1418 (18.4)	978 (12.7)	<0.001
Snus ≤ 4 cans/week n (%)	238(2.7)	454 (5.2)	<0.001	1449 (18.9)	1487 (19.3)	<0.001
Snus > 4 cans/week n(%)	32 (0.4)	68 (0.8)	<0.001	438 (5.7)	532 (6.9)	<0.001
Physically inactive[3] n (%)	3147 (37.4)	3677 (43.7)	<0.001	2797 (37.9)	3365 (45.6)	<0.001
Physically active[4] n (%)	990 (11.8)	1513(18.0)	<0.001	1143 (15.5)	1380 (18.7)	<0.001
Alcohol[5] n (%)	180 (2.0)	216 (2.8)	<0.001	727 (9.4)	694 (9.0)	<0.001
Family history[6] n (%)	1336 (32.1)	1609 (38.7)	<0.001	1032 (28.8)	1233 (34.4)	<0.001

IDF=International Diabetes Federation. WHO=World Health Organization. [1]Frequency missing data among women and men at baseline 87.9 and 86.2% respectively, at follow-up 75.2 and 71.4% respectively. [2]Measured on capillary plasma at an oral glucose tolerance test. [3]Exercise/training in leisure time: never. [4]Exercise/training: at least twice a week. [5]Cage questionnaire: Answered yes on at least two of the four questions. [6]Family history of cardiovascular disease or/and diabetes in first-degree relatives

MetSy according to the IDF definition. The odds ratio (OR) for family history of CVD and/or diabetes was 1.4 (CI 95% 1.29–1.59). The Cage questionnaire on alcohol habits showed a trend with increasing ORs with number of positive answers to the four questions. Ex-smoking, daily smoking, and consumption of >4 cans of snus/week were significantly associated with MetSy in univariate analysis, but only ex-smoking and high snus consumption contributed to the multivariate model. When the analyses were repeated using the WHO definition of MetSy, results were similar (data not shown). In additional analyses the original variable on snus use was applied with never use of snus as reference. Both in the bivariate and the full model there were significant ORs only for high doses of snus, in the multivariate model 1.5 (1.13–2.10) for consumption of 5–6 cans/week and 2.0 (1.20–3.39) for ≥7cans/week and all other ORs were unchanged.

We also evaluated possible associations of lifestyle factors with the separate components of the metabolic syndrome, i.e. according to the IDF definition, with adjustment for age, sex, educational level, Cage questionnaire, exercise habits, and family history of CVD and/or diabetes (Table IV). In this multivariate analysis daily smoking was not associated with obesity, while there seemed to be a decreased risk of hypertension and increased risk of the other components. We found increased ORs among ex-smokers for all MetSy components except low HDL cholesterol. Any use of snus was associated with hypertriglyceridemia and high snus consumption was associated with obesity. Further adjustment with BMI at baseline and BMI at follow-up in the multivariate analysis with hypertriglyceridemia as outcome showed excess risk for ex-smoking, daily smoking, low-dose and high-dose snus consumption with ORs 1.2 (1.10–1.35), 1.6 (1.48–1.81), 1.2 (1.06–1.37) and 1.4 (1.16–1.78) respectively.

Discussion

To our knowledge, this large-scale longitudinal panel study is the first study to show an independent association between metabolic syndrome and high snus consumption, even when controlling for smoking. However, we could not demonstrate an impact of snus on each of the separate features of metabolic

Table III. Bivariate regression analyses for lifestyle risk factors at baseline with the outcome metabolic syndrome at follow-up.[1]

	MetSy at follow-up *n*		Univariate model		Multivariate model	
Risk factors at baseline	Yes	No	OR	CI (95%)	OR	CI (95%)
Education						
High	248	3,534	1.0			
Medium	922	7,557	**1.8**	1.53–2.05	**1.7**	1.43–1.92
Low	586	3,342	**2.5**	2.10–2.87	**2.2**	1.91–2.63
Alcohol problem[2] (4 questions)						
No	1,563	12,696	1.0			
1 yes	134	1,192	1.0	0.80–1.17	1.0	0.81–1.19
2 yes	73	583	1.1	0.84–1.40	1.1	0.85–1.42
3 yes	24	160	1.3	0.86–2.05	1.2	0.74–1.83
4 yes	12	55	**1.9**	1.00–3.51	1.4	0.68–2.68
Exercise/training						
At least twice a week	182	1977	1.0			
Once/week	276	3136	0.9	0.76–1.13	1.0	0.79–1.17
Now and then	503	3861	**1.4**	1.16–1.65	**1.4**	1.14–1.64
Never	764	5245	**1.5**	1.29–1.82	**1.5**	1.22–1.73
Smoking						
Non-smoking	988	8918	1.0			
Ex-smoker	416	2795	**1.3**	1.18–1.51	**1.2**	1.06–1.38
Daily smoking	402	2973	**1.2**	1.06–1.35	1.0	0.89–1.16
Swedish moist snuff, snus						
No use	1498	12,344	1.0			
⩽4 cans/week	174	1516	1.1	0.90–1.27	1.0	0.85–1.22
>4 cans/week	74	396	**1.8**	1.36–2.30	**1.6**	1.26–2.15

[1]The analyses were adjusted for age, sex, and family history of CVD and/or diabetes in first-degree relatives at follow-up. Statistically significant findings are shown in bold. [2]Cage questionnaire.

syndrome. There was an independent association between high, but not low, snus consumption and obesity development [17]. Second, there was a significant and dose-dependent association between the use of snus at baseline and hypertriglyceridemia after 10 years. Lastly, high-dose snus consumption was associated with hypertension although this did not reach statistical significance. In contrast, we could not demonstrate a link to dysregulation of glucose or HDL cholesterol. Our results are similar to a recent cross-sectional study that showed a dose-dependent association between smoking and MetSy and hypertriglyceridemia, low HDL cholesterol, and abdominal obesity [30]. Our results also support previous findings of associations between family history of CVD and diabetes, educational level, physical inactivity, and smoking with metabolic syndrome.

Table IV. Odds ratios (95% confidence intervals) for smoking and snus consumption in multivariate regression analyses with the components of the metabolic syndrome as outcomes.

	OR of components of Metabolic Syndrome at 10-year follow-up				
Risk factors at baseline[1]	f- P-glucose⩾5.6 or diabetes[2]	Triglycerides⩾1.7	Low HDL cholesterol[3]	Hypertension[4]	Body mass index⩾30
Smoking					
Ex-smoker	**1.2** (1.15–1.35)	**1.3** (1.16–1.41)	1.1 (1.00–1.27)	**1.2** (1.07–1.27)	**1.2** (1.04–1.30)
Daily smoking	**1.3** (1.23–1.45)	**1.6** (1.43–1.73)	**1.2** (1.07–1.35)	**0.8** (0.75–0.89)	1.1 (0.98–1.23)
Use of snus					
⩽4 cans/week	1.0 (0.86–1.08)	1.2 (1.05–1.35)	1.0 (0.86–1.18)	0.9 (0.84–1.05)	1.0 (0.88–1.20)
>4 cans/week	0.8 (0.69–1.02)	**1.6** (1.30–1.95)	1.1 (0.82–1.42)	1.2 (0.99–1.46)	**1.7** (1.36–2.18)

The metabolic syndrome was defined according to the International Diabetes Federation (IDF). [1]Non-smoking and no use of snus are references with OR 1.0. Multivariate regression analyses were adjusted for age, sex, educational level, alcohol use by Cage questionnaire, physical activity/exercise in leisure time, and family history in first-degree relatives of CVD and/or diabetes. Statistically significant findings are shown in bold. [2]Fasting plasma glucose⩾5.6 mmol/L or diabetes known before the health survey. [3]HDL cholesterol ⩽ 1.03 in men and HDL ⩽ 1.29 mmol/L in women or lipid-lowering medication. [4]Blood pressure⩾130/85 mmHg or ongoing antihypertensive medication.

Our results agree with several previous studies showing associations between snus and MetSy components of obesity [17,21], hypertriglyceridemia [15] and hypertension [21]. Dose–response relationships between snus and metabolic parameters, as indicated by our results, might explain why previous studies with smaller sample sizes or samples that did not dose-stratify have failed to show associations [16] or have shown non-significant trends [14,31]. A dose-dependent effect from snus is supported by animal studies, which show that high doses of nicotine induce lipolysis in adipose tissue, leading to increased levels of free fatty acids, thereby causing increased levels of triglycerides by the production of very low-density lipoproteins in the liver [25]. Snus may cause impaired endothelial function [18] and thereby further increase cardiovascular risks. This effect and a hypertensive effect have also been suggested as explanations of adverse pregnancy outcomes in snuff users [32]. However, our study can not explain the mechanism of the dysmetabolic effects, particularly at high doses, from snus. In addition to a direct effect from nicotine, or any other chemical substance in snus, the use of snus might also be a marker of other unhealthy behaviours, e.g. food or alcohol habits, as has previously been shown for smoking [33].

Studies on snus and disease outcomes, particularly cardiovascular disease and diabetes, have shown inconsistent results [13,19,20,22,23]. This might be attributed to methodological problems. The large study by Bolinder showed a significant excess risk of cardiovascular disease in snus users compared with non-users of tobacco, but a significantly lower risk than that of smokers [19]. That study has been criticized as it was not adjusted for alcohol consumption and cholesterol. In the studies by Huhtasaari and Asplund [20,22] the snuff-using group was confounded by ex-smokers. In a recent study on myocardial infarction by Hergens the analysis was based on very few cases of former ($n=7$) or current ($n=10$) snuff users not being former or current smokers. Similar concerns can be raised regarding recent studies on diabetes risk and snus [13,23] although the study by Eliasson also had a prospective longitudinal observational design.

In this study we did not stratify smokers by number of cigarettes smoked. However, it is shown that ex-smokers have higher and smokers have lower BMI than non-smokers, and that smokers have a more central fat distribution than non-smokers, with higher waist the more smoked cigarettes (pack years) [34]. Visceral fat has more adverse metabolic effects [5] and this might explain why daily smoking, although not significantly associated with obesity, affected the other components of MetSy in different directions, i.e. increased risk of dysglycemia, hypertriglyceridemia, and low HDL cholesterol and reduced risk of hypertension (see Table IV). These findings support other studies [30], and might explain why we did not find any independent association between daily smoking and MetSy. Ex-smoking, on the other hand, was independently associated with obesity and this might explain the association with MetsSy and its components.

The study should be interpreted with some methodological issues in mind. First it has the strength that it is population-based, large, and longitudinal. Because it is prospective there is no issue of recall bias in the evaluation of the long-term lifestyle habits. One weakness is that we were not able to evaluate alcohol consumption objectively, but were dependent on self-report. The Cage questionnaire is only able to evaluate problems from alcohol abuse. We could not evaluate social conditions in terms of economic situation or occupation but education should be relevant as a socioeconomic measure.

According to the IDF definition we assumed central obesity when BMI was ≥ 30 and did not include the waist. Therefore subjects with BMI < 30 with central obesity and MetSy were missed. VIP has been launched as an intervention programme and therefore subjects who already have established contact with a physician or have a disease might be less prone to participate in the health survey, leading to a possible selection towards a healthy population and contributing to the considerably lower prevalence of MetSy as compared with other studies [2]. However this should not weaken the results with regard to possible effects from snus and other variables, as the effects on less healthy populations probably should be at least as large. The missing values of HDL cholesterol could also to some extent explain the comparatively low prevalences for MetSy in this study.

MetSy includes several single risk factors and this might be especially relevant to snus since it appears to be a product that has the potential to influence several biological metabolic systems. We consider MetSy to be a clinically relevant outcome for research on effects of snus. MetSy is also applicable in the clinical setting because it enables us to focus on individuals at high risk of CVD with multiple possible ways to intervene [4,5]. In our study, the results were essentially the same irrespective of whether the IDF or the WHO definition of MetSy was applied. Therefore it should be possible to generalize our results to cardiovascular morbidity

and mortality as is shown for MetSy by the WHO definition [2]. However, more research is needed to explore the possible role of snus in CVD and diabetes. Both longitudinal studies and experimental mechanistic studies would shed needed light on this subject. The consumption pattern of snus is complicated and highly associated with smoking. People shift from current to former use of either snus or smoking and some use both products concomitantly. Since the CVD risk of smoking is considered to be greater than that of snus, further large studies are needed to separate potential snus effects, at different doses, from effects of smoking and other lifestyle habits. Even if snus carries a smaller individual risk than smoking, from a public health perspective the rapidly increasing use of snus, in both men and women and particularly in the younger subgroups of the population, must be seen as a highly relevant concern.

In summary, in addition to the well-known health risks of cigarette smoking and physical inactivity, high doses of snus increase the risk of metabolic syndrome. Snus has the greatest effect on obesity and hypertriglyceridemia but may also increase risk of hypertension. This is an important public health issue, at least in societies with widespread snus use. At the present time it would be wise to abstain from declaring snus harmless in respect of MetSy with subsequent risk of CVD and diabetes.

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Relationship between semen quality and tobacco chewing in men undergoing infertility evaluation

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Objective: Male fertility is affected by a variety of lifestyle habits that include tobacco use. A large population of Indian men is addicted to tobacco chewing. The objective of our study was to assess the relationship between tobacco chewing in these Indian men—who were part of an infertile couple—and their sperm characteristics.
Design: Retrospective study.
Setting: Private infertility clinic.
Patient(s): Six hundred thirty-eight male patients undergoing infertility evaluations were grouped according to the frequency of their tobacco chewing habit: mild (<3 times/day, n = 177), moderate (3–6 times/day, n = 264), and severe (>6 times/day, n = 197).
Intervention(s): None.
Main Outcome Measure(s): Sperm characteristics (concentration, motility, morphology, and viability).
Result(s): Sperm concentration, percentage motility, morphology, and percentage viability were significantly higher in the mild group vs. the moderate group and in the moderate group vs. the severe group. The percentage of men with azoospermia rose with the level of addiction (1%, 3%, and 14%) as did the percentage of men with oligoasthenoteratozoospermia (2%, 8%, and 29%), although the differences were not statistically significant.
Conclusion(s): In our study, use of chewing tobacco by a group of Indian men who were undergoing infertility evaluation was strongly associated with a decrease in sperm quality and to a lesser extent with oligoasthenozoospermia or azoospermia. Infertile men should be counseled about the adverse effects of tobacco chewing on sperm quality. (Fertil Steril® 2005;84:649–53. ©2005 by American Society for Reproductive Medicine.)

Key Words: Male infertility, tobacco chewing, sperm quality

Tobacco chewing constitutes one of the forms of smokeless tobacco. In the United States, smokeless tobacco consumption has increased threefold, and manufacturing output grew 8 years in a row as reported by the United States Department of Agriculture in 1993. Estimates of smokeless tobacco users in the United States range from 6 million to 22 million (1). A national survey conducted on 5,894 college and university students from different regions of the United States revealed that 8%–15% of the students used smokeless tobacco (2). Moreover, a recent study has identified that 14.8% of male high school students in the United States were current users in 2001 (3).

The habit appears to be very common among specific population groups. As an example, lower-income black and white men regularly chew tobacco more so than upper-income classes (4). The habit also appears to be common in young amateur and professional baseball athletes (5) and in other parts of the world, such as India, China, and the southeast Asia region (6). In India, chewing tobacco is systematically associated with socioeconomic markers at the individual and household level. Individuals with no education are 2.69 times more likely to smoke and chew tobacco than those with a postgraduate education (7).

In general, smokeless tobacco is substantially less harmful than smoking (8). A meta-analysis showed that tobacco chewing increases the risk of respiratory tract cancers minimally (9). It is also true that tobacco chewing is associated with a lower risk for adverse cardiovascular effects than is smoking (10). However, the habit has been strongly associated with oral malignant diseases and is considered the most important risk factor for multiple oral premalignant lesions (11).

Several carcinogens have been identified in smokeless tobacco; the tobacco-specific N-nitrosamine (TSNA), N′-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are the most important. NNN and NNK are formed from nicotine during curing, aging, and

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TABLE 1

Comparison of sperm parameters in all semen samples collected from mild, moderate, and severe tobacco chewing groups.

Parameter	Mild group (n = 177)	Moderate group (n = 264)	Severe group (n = 197)
Sperm count (10^6/mL)	77.95 ± 49.36[b,c]	47.59 ± 27.39[a,c]	27.25 ± 29.49[a,b]
Motility (%)	60.87 ± 8.74[b,c]	56.69 ± 10.4[a,c]	49.29 ± 16.88[a,b]
Morphology (%)	33.79 ± 12.92[b,c]	27.0 ± 10.53[a,c]	18.62 ± 9.27[a,b]
Viability (%)	64.1 ± 8.98[b,c]	59.38 ± 10.39[a,c]	52.55 ± 15.51[a,b]

Note: Values are expressed as mean ± standard deviation. $P<.001$ was considered significant using one-way ANOVA compared to: [a] mild group; [b] moderate group; [c] severe group.

Said. Tobacco chewing and male infertility. Fertil Steril 2005.

especially during fermentation (12). Other compounds, such as 3-methylnitrosaminopropionaldehyde (MNPA), negatively affect DNA by causing single-strand breaks and protein cross-links (13).

The relationship between tobacco consumption and male infertility remains controversial. A number of studies have shown that smoking detrimentally affects sperm concentration, motility, and morphology and damages DNA (14–17). In addition, cigarette smoking has been correlated with poor sperm function (18, 19). On the other hand, a handful of studies have found no association between smoking and sperm quality (20, 21) or sperm function (22).

An increasing number of reports suggest that chemical and physical agents in the environment may affect male fertility in humans. Scientific and public concern exists about the potential reproductive health effects of tobacco consumption. Little is known about the effect of tobacco chewing on male reproduction. Thus, the objective of our study was to evaluate the relationship between tobacco chewing and sperm quality in male partners of infertile couples undergoing infertility evaluation.

MATERIALS AND METHODS

The medical charts of patients attending the infertility clinic at the Karthekeya Medical Research and Diagnostic Center in Mumbai, India, were reviewed. Our study included 638 male partners of infertile couples undergoing infertility evaluation from November 1998 to December 2003. All participants provided informed consent.

The patients' ages ranged from 18 to 40 years. All had a history of tobacco chewing of 4–10 years' duration but no other relevant social habits. Patients were grouped according to the frequency of their habit of tobacco chewing: mild (<3 times/day, n = 177), moderate (3–6 times/day, n = 264), and severe (>6 times/day, n = 197). Semen analysis was performed manually according to the World Health Organization (WHO) standard guidelines. Azoospermia was diagnosed if sperm were completely absent in the ejaculate; oligozoospermia if sperm concentration was $<20 \times 10^6$/mL; asthenozoospermia if <50% of sperm were progressively motile; and teratozoospermia if >30% of sperm had abnormal forms (23).

Statistical Analysis

Comparisons between the three groups were performed using one-way analysis of variance (ANOVA), and unpaired *t* test was used for comparisons between two groups. All hypothesis testing was two-tailed with a significance level of .05. Calculations were performed with GraphPad InStat version 3.00 statistical software (GraphPad Software, San Diego, CA).

RESULTS

Sperm parameters were significantly higher in samples from men in the mild group compared to moderate, and in the moderate compared to the severely addicted group (Table 1). Semen samples from men with a mild tobacco chewing habit had normal sperm count, motility, morphology, and viability according to the WHO standards (23). On the other hand, samples from men in the moderate and severe groups were characterized by teratozoospermia (Fig. 1).

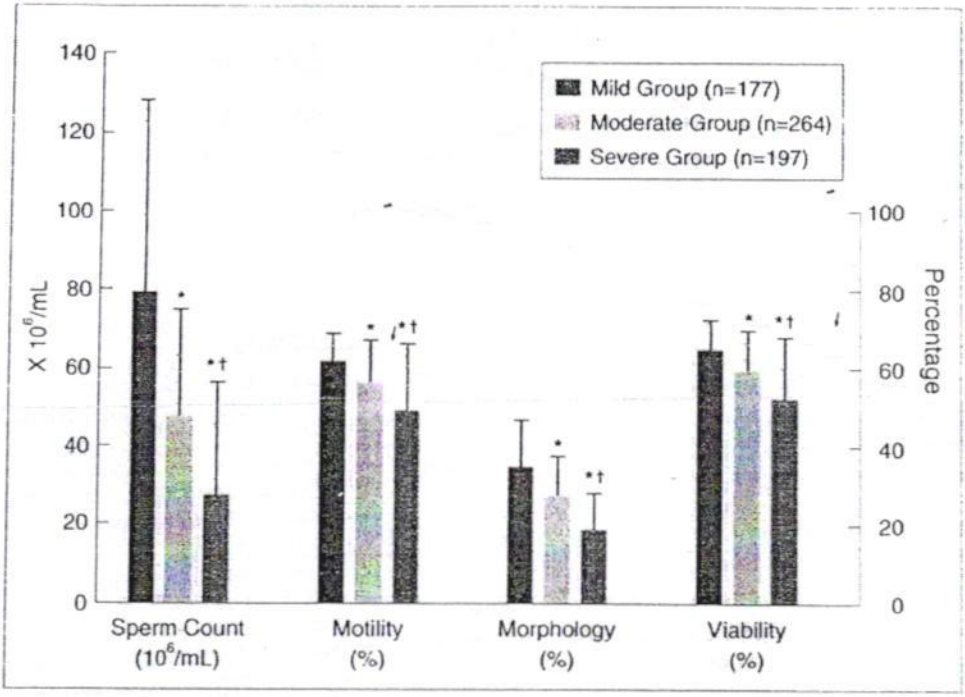
The percentage of azoospermia observed in the mild, moderate, and severe tobacco chewing groups was 1% (2/177), 3% (8/264), and 14% (28/197), respectively, indicating an increase in prevalence in the severely addicted group.

The incidence of oligoasthenoteratozoospermia (OAT) showed an increasing trend from mild (2%) to moderate (8%) to severe addiction (29%). The incidence of OAT was highly significant in the severely addicted group as compared to mild and moderate users. Within semen samples characterized by OAT, we were able to detect lower values in men with a severe tobacco chewing habit compared to those with a moderate habit as regards sperm motility ($P=.03$) and morphology ($P=.05$) (Table 2). No comparisons were made with the mild tobacco chewing group owing to the limited number of samples characterized by OAT in this group (n = 4).

When men with normal sperm count, motility, and viability from the three study groups were compared, the values of

FIGURE 1

Comparison of sperm parameters in semen samples collected from mild, moderate, and severe tobacco chewing groups. Values are expressed as mean ± standard deviation. Using unpaired *t* test, $P<.0001$ was considered significant compared to *mild group and to †moderate group.



Said. Tobacco chewing and male infertility. Fertil Steril 2005.

sperm parameters were significantly lower in the men with a severe tobacco chewing habit versus the moderate group and in the moderate versus the mild group. The presence of normal sperm count, motility, and viability was associated with normal sperm morphology in the mild tobacco chewing group. In contrast, samples with normal sperm count, motility, and viability were characterized by teratozoospermia in the moderate and severe tobacco chewing groups (Table 3).

DISCUSSION

Regardless of how tobacco is consumed, its adverse effects on disease and mortality rates are clear. The use of smokeless tobacco products is associated with gum recession, leukoplakia, nicotine addiction, increased cardiovascular disease mortality, and cancers of the oral cavity, larynx, and pharynx (24). Furthermore, smokeless tobacco is highly addictive (25).

TABLE 2

Comparison of sperm parameters in samples characterized with oligoastheno-teratozoospermia from moderate and severe tobacco chewing groups.

Parameter	Moderate group (n = 22)	Severe group (n = 49)	*P* value[a]
Sperm count (10^6/mL)	4.62 ± 1.9	4.08 ± 2.54	.37
Motility (%)	32.27 ± 7.33	25.88 ± 12.93	.03
Morphology (% normal)	7.63 ± 2.3	6.43 ± 3.06	.05
Viability (%)	35.72 ± 6.98	30.84 ± 10.72	.1

Note: Values are expressed as mean ± standard deviation.
[a] $P<.05$ considered significant using unpaired *t* test.

Said. Tobacco chewing and male infertility. Fertil Steril 2005.

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TABLE 3

Comparison of sperm parameters in samples characterized with normal sperm count from mild, moderate, and severe tobacco chewing groups.

Parameter	Mild group (n = 171)	Moderate group (n = 234)	Severe group (n = 120)
Sperm count (10^6/mL)	79.69 ± 48.6[b,c]	51.63 ± 25.1[a,c]	36.51 ± 30.26[a,b]
Motility (%)	61.6 ± 7.36[b,c]	59.0 ± 7.21[a]	58.68 ± 4.71[a]
Morphology (%)	34.46 ± 12.29[b,c]	28.82 ± 9.06[a,c]	23.51 ± 5.72[a,b]
Viability (%)	64.84 ± 7.57[b,c]	61.61 ± 7.48[a]	61.23 ± 5.03[a]

Note: Values are expressed as mean ± standard deviation. $P<.001$ was considered significant using one-way ANOVA compared to: [a] mild group; [b] moderate group; [c] severe group.

Said. Tobacco chewing and male infertility. Fertil Steril 2005.

Our study reports, for the first time, a significant decrease in semen quality (sperm count, motility, morphology, and viability) associated with a chewing tobacco habit in men undergoing infertility evaluation. No significant changes in sperm parameters were observed in the men with a mild habit compared to normal standard WHO values.

Our results contradict the finding of another study that consisted of 119 tobacco chewers. In that study, no significant difference was found in sperm parameters between tobacco consumers and nonusers (20). Our study included a much larger number of patients (n = 638), which may be the reason we were able to detect more significant differences. Also, we chose to demonstrate the effect of tobacco chewing by comparing patients according to their rate of consumption. The other study compared tobacco chewers to infertile men who were nonusers. However, one limitation of our study may be the lack of information regarding the exact etiology of infertility in these patients.

Chronic systemic exposure to nicotine could contribute to accelerated coronary artery disease, acute cardiac ischemic events, and hypertension (26). In the context of male infertility, nicotine is absorbed in substantial quantities as a result of tobacco chewing and could contribute to the adverse consequences of this habit. Experiments using murine models have documented virulent inflammatory reaction and marked ultrastructural changes in the testes of animals exposed to nicotine (27, 28). In addition, levels of nicotine and its major metabolites cotinine and trans-3′-hydroxycotinine in human seminal plasma negatively correlated with sperm parameters (5). However, further studies are needed to substantiate the impact of nicotine on spermatogenesis.

Men addicted to tobacco chewing also have the least access to infertility medical services. Therefore, prevention and cessation programs should be directed towards specific high-risk groups. Strategies should be developed to direct the attention of the general public towards the possible relationship between tobacco chewing and the incidence of male infertility. In addition, infertile men who have a habit of tobacco chewing should be advised about the potential adverse effects of their habit on sperm quality.

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Annexe 93

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Tobacco smoking and chewing as risk factors for multiple human papillomavirus infections and cervical squamous intraepithelial lesions in two countries (Côte d'Ivoire and Finland) with different tobacco exposure.

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Abstract

Our objective was to compare the association between tobacco smoking and chewing and the risk of multiple human papillomavirus (HPV) infections and cervical squamous intraepithelial lesions (SILs) in two populations with different tobacco exposure. We studied 2,162 women from Côte d'Ivoire, West Africa, and 419 women from Finland, Northern Europe, with baseline data on cervical screening, HPV DNA status and smoking and chewing habits. The proportion of women who smoked and/or chewed tobacco was higher in Finland (36.8%) than in Côte d'Ivoire (3.7%), where tobacco chewing (2.6%) was more common than tobacco smoking (1.4%). Having multiple HPV infections was common in HPV16 and/or 18-infected women (60.4% in Finland and 47.2% in Côte d'Ivoire). There was no increased risk of multiple HPV infections among tobacco consumers. We found that women >or=30 years of age exposed to tobacco through smoking in Finland (OR: 2.2, 95% CI: 0.5-8.7) and chewing in Côte d'Ivoire (OR: 5.5, 95% CI: 2.1-14) had a moderately or highly increased risk of high-grade SIL, respectively. In the latter, the risk was statistically significant. Our findings emphasize the need for health initiatives targeted to prevent tobacco smoking or chewing among women especially in less industrialized countries.

Original Article

Use of 'Mishri' A Smokeless form of Tobacco During Pregnancy and its Perinatal Outcome

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ABSTRACT

Background: Use of 'Mishri' (Tobacco containing teeth cleaning powder) is common in the central and southern part of India. **Objectives:** To study the effects of Mishri use on the fetus during pregnancy and the perinatal outcome, and stopping its use. **Materials and Methods:** All apparently healthy pregnant women were enrolled at 20 weeks of gestation from rural Maharashtra, India. Information related to use and giving up of Mishri, previous obstetrical history, current pregnancy, delivery and outcome during the perinatal period were recorded. Appropriate tests of significance were applied. **Results:** Out of 705 enrolled pregnant women, 218 (30.9%) were using Mishri. The proportion of women with complications during the previous perinatal period, complaints and complications during the current pregnancy/delivery and the number of stillbirths were significantly more among Mishri users. A relative risk of abnormal delivery was 2.7 for the users. In spite of counseling, 153 women never stopped the use of Mishri and gave birth to babies weighing on an average 169.9 gm less (statistically significant) than babies born from the group that never used it. Babies of 28.8% who stopped/reduced consumption of Mishri were significantly benefited. **Conclusions:** The improvement seen in babies born to 28.8% mothers who stopped/reduced consumption of Mishri by 32 weeks during the current pregnancy is of paramount importance in the developing world for primary prevention of low birth weight.

Key words: Smokeless Tobacco, perinatal outcome, Mishri – tobacco containing teeth cleaning powder, stopping consumption of tobacco

Introduction

Although smoking by women is not well accepted in Indian society, consumption of smokeless tobacco is well accepted, and use of Mishri (tobacco containing teeth cleaning powder) is very common. Various studies have estimated the prevalence of the use of Mishri from 17 to 45%[1-10] It is a known fact that smoking during pregnancy leads to higher incidence of Low Birth Weight (LBW).[11-13] Incidence of antepartum hemorrhage, placental abruption, placenta previa, and premature rupture of membranes is also high in women who smoke during pregnancy. Mishri is prepared by roasting tobacco leaves, principal constituent being alkaloid nicotine in 1 to 7%. The roasted tobacco leaves are powered and it is known by various names like 'Mishri,' 'Masherior,' 'Misheri'. It is mainly a homemade preparation, but is also available in the market under different names. It does not contain anything other than tobacco leaves.

Considering a high prevalence of Mishri use by women and the possible harmful effects on the growing fetus, a study was planned on the use of smokeless tobacco by pregnant mothers and its effect on the baby.

This project received financial support from the Ministry of Health and Family Welfare, Government of India.

Materials and Methods

A community-based interventional study was started in the Primary Health Centers, 'Kunjirwadi' and 'Yawat' of Pune District, in the rural areas of Maharashtra, India.

All apparently healthy pregnant women of 20 weeks gestation were enrolled. Any woman with any known major illness, multiple pregnancies, as well as those who had planned their delivery outside the study area were excluded from the study. Thus a total of 705 eligible pregnant women were enrolled for the study from Mach

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2003 till July 2005, for a period of 29 months and followed up till December 2005 (i.e., till the last enrolled woman delivered). Modular training of two days was given to all health workers explaining the ill effects of tobacco.

A group meeting was organized in every village and hamlet and women folk were explained the purpose of study and the methodology. A written consent was taken from all the eligible pregnant women in the vernacular language before collecting information. If a woman did not attend the antenatal clinic, antenatal care was given at home and consent was taken at home after explanation similar to the one given in the group meeting.

In addition to routine antenatal care (ANC), all pregnant women were motivated to give up the use of Mishri for the benefit of the growing fetus.

Counseling about the ill effects of tobacco on the health of the woman and her growing fetus was undertaken every time the woman was examined antenatally either at the clinic or at home. Every pregnant woman using 'Mishri' had a minimum of three such sessions.

All information related to the use of Mishri, previous obstetrical history, current pregnancy, and the delivery and its outcome, during the perinatal period, were recorded on a pretested proforma. Information about the duration and frequency of the use of Mishri was collected. It was not possible to measure the amount of 'Mishri' consumed by each mother, but it was possible to recognize whether she had stopped using 'Mishri' completely or reduced the frequency of its use. Those who never used Mishri were graded as having no exposure, those who stopped at 28 weeks as having low exposure, those who stopped at 32 weeks or reduced frequency of use as moderate exposure, and those who did not change their habit as high exposure, as they were a hard core group and so addicted that they could not reduce or give up the use of tobacco. Analysis was done by applying appropriate tests of significance.

Results

In all 705 pregnant women were enrolled from March 2003 to July 2005 and followed up from 20 weeks of gestation till delivery. By December 2005 all enrolled women had delivered. There were 343 women enrolled from Primary Health Centere (PHC) Kunjeerwadi and 362 from PHC Yawat. Out of them 218 (30.9%) were using tobacco containing teeth cleaning powder (Mishri) and 487 (69.1%) did not use tobacco in any form. The profiles of pregnant women using Mishri and not using Mishri are given in Table 1.

Biologically predisposing factors such as maternal age less than 20 years, primi parity, and maternal weight less than 45 kg at 28 weeks, were significantly higher among the nonuser group. In spite of this, significantly higher low birth weight babies were seen in users as compared to nonusers.

Factors such as occupation of wife, per capita income, caloric and protein intake during pregnancy, inter-pregnancy interval, maternal height, maternal hemoglobin level, and sex of the newborn were comparable in the two groups.

Only one sociocultural risk factor that was significantly higher among the user group was illiteracy.

It was seen that the rate of complications during the previous pregnancies were higher among the current Mishri users than in non-users [Table 2]. History of spontaneous abortions was the most frequent complication as reported by 9.6% users and 6.3% nonusers. Users had a significantly higher relative risk of LBW and prematurity.

It was evident that women using Mishri had significantly

Table 1: Comparison of profiles of Mishri users and non users

Characteristics	Mishri users (n = 218)		Non users (n = 487)		Z	*P* value
	No.	%	No.	%		
Maternal age < 20 years	61	28	179	36.8	2.4	< 0.05*
Parity I	57	26.1	175	35.9	2.6	< 0.05*
Inter-pregnancy interval < 24 months	36	22.3	72	23.1	0.2	> 0.05
Occupation of wife as housewife	194	88.9	438	89.9	0.4	> 0.05
Illiteracy	67	30.7	44	9.0	6.5	< 0.05*
Per capita income < Rs. 500 per month	142	65.1	316	64.9	0.05	> 0.05
Caloric intake < 1500 calories/day	86	39.5	180	36.9	0.6	> 0.05
Protein intake < 40g/day	201	92.2	441	90.6	0.6	> 0.05
Maternal height < 145 cm	43	19.7	93	19.1	0.2	> 0.05
Maternal weight at 28 weeks < 45 kg	67	30.7	186	38.2	2.0	< 0.05*
Maternal Hb < 8 g	22	11.1	42	8.6	0.6	> 0.05

*Statistically significant

higher untoward outcomes in the current pregnancy than the non-Mishri users. The proportion of women having complaints during pregnancy, complications during delivery, proportion of low birth weight babies, and stillbirths [Table 3] were significantly higher among the Mishri users as compared to the non-users.

Out of a total 705 women enrolled in this study, 176 (25%) women had one or the other complaint during the present pregnancy, common ones being anorexia, nausea, vomiting, weakness, swelling over legs, low backache, acidity, white discharge, giddiness, and so on. The proportion of women having complaints was higher in the users 65 (29.8%) than in the non-users 111 (22.8%), and this difference was statistically significant. ($\chi^2 = 3.9$; $P<0.05$)

The rate of all the complications, except oligohydramnios, was higher in users (21.1%) than in non-users (8.6%) [Table 4]. Fetal distress was the most common and significant complication that was seen in 31 (14.2%) users and 30 (6.1%) nonusers. The relative risk of 5.5 was significant and the highest for pregnancy-induced hypertension.

A higher proportion of nonusers (96.1%) had a normal vaginal delivery as compared to users (89.4%). There were 23 (10.6%) operative deliveries among the Mishri users as compared to 19 (3.9%) among the nonusers. This difference was statistically significant ($\chi^2 = 10.1$, $P < 0.05$), the relative risk of operative delivery (forceps, ventouse, LSCS) for Mishri users was 2.7, with a confidence interval of 1.46 to 27.94.

Duration of use of $\leq$ 2 years (22%) was associated with significantly higher ($Z = 2.63$) mean birth weights (2698.5 g) than those who used it for six years or more (31.7%), with mean birth weights of (2570.1 g). Those who used it for more than two years, but less than 6 years (46.3%) did not differ significantly from its use of a shorter or longer duration.

Table 2: Previous perinatal history among Mishri users and non users

Obstetrical history	Users (n = 218)		Non users (n = 487)		RR*	95% CI** for R.R. 95% CI
	No.	%	No.	%		
H/O Spontaneous abortion	21	9.6	1.5	31	6.3	0.84–2.67
H/O LBW	24	11.0	2.1	25	5.1	1.17–3.77***
H/O Prematurity	14	6.4	2.2	14	2.8	1.03–4.69***
H/O Early neonatal deaths	4	1.8	2.2	4	0.8	0.55–8.88
H/O PPH	1	0.4	2.2	1	0.2	0.14–16.06

*RR Relative risk, **Confidence Interval, ***Statistically significant

Table 3: Current pregnancy outcome and Mishri use

Characteristics	Mishsri users (n = 218)		Non users (n = 487)		χ^2	*P* value
	No.	%	No.	%		
Complaints during pregnancy	65	29.8	111	22.8	3.9	<0.05*
Complications during pregnancy	46	21.1	42	8.6	12.4	<0.05*
Operative deliveries	23	10.6	19	3.9	11.8	<0.05*
Low birth weight	42	19.3	44	9.0	14.6	<0.05*
Preterm births	21	9.6	35	7.1	1.2	>0.05
Stillbirths	6	2.7	3	0.6	5.4	<0.05*
Early neonatal deaths	8	4.7	8	1.7	2.9	>0.05

*Statistically significant

Table 4: Complications during delivery and Mishri use

Complications during delivery	Users		Non users		Relative risk	95% CI** for R.R.
	No.	%	No.	%		
Fetal distress	31	14.2	30	6.1	1.8	1.06 - 3.06***
Pregnancy induced hypertension (PIH)	5	2.3	2	0.4	5.5	1.06 - 28.57***
Premature rupture of membranes (PROM)	4	1.8	0	0.0	-	-
Antepartum hemorrhage (APH)	3	1.3	5	1.0	1.3	0.30 - 5.49
Polyhydramnios	1	0.4	1	0.2	2.2	0.14-35.33
Oligohydramnios	0	0.0	1	0.2	-	
Post partum hemorrhage (PPH)	2	0.9	3	0.6	1.4	0.23 - 8.44
Total	46	21.1	42	8.6	2.1	1.33 - 3.31

***Statistically significant

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Table 5: Effect of counseling on Mishri consumption and mean birth weight

Group and exposure status	Number	%	MBW*	SD
Never used (No exposure)	487	69.1	2750.3	344.0
Used and completely stopped at 28 weeks (Low exposure group)	29	4.1	2736.2	272.3
Used and stopped at 32 weeks or reduced consumption (Moderate exposure group)	36	5.1	2708.8	210.6
Never stopped (High exposure group)	153	21.7	2580.4	275.6
Total	705	100.0	2710.0	313.9

*Z values for mean birth weights were as follows: 1) Never used never stopped (significant) $Z = 6.2$, $P < 0.05$. 2) Stopped at 28 weeks vs. never stopped (significant) $Z = 2.81$, $P < 0.05$. 3) Reduced consumption or stopped late by 32 weeks vs. never stopped. (Significant) = Z 3.08, $P < 0.05$

- 14.7% used Mishri only once, 44.5% twice, 22.9% thrice, and 17.9%, four times or more. Frequency of use was not associated with significant differences in the mean birth weights.

Intensive health education was undertaken on a one-to-one basis, as well as group counseling. Various charts were used to explain the ill effects of tobacco, with special reference to the growing fetus.

Out of 218 (30.9%) women using Mishri, only 29 (13.3%) stopped use of smokeless tobacco by 28 weeks of gestation. Thirty-six (16.5%) reduced consumption or stopped at 32 weeks, and the remaining 153 (70.2%) did not change their habit of using Mishri at all.

It was seen that the mean birth weight was highest for babies born to the 'never used' group, followed by those who 'stopped Mishri use by 28 weeks,' followed by those who 'reduced consumption or stopped its use late in pregnancy by 32 weeks,' and it was lowest in the group whose 'Mishri' use was unabated [Table 5]. There was no significant difference between the mean birth weights of babies born to the first three groups, but all of them differed significantly with the 'never stopped' group. The 153 women who never stopped the use of Mishri gave birth to babies weighing, on an average, 169.9g less (statistically significant) than the 'never used group'.

Discussion

The proportion of women using Mishri in this study of 30.9% is comparable to others studies.[1-10]

The profile of Mishri users and Non-Mishri users was similar, except for the level of literacy, proportion of teenage pregnancies, proportion of primiparity, and the average maternal weight at 28 weeks [Table 1]. Difference in educational status was not surprising as the use of Mishri was more common among the illiterate population. The lower proportion of women, with age less than 20 years and primiparity, among Mishri users, could be due to a higher proportion of women experiencing obstetrical mishaps during their previous pregnancies. A higher proportion of women with lower body mass among non-users, could be related to the higher proportion of teenage mothers.

In the present study bad obstetrical history and complications during the current pregnancy were associated with current Mishri use [Tables 2-4].

Reliable information about the use of Mishri at the time of occurrence of an untoward event in the past was not possible, but considering the short inter-pregnancy interval and prolonged use of Mishri by women folk, it was very likely that the untoward outcome in the previous pregnancy was also related to the use of Mishri. However, this aspect of repeated untoward outcomes could be tested in a community-based prospective study of a longer duration. The nicotine caused decreased blood supply, reducing both oxygen and nutrition supplies to the uterus and placenta, hence the incidence of spontaneous abortion, placental abruptions, premature rupture of membranes, and fetal distress is high in women who smoke.[14-17] Nicotine also retards intrauterine growth, and could cause preterm deliveries and stillbirths.[17]

The high proportion of operative deliveries among Mishri users could probably be due to a higher rate of complications during pregnancy and delivery.

There were 4.7% early neonatal deaths in the users as compared to 1.7% in the nonusers [Table 3]. This difference in the proportion of early neonatal deaths and survivors in the two groups was not significant statistically, although smoking could increase the risk of neonatal deaths. This was observed among babies of smokers[20] The mean birth weight of the babies born to unabated Mishri users was 2580.4gm. which was 169.9 g lower (statistically significant) than the mean birth weight of babies born to the 'never used' group.

There are many studies on the use of tobacco during pregnancy (smokable forms) and its adverse effects on the birth weight of the baby.[17-20] Indian workers have found 100 – 450 g lesser values of mean birth weights of the babies born to Mishri users as compared to non-users.[6-8,10] Our results are in this range. There is a wide spread belief that topical use of tobacco improves oral hygiene, prevents dental carries, and because the tobacco is not swallowed there are no adverse systemic side effects. As,

there is a social sanction for the use of tobacco in the form of 'Mishri', the habit is very often inculcated by parents to the offsprings from early childhood itself. As this practice of the use of Mishri is deeply rooted in the families, homemade preparations are very common. Very often Mishri is applied more than once to the gums and teeth and retained in the mouth for a period of 10 to 15 minutes before it is washed, allowing absorption of a substantial amount of active ingredients, principally nicotine.

The finding in this study that babies born to those who reduced or stopped the use of Mishri had mean birth weights similar to those who never used Mishri, is of paramount importance.

The decreasing trend of mean birth weights with increased exposure to Mishri is very clear and indicates dose response. Although the actual amount of mishri used by the pregnant women could not be measured, grading of exposure was possible by finding out the time of stopping or reduction in consumption of Mishri [Table 5]. A similar observation was made among smokers. The babies born to smokers who abstained for the last half of the pregnancy were of the same birth weight as those babies born to non-smokers.

Primary prevention of the use of tobacco is definitely desirable and is a long-term objective, although difficult to achieve. Those who are habituated to the use of Mishri, at least some of them may, with intensive health education and counseling, give it up or reduce its use during pregnancy, with a favorable outcome of pregnancy. In this study, over 70% of the mothers using smokeless tobacco did not respond to the health educational drive. It is not surprising, as tobacco is a psychoactive and addiction causing substance and it is very difficult to stop using it, be it the smoking or the smokeless form.

Wide dissemination of knowledge and awareness generation programs for all adolescents and women folk in general and pregnant mothers in particular may go a long way in reducing this dreaded habit of Mishri use, thereby reducing the risk of low birth weight and adverse perinatal outcome in the babies born to them.

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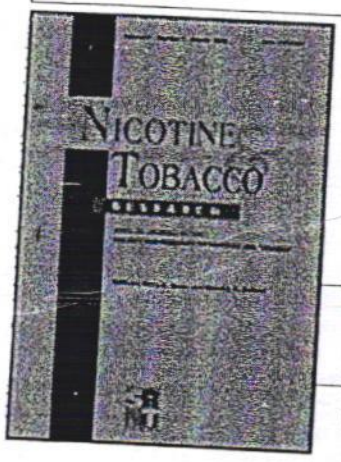
Annexure 95



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Anemia in pregnant women who use smokeless tobacco

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Brief Report

Anemia in pregnant women who use smokeless tobacco

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A significantly higher mean hemoglobin level in women smokers in comparison to nonsmokers with a generalized rightward shift of the hemoglobin distribution curve has been reported at the population level. Studies on pregnant women, however, have often associated smoking with decreased hemoglobin levels, although not consistently. We examined whether smokeless tobacco use during pregnancy influenced hemoglobin levels in a population-based cohort of 918 pregnant women in Mumbai, India. Mean hemoglobin levels (Hb) were significantly lower in users (10.00 g/dl) compared with nonusers (10.46 g/dl), $p<.000$. Anemia (Hb<10 g/dl) was significantly associated with smokeless tobacco in the univariate analysis ($OR=1.7$, 95% CI 1.2–2.5). There was no change after adjusting odds ratios for potential confounders in multivariate analysis ($OR=1.7$, 95% CI 1.2–2.5). The odds ratios for anemia were adjusted for age of mother, education, socioeconomic status, type of residence, lower body mass index, parity, vegetarian or nonvegetarian food habit, and hemodilution during pregnancy. The results suggest that smokeless tobacco use during pregnancy is associated with lower hemoglobin levels, as has often been observed with cigarette smoking. Smokeless tobacco use is widely prevalent among women in Southeast Asia and is gaining popularity across the world as a safe alternative to smoking. Further exploration and clarification of this association is therefore of considerable importance to public health.

Introduction

Anemia in pregnancy is a common clinical problem in many developing countries (World Health Organization [WHO], 1992). It contributes significantly to maternal mortality and to adverse pregnancy outcomes (Brabin, Hakimi, & Pelletier, 2001; Ezzati, Lopez, Dogers, Vander, & Murray, 2002; Malhotra et al., 2002; Ronnenberg et al., 2004). Estimates of anemia among pregnant women in India range from 50% (International Institute for Population Sciences, 2002) to about 85% (Indian Council of Medical Research, 1989). Despite the National Nutritional Anemia Prophylaxis Programme operational in India since 1970, anemia in pregnant women continues to be a public health challenge (Agarwal et al., 2006; Ahluwalia, 2002).

Smoking is known to affect hemoglobin levels. Studies on adult women have often revealed higher hemoglobin levels in smokers (Nordenberg, Yip, & Binkin, 1990; Van Tiel et al., 2002; Yamada, Wong, & Suzuki, 2003). However, studies on pregnant women have often associated smoking with decreased hemoglobin levels (Chang, O'Brien, Nathanson, Mancini, & Witter, 2003; Strinic et al., 2005; Wingerd, Christianson, Lovitt, & Schoen, 1976), although not consistently (Bodnar, Siega-Riz, Arab, Chantala, & McDonald, 2004; Cope, Nayyar, & Holder, 2001). It is entirely plausible that smokeless tobacco use may also affect blood hemoglobin, but we could not find any such report in the literature. The present study examined whether smokeless tobacco use during pregnancy influenced hemoglobin levels in a cohort of pregnant women in Mumbai, India.

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Method

A cohort of pregnant women was assembled in Mumbai during 2002 to study the effect of smokeless tobacco use on reproductive outcomes (Gupta & Subramoney, 2004, 2006). Recruitment was carried out after first producing a list of all pregnant women (on a house-to-house basis) in eight health administrative units in Mumbai. All women 3–7 months pregnant and planning to remain in Mumbai for delivery were considered eligible for recruitment. The objectives and requirements for study participation were explained to study subjects, their queries were answered, and oral informed consent was sought. The WHO SEARO approved the study, and field procedures conformed to the guidelines laid down by the Indian Council of Medical Research for research on human subjects. All eligible and consenting women from these areas ($N=1,217$) were interviewed at their residences by trained interviewers. The response rate from the community was 100%, as this project was carried out in association with the local health workers. Demographics, food habits, obstetric history, and date of last menstrual period were obtained. Detailed information was obtained on tobacco use. Height was measured with 0.1-cm accuracy with a measuring tape with the woman standing in bare feet against a vertical wall. Weight was measured with 0.1-kg accuracy on a bathroom weighing scale. Weight measurements were taken on two calibrated weighing scales carried house-to-house by two projects interviewers. A second interview by a different social worker, within a month of recruitment, on 5% of the recruited sample, found close to 100% agreement on major variables such as age and tobacco use.

Antenatal records available for the women were abstracted into structured and pilot-tested questionnaire formats. Hemoglobin measurements were available for 918 women; henceforth, all analyses pertain to these women. In India, hemoglobin during pregnancy is generally measured during the first antenatal visit and then at subsequent visits if indicated. When multiple hemoglobin measurements were available, hemoglobin at first visit was recorded. No other blood parameter was abstracted. Date at first antenatal visit was recorded.

Of the 918 women included in this analysis, 158 (17.2%) were smokeless tobacco users. None smoked tobacco. All women who had used a smokeless tobacco product at least once a day for the past 6 months were included as users. The most commonly used product was mishri ($n=124$), a pyrolyzed and powdered tobacco product used as a dentifrice, followed by Gutka ($n=16$), an industrially manufactured smokeless tobacco product containing tobacco, areca nut, slaked lime (calcium hydroxide), condiments, flavoring agents, and preservatives.

The independent-samples t test was used to compare means. Women with a hemoglobin level (Hb) of less than 10 g/dl ($n=238$) were defined as anemic. Odds ratios for anemia with smokeless tobacco use were calculated and were adjusted for potential confounders using logistic regression analysis. Confounders considered were age of mother (age <20 or age ≥30 vs. age 20–29), education (<10th grade vs. 10th grade or higher), parity (one or higher), vegetarian or nonvegetarian food habit, and underweight (body mass index [BMI]<19 kg/m^2 vs. BMI≥19; Table 1). Because prepregnancy weight was not known, the gestational age at recruitment was included in the model as a correction on the BMI. The type of house the woman lived in (apartment vs. others) was considered as a proxy for socioeconomic status. Timing of first antenatal visit was variable. The first antenatal visit was accomplished by the third month by 52% of women, by the fifth month by 26%, and by the seventh month for most other women (Table 1). Trimester at first antenatal visit was included in the regression models for adjustment of the time factor in hemoglobin measurement. This accounted for hemodilution occurring during the second trimester and also for any effect of smokeless tobacco similar to smoking.

Table 1. Demographic and other characteristics by smokeless tobacco use.

	Number of users (%)	Number of nonusers (%)
Age of mother		
20–29 years	121 (76.6)	605 (79.6)
≥30 years	23 (14.6)	83 (10.9)
<20 years	14 (8.9)	72 (9.5)
Educational status of mother		
<10 years of education	147 (93.0)	597 (78.6)
≥10 years of education	11 (7.0)	163 (21.4)
Type of housing		
Mud/tin sheet	22 (13.9)	74 (9.7)
Cement sheet	50 (31.6)	248 (32.6)
Chawl	82 (51.9)	418 (55.0)
Apartment	4 (2.5)	20 (2.6)
Parity		
More than one pregnancy	137 (86.7)	559 (73.6)
First pregnancy	21 (13.3)	201 (26.4)
Interpregnancy interval[a]		
≤6 months	14 (10.2)	79 (14.1)
6 months to 3 years	91 (66.4)	348 (62.3)
>3 years	32 (23.4)	132 (23.6)
Body mass index		
<19 kg/m^2	47 (29.7)	161 (21.2)
≥19 kg/m^2	111 (70.3)	599 (78.8)
Food habit		
Nonvegetarian	147 (93.0)	663 (87.2)
Vegetarian	11 (7.0)	97 (12.8)
Trimester at first antenatal visit		
First	65 (41.1)	412 (54.2)
Second or above[b]	93 (58.9)	348 (45.8)

Note. [a]For 696 women with previous pregnancies. [b]A total of 4% of women had contacted antenatal care after the end of the second trimester.

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Results

Demographic and other characteristics of the women by smokeless tobacco use status are presented in Table 1. Of all women, 26% had Hb levels below 10 g/dl; about 5% of all women had hemoglobin levels of 8 g/dl or lesser. Mean hemoglobin level was significantly lower in users (10.00 g/dl) in comparison to nonusers (10.46 g/dl), $p<.000$. A greater representation of smokeless tobacco users was found in those with lower hemoglobin levels throughout the spectrum (Figure 1).

Anemia was significantly associated with smokeless tobacco use. Users were 1.7 times more likely to be anemic in comparison to nonuser women (*OR*=1.7, 95% *CI* 1.2–2.5). Smokeless tobacco use also was associated with lower educational status (*OR*=3.6, 95% *CI* 1.9–6.9), nonvegetarian food habit (*OR*=1.95, 95% *CI* 1.02–3.74), and underweight (BMI<19; *OR*=1.6, 95% *CI*=1.1–2.3). These items were included as potential confounders in addition to age, parity, and other variables.

After multivariate logistic regression analysis, smokeless tobacco use (*OR*=1.7, 95% *CI* 1.2–2.5) was the only significant determinant of hemoglobin levels other than socioeconomic status, *OR* =2.7, 95% *CI* 1.2–6.3). In a linear regression with hemoglobin level as a continuous variable, smokeless tobacco use remained the only significant predictor of hemoglobin levels other than SES, trimester of measurement, and BMI. Lower mean hemoglobin and occurrence of anemia increased with increasing smokeless tobacco use frequencies; however, these differences did not attain statistical significance, most likely because of inadequate numbers.

Discussion

The results suggest that smokeless tobacco use during pregnancy is associated with lower hemoglobin levels, an association often observed with cigarette smoking. However, given that this study was not undertaken with the primary objective of studying the association between hemoglobin level and smokeless tobacco use, the finding should be considered preliminary and subject to further clarification.

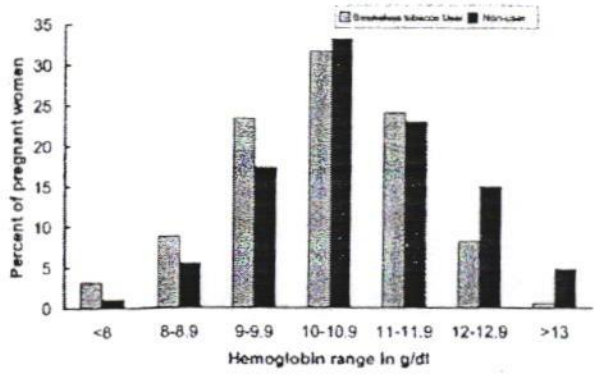

Figure 1. Distribution of hemoglobin level by smokeless tobacco use status.

Smokeless tobacco use has been associated with underweight, a known risk factor for anemia; the odds ratio for a low body mass index (<18.5) among women using smokeless tobacco in Mumbai was 1.50 (95% *CI* 1.43–1.59; Pednekar, Gupta, Shukla, & Hebert, 2006). However, the odds ratio for anemia in this study remained significant after adjusting for low BMI. Given the rather limited literature on smokeless tobacco, the literature on smoking may be considered as a pointer to the effects that might occur with smokeless tobacco.

Although some studies have reported increased hemoglobin levels with smoking during pregnancy, evidence on the association with anemia appears to be plausible, because of related findings in other studies. Smoking has been associated with decreased maternal red blood cell count and decreased maternal hematocrit (Habek, Habek, Ivanisevic, & Djelmis, 2002; Habek, Habek, Jugovic, & Salihagic, 2002). Smoking during pregnancy also has been associated with other blood parameters that are closely related to blood hemoglobin, such as decreased serum vitamin B12 and maternal red blood cell folate (Casanueva et al., 2003). The human fetus' response to prenatal exposure to cigarette smoke may indicate possible biochemical responses in the adult. Such responses include increased erythropoietin (Varvarigou, Beratis, Makri, & Vagenakis, 1994) and evidence of erythron impairment such as disorders of iron metabolism, processes of hemoglobin formation, and red blood cell metabolism (Gavalov, Soboleva, Deriagina, & Demchenko, 1991).

Thus, based on the present study, the relationship between anemia and smokeless tobacco use during pregnancy appears to be real. Although high hemoglobin levels in midpregnancy are associated with fetal growth restriction and preeclampsia (Koller, Sandvei, & Sagen, 1980; Scanlon, Yip, Schieve, & Cogswell, 2000; Steer, 2000), achieving normal hemoglobin levels during pregnancy will be beneficial for the fetus. Smokeless tobacco use is widely prevalent among women in Southeast Asia (Gupta & Ray, 2003) and is slowly gaining acceptance across the world as a safe alternative to cigarette smoking. Further exploration and clarification of this association is therefore of considerable importance to public health.

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personnel in the Mumbai Municipal Corporation for their help. Neither author has any competing interests to declare.

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AN ASSESSMENT OF FETAL LOSS AMONG CURRENTLY MARRIED WOMEN IN INDIA

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Summary. The present paper assesses fetal loss among currently married women in India. In addition, the effects of social, economic, demographic and health factors on fetal loss are studied. The study uses data from the second National Family Health Survey conducted in India during 1998–2000. The results show wide variations in fetal loss (induced abortion, spontaneous abortion and still-birth) measures across the country. The importance of mother's nutritional status, birth spacing, risky behaviours such as smoking, drinking and chewing tobacco and age at marriage for pregnancy outcomes in India is also discussed. The study results imply a broad understanding of reproductive health in India, and emphasize the importance of widening the scope of community-based reproductive health education programmes to improve the reproductive health of women.

Introduction

The reproductive performance of human beings is a relatively inefficient process (Regan & Rai, 2000) and some studies have indicated that only about 57% of all conceptions advance beyond 20 weeks (Arias, 1993). However, most of the pregnancies lost before implantation are not recognized clinically and, in practice, the problem of early pregnancy loss is limited to those pregnancies aborted after implantation. Recent figures show that about 9 million babies are either born dead or die within first 28 days of life (WHO, 1998). While, globally, infant mortality declined markedly between the early 1980s and late 1990s, most of this improvement was among older infants. The perinatal death toll during the same period fell only slightly from 64 to 57 deaths per 1000 births.

Generally, women make a major investment in themselves during pregnancy and childbirth. Thus, an unfavourable outcome of pregnancy, including perinatal mortality, still-birth and spontaneous abortion, can be stressful and emotionally challenging to women and the family. Further, these events can have considerable impact on the physical and social well-being of women. The incidence of unfavourable pregnancy outcomes also affects future reproductive performance as well as reproductive aspirations of having children. Examining the level as well as the social and

cultural context within which these unfavourable events occur is significant for improving the conditions discussed above. Although this aspect of reproductive health is an important issue, it is a neglected area of research due to lack of data. Thus, the present paper examines unfavourable pregnancy outcomes among currently married women in India.

Studies conducted in many different settings have identified several biological, demographic, behavioural, contextual, social and economic and health factors that influence the outcome of pregnancy (Rajab *et al.*, 2000; Kang *et al.*, 2001; Cai & Feng, 2005). Numerous risk factors have been detected in the medical setting and are assumed to be direct causes of unfavourable pregnancy outcomes (see, Arias, 1993; Regan & Rai, 2000; Choe & Kim, 2007). However, there is no common agreement among researchers on the role of these risk factors (Simpson & Carson, 1993).

Contextual–social dimensions are considered influential in describing the unfavourable pregnancy outcomes indirectly. Availability and accessibility of health services are generally better in urban areas compared with rural areas. Similarly, the level of prenatal care and family planning practice by women vary according to socioeconomic status and place of residence. Further, it is assumed that the rate of accidents and violence against women is higher in rural areas and among women of low socioeconomic status. So, it is expected that the experiences of unfavourable pregnancy outcomes are fewer in urban areas and among women of higher compared with lower socioeconomic status.

Several researchers have highlighted the relationship between demographic factors such as age, pregnancy order, pregnancy interval and the experience of unfavourable pregnancy outcomes (Naylor, 1974; Pebley *et al.*, 1985; Casterline, 1989a; Rutstein, 2005). As women age, the relationship between age and fetal loss takes either a J- or a U-shape. Maternal age can affect the survival status of the fetus in a number of ways. It is documented that the risk of various ailments is cumulative and genetic defects become more salient at advanced ages. The majority of studies indicate a positive relation between the experience of fetal wastage and pregnancy order (El-Saadani, 2000). Plausible explanations for this include immunological problems, the likelihood of anatomical damage and cumulated malnutrition. All these are possibly aggravated in a higher-order pregnancy. Similarly, almost all studies indicated that short pregnancy intervals might adversely affect the chance of fetal survival. The mechanisms underlying this association are depleted maternal resources and competition between pregnancies for these resources (Pebley *et al.*, 1985; Casterline, 1989b). Evidence also suggests that behaviours such as cigarette smoking and alcohol consumption among mothers are positively associated with unfavourable pregnancy outcomes (Shu *et al.*, 1995; Savitz *et al.*, 2001). Additionally, considering the skewed sex ratios in the Indian states and the probable high prevalence of sex-selective abortion, the sex composition of the number of living children may also be an important factor in explaining fetal loss.

Data and Methods

The second National Family Health Survey (NFHS-2), conducted in India during 1998–2000, is used to explore the experience of fetal loss among currently married

women. The survey provides information on a variety of demographic and socio-economic background characteristics. The NFHS-2 survey covered a representative sample of more than 90,000 ever-married women aged 15–49 from 26 states that comprise more than 99% of India's population. Details about the survey can be found in the NFHS-2 report (IIPS & ORC Macro, 2000). The main objective of the NFHS-2 was to provide state- and national-level estimates of fertility, the practice of family planning, infant and child mortality, maternal and child health, and the utilization of health services provided to mothers and children. Another feature of the NFHS-2 is the measurement of the nutritional status, such as height and weight measurements, of women. Detailed birth history, as well as the number of spontaneous abortions, induced abortions and still-births up to the time of the survey, were also collected. Thus, the data provide the cumulative incidence of pregnancy loss and not a detailed pregnancy history. Since the data come from a retrospective survey, information on pregnancy loss will be neither totally complete nor accurate. Sources of errors for studying pregnancy loss using retrospective survey data have been documented elsewhere (for details, see Casterline, 1989a, b).

As mentioned, the present data provide information on each live birth, number of abortions and still-births. The total number of pregnancies each woman had is the sum of all the live births, induced and spontaneous abortions and still-births. Multiple births are considered as single pregnancies and the current pregnancy is not included in the analysis. The present analysis is restricted to currently married women in the age group 15–49 who had experienced at least one pregnancy termination before the survey.

First the outcome of lifetime pregnancies in terms of live birth, induced abortion, spontaneous abortion and still-birth is examined. In order to carry out this analysis, a pregnancy history file was generated using the information on number of live births, spontaneous abortions, induced abortions and still-births. In the next step, the experience of fetal loss in terms of number of induced abortions and number of natural fetal losses per woman is examined. Natural fetal loss includes spontaneous abortions and still-births. Finally, negative binomial regression is used to examine the net effect of various risk factors on the experience of number of induced abortions and number of natural fetal losses. Generally, Poisson regression is the standard method used to model count response data. However, Poisson distribution assumes the equality of its mean and variance – a property that is rarely found in real data. Data that have greater variance than the mean are termed *Poisson overdispersed*, but are more commonly designated as simply *overdispersed*. Negative binomial regression is a standard method used to model overdispersed Poisson data.

One derivation of the negative binomial mean dispersion model is that individual units follow a Poisson regression model, but there is an omitted variable u_i such that e^{u_i} follows a gamma distribution with mean 1 and variance a and the model is:

$$y_i \sim \text{Poisson } (\mu_i),$$

where

$$\mu_i^* = \exp\ (x_i\beta + u_i),$$

and

$$\exp(u_i) \sim \text{Gamma}\ (1/\alpha,\ \alpha),$$

for observed counts y_i with covariates x_i for the i^{th} observation. Parameter a is an estimate of the degree of overdispersion. When a is zero, the negative binomial has the same distribution as Poisson. The larger a is the greater the amount of overdispersion in the data. When there is overdispersion, the Poisson estimates are inefficient with standard errors biased downward yielding spuriously large-z-values. The overdispersion in the raw data tested by the likelihood-ratio test for a is zero. The staggering value of test statistics asserts that the probability that we would observe these data conditional on $a=0$ is virtually zero. (The value of $\bar{\chi}^2$ (01)=1171·19 and Prob$\geq\bar{\chi}^2=0$ for the induced abortion model; the value of $\bar{\chi}^2$ (01)=1366 and Prob$\geq\bar{\chi}^2=0$ for natural fetal loss.) In other words, the test statistics support the data not being Poisson. The above equation implies that:

$$\mu_i^* \sim \text{Gamma}\ (1/\alpha,\ \alpha\mu_i).$$

Another alternative parameterization, known as constant dispersion, is used in the present paper and the constant dispersion model assumes that:

$$\mu_i^* \sim \text{Gamma}\ (1/\delta,\ \delta).$$

Results

First, the pregnancy outcomes among currently married women aged 15–49 are examined. Table 1 shows the outcome of all pregnancies reported by currently married women aged 15–49 in different Indian states. In total, the currently married women aged 15–49 reported 277,035 pregnancies. Of these, 91% resulted in live births, 2% in induced abortions, 5% in spontaneous abortions and 2% in still-births.

Pregnancies of currently married women resulting in live births range from a low of 84% in Tamil Nadu to a high of 94% in Sikkim and Bihar. Experience of live birth is lower than the national average of 91% in Tamil Nadu, Manipur, Goa, Assam, New Delhi, Nagaland, Punjab, Haryana, Tripura, Orissa, Jammu & Kashmir and Kerala. However, pregnancies resulting in live births are higher than the national average in the states of Rajasthan, Uttar Pradesh, Andhra Pradesh, Karnataka, Maharashtra, Madhya Pradesh, Arunachal Pradesh, Bihar and Sikkim. The reported incidence of induced abortion is more in Manipur, followed by Tamil Nadu and New Delhi. Pregnancies resulting in spontaneous abortion are highest in Goa and lowest in Bihar. In total, fourteen states have incidences of spontaneous abortion above the national average. The reported incidence of still-birth is lowest in Goa followed by Kerala. The experience of still-birth is high in the states of Meghalaya, Assam, Arunachal Pradesh, Haryana and Punjab.

Table 2 provides the results of pregnancy outcomes by selected background variables. By place of residence, a greater percentage of pregnancies in urban areas terminated through spontaneous and induced abortions but a smaller percentage resulted in still-births compared with pregnancies in rural areas. As the educational level of the women increases, the percentage of pregnancies resulting in induced and

Table 1. Percentage distribution of all pregnancies of currently married women aged 15–49 by their outcome, according to state, India

State	Outcome of pregnancy				Number of pregnancies
	Live birth	Induced abortion	Spontaneous abortion	Still-birth	
Andhra Pradesh	91·78	0·86	4·90	2·46	10,862
Assam	86·51	3·49	6·70	3·30	10,860
Bihar	93·83	0·35	3·54	2·29	23,168
Goa	86·33	4·24	8·28	1·16	3012
Gujarat	90·80	2·34	5·36	1·50	11,317
Haryana	89·48	1·42	6·02	3·08	9317
Himachal Pradesh	90·85	1·66	4·82	2·66	8599
Jammu & Kashmir	90·10	2·66	5·42	1·82	9812
Karnataka	91·88	0·96	4·70	2·45	12,216
Kerala	90·36	2·06	6·33	1·25	6669
Madhya Pradesh	92·91	0·98	4·18	1·94	23,368
Maharashtra	92·09	1·98	4·26	1·67	14,954
Manipur	85·31	6·51	6·86	1·32	5112
Meghalay	90·63	0·77	5·23	3·37	3407
Mizoram	91·36	0·68	5·65	2·31	3167
Nagaland	89·26	2·40	5·82	2·52	3092
Orissa	90·10	1·73	5·92	2·26	13,039
Punjab	89·30	3·05	4·61	3·05	8122
Rajasthan	91·50	1·02	5·31	2·18	23,861
Sikkim	93·92	0·99	2·10	2·99	3292
Tamil Nadu	84·17	5·36	7·88	2·59	12,074
West Bengal	91·30	2·30	4·43	1·97	12,166
Uttar Pradesh	91·69	1·45	4·94	1·93	34,449
New Delhi	87·36	4·91	6·36	1·37	7354
Arunachal Pradesh	93·17	0·98	2·71	3·15	3194
Tripura	89·64	4·49	4·36	1·52	2978
All India	91·15	1·75	4·98	2·12	277,035

Note: All India sample weight is used to generate the results for All India. State-level results are generated using the individual state weights.

spontaneous abortions also increases. A reverse relationship is identified between women's education and the percentage of pregnancies resulting in still-births.

A greater percentage of pregnancies terminated in fetal loss among women who experienced domestic violence. No clear relationship is established between the height of the women and pregnancies ending in spontaneous abortions, but the percentage of pregnancies terminating in still-births decreases as the height of the women increases. A positive relationship is found between household standard of living index and pregnancies terminating in induced and spontaneous abortions. This index is

Table 2. Percentage distribution of all pregnancies of currently married women aged 15–49 by their outcome, according to selected background characteristics, India

Background characteristic	Outcome of pregnancy				Number of pregnancies
	Live birth	Induced abortion	Spontaneous abortion	Still-birth	
Place of residence					
Rural	91·86	1·17	4·69	2·28	210,199
Urban	88·91	3·59	5·89	1·60	66,836
Education					
Illiterate	92·42	0·84	4·44	2·30	182,932
Literate, <middle complete	90·39	2·34	5·33	1·94	50,405
Middle school complete	87·53	4·13	6·64	1·70	17,319
High school and above	86·14	5·42	6·97	1·46	26,341
Work status					
Not working	90·84	2·02	5·08	2·06	164,311
Working	91·60	1·37	4·83	2·20	112,553
Tobacco chewing/smoking/drinking habit					
No	91·08	1·86	4·99	2·07	236,188
Yes	91·56	1·16	4·88	2·40	40,709
Experienced domestic violence since age 15					
No	91·56	1·72	4·68	2·04	211,668
Yes	89·81	1·86	5·94	2·39	65,341
Height (cm)					
<145	91·04	1·37	4·87	2·72	34,388
145–150	90·94	1·60	5·15	2·31	72,855
150–155	91·23	1·83	4·92	2·02	85,523
155+	90·71	2·26	5·21	1·82	60,519
Missing	92·79	1·23	4·21	1·77	23,750
Standard of living index					
Low	92·13	0·79	4·66	2·42	94,262
Medium	91·37	1·59	4·91	2·13	131,034
High	88·61	4·05	5·82	1·53	48,596
Caste/tribe					
Scheduled caste	91·56	1·19	4·88	2·37	53,316
Scheduled tribe	92·57	0·96	4·46	2·01	24,707
Other backward caste	91·05	1·72	5·12	2·11	90,247
None of them	90·70	2·28	5·01	2·02	105,546
Religion					
Hindu	91·09	1·75	5·05	2·10	222,309
Muslim	92·01	1·30	4·47	2·22	40,439
Christian	89·55	2·77	5·58	2·10	6051
Other	89·66	3·27	4·91	2·16	7988

Table 2. *Continued*

Background characteristic	Outcome of pregnancy				Number of pregnancies
	Live birth	Induced abortion	Spontaneous abortion	Still-birth	
Current age					
15–19	86·51	1·02	9·55	2·91	5867
20–24	89·43	1·58	6·59	2·40	29,753
25–29	90·65	1·96	5·31	2·08	51,614
30–34	90·76	2·13	4·91	2·21	55,520
35–39	91·54	1·87	4·56	2·03	52,774
40–44	92·20	1·53	4·22	2·05	45,468
45–49	92·75	1·26	4·09	1·90	36,039
Age at first union					
<16	92·61	0·90	4·36	2·12	123,147
16–18	91·12	1·77	4·98	2·12	102,207
19–22	88·51	3·41	5·96	2·13	42,613
23+	84·01	5·30	8·69	2·01	9068
Average pregnancy interval (years)					
<1	61·28	7·29	29·05	2·39	1181
1–2	84·97	3·39	8·68	2·96	43,449
2–3	91·38	1·65	4·81	2·16	98,076
3–4	93·04	1·33	3·66	1·97	62,461
4+	93·42	1·19	3·71	1·68	71,868
Number of living children					
None	34·19	4·22	47·58	14·01	3163
One child					
1 son	83·96	2·81	9·62	3·6	10,405
0 sons	83·16	2·42	10·62	3·8	9201
Two children					
2 sons	89·41	3·22	5·05	2·32	16,098
1 son	87·82	3·57	6·05	2·56	27,867
0 sons	87·9	2·7	6·84	2·57	8974
Three or more children					
3+ sons	94·41	0·93	3·14	1·52	71,167
2 sons	93·64	1·19	3·53	1·65	74,047
1 son	92·56	1·64	3·99	1·82	46,957
0 sons	90·75	1·57	5·15	2·54	9154
Total	91·15	1·75	4·98	2·12	277,035

Note: Due to missing observations, for some of the background characteristics, the sum of the number of pregnancies of each category may not add to the total number of pregnancies.

provided in the data file. It is calculated by adding the scores from variables such as house type, toilet facility, source of lighting, main fuel for cooking, source of drinking water, separate room for cooking, ownership of house, ownership of agricultural land, ownership of irrigated land, ownership of livestock and ownership of durable goods. The index scores range from 0–14 for a low standard of living index (SLI), 15–24 for a medium SLI and 25–67 for high SLI (IIPS & ORC Macro, 2000).

On the other hand, a negative relationship between standard of living index and incidence of still-births is identified, but the differentials are less. The percentage of pregnancies resulting in induced abortions is higher among women not belonging to Hindu, Muslim or Christian faiths compared with women of those three faiths.

The percentage of pregnancies ending in induced abortions is highest among 30- to 34-year-old women. Spontaneous abortions and still-birth are highest among the youngest women (15–19 years), with more than 12% of pregnancies lost. There is a positive relationship between age at first union and pregnancies resulting in either induced abortion or spontaneous abortion. Women who have an average pregnancy interval of less than 12 months experience more pregnancies ending in either induced abortions or spontaneous abortions. In total, 38·73% of pregnancies with less than one year interval resulted in fetal loss. The likelihood of pregnancy loss decreases to 6·58% as the average pregnancy interval increases. Women with no living children are less likely to have pregnancies resulting in a live birth. Consequently, pregnancies ending in induced abortion, spontaneous abortion and still-birth are highest among women with no living children.

The previous analysis considered all pregnancies, but the subsequent analysis considers the woman as the basis of analysis. The number of induced abortions and natural fetal losses (i.e. spontaneous abortions and still-births) per woman is considered. The rates of induced abortions and natural fetal losses per 100 currently married women according to state are provided in Table 3. Overall the rate of induced abortion per 100 currently married women is 6, and wide differentials are observed according to state. The rate of induced abortion is highest is Manipur (27 per 100 women) state followed by Tamil Nadu and New Delhi. The other states that have induced abortion rates of above the national average are: Maharashtra, West Bengal, Gujarat, Punjab, Nagalanad, Jammu & Kashmir, Goa, Assam and Tripura. The rate of induced abortion is lowest in Bihar, followed by Mizoram and Andhra Pradesh.

In total, the rate of natural fetal loss is about 26 per 100 currently married women. Assam state has the highest rate of natural fetal loss, followed by the north-eastern states of Meghalay, Nagaland and Manipur. The states that have a natural fetal loss rate of above national level are New Delhi, Goa, Orissa, Jammu & Kashmir, Mizoram, Uttar Paradesh, Rajasthan, Tamil Nadu and Haryana. The lowest rate of natural fetal loss is observed in Sikkim, followed by Tripura, Maharashtra and Arunachal Pradesh. For both induced abortion and natural fetal loss, the states of New Delhi, Tamil Nadu, Goa, Manipur, Assam, Jammu & Kashmir and Nagaland have rates above the national level.

The number of induced abortions and natural fetal losses per 100 women according to selected socioeconomic and demographic characteristics are provided in Table 4. The results suggest that the rate of induced abortions is more than double

Table 3. The number of induced abortions and natural fetal losses per 100 currently married women aged 15–49, by state, India

State	Induced abortions	Natural fetal losses[a]	Number of women
Andhra Pradesh	2·78	23·93	3344
Assam	13·15	37·68	2881
Bihar	1·36	22·83	5913
Goa	12·10	26·97	1054
Gujarat	8·07	23·67	3279
Haryana	5·07	32·54	2606
Himachal Pradesh	5·36	24·11	2669
Jammu & Kashmir	10·58	28·74	2472
Karnataka	3·19	23·68	3689
Kerala	5·62	20·69	2443
Madhya Pradesh	3·87	24·21	5901
Maharashtra	6·54	19·59	4528
Manipur	27·13	34·10	1227
Meghalay	3·32	37·26	786
Mizoram	2·48	29·13	866
Nagaland	10·47	36·45	708
Orissa	5·98	28·28	3770
Punjab	9·96	25·00	2486
Rajasthan	4·10	30·21	5913
Sikkim	3·34	17·17	975
Tamil Nadu	16·44	32·11	3936
West Bengal	7·50	20·91	3724
Uttar Pradesh	6·25	29·70	7968
New Delhi	16·38	25·80	2204
Arunachal Pradesh	3·29	19·73	948
Tripura	14·20	18·60	941
All India	6·33	25·62	76,738

Note: All India sample weight is used to generate the results for All India. State-level results are obtained by using individual state weights.
[a]Includes spontaneous abortions and still-births.

in urban areas compared with rural areas, but there is no difference in the rate of natural fetal loss observed between rural and urban women.

The results indicate that the risk of experiencing natural fetal loss declines significantly with an increase in level of education of women. In contrast, the rate of induced abortion increases with increases in the educational level of women. The frequency of natural fetal loss is found to be higher among women who consume tobacco and/or alcohol and for women who have experienced domestic violence. The rates of induced abortions and natural fetal loss are highest among women whose height is less than 145 cm and a negative relationship is shown between the height of

Table 4. The number of induced abortions and natural fetal losses per 100 currently married women aged 15–49, according to selected background characteristics

Background characteristic	Induced abortions	Natural fetal losses[a]	Number of women
Place of residence			
Rural	4·34	25·92	56,521
Urban	11·88	24·78	20,217
Education			
Illiterate	3·43	27·60	44,672
Literate, <middle complete	7·89	24·47	14,972
Middle school complete	11·51	23·19	6224
High school and above	13·16	20·46	10,859
Work status			
Not working	7·00	24·77	47,350
Working	5·24	26·97	29,356
Tobacco chewing/smoking/drinking habit			
No	6·49	24·73	67,470
Yes	5·14	32·11	9229
Experienced domestic violence since age 15			
No	6·03	23·58	60,301
Yes	7·42	33·12	16,430
Height (cm)			
<145	5·12	28·43	9188
145–150	5·89	27·54	19,756
150–155	6·52	24·69	24,030
155+	7·67	23·86	17,826
Missing	4·91	23·94	5937
Standard of living index			
Low	3·04	27·32	24,424
Medium	5·82	25·84	35,700
High	12·50	22·69	15,735
Caste/tribe			
Scheduled caste	4·56	27·70	13,942
Scheduled tribe	3·61	24·41	6553
Other backward caste	6·17	26·00	25,100
None of them	7·90	24·38	30,411
Religion			
Hindu	6·21	25·36	62,713
Muslim	5·47	28·08	9634
Christian	8·68	24·11	1928
Other	10·89	23·58	2395

Table 4. *Continued*

Background characteristic	Induced abortions	Natural fetal losses[a]	Number of women
Current age			
15–19	1·43	17·41	4199
20–24	3·42	19·46	13,749
25–29	6·14	23·21	16,448
30–34	8·36	27·96	14,119
35–39	8·21	29·03	11,995
40–44	7·48	30·56	9323
45–49	6·59	31·26	6904
Age at first union			
<16	3·77	27·07	29,506
16–18	6·28	25·19	28,822
19–22	10·05	23·77	14,483
23+	12·24	24·70	3927
Average pregnancy interval (years)			
<1	20·88	90·08	412
1–2	12·84	44·11	11,466
2–3	6·86	29·08	23,538
3–4	5·24	22·10	15,901
4+	3·35	15·24	25,421
Number of living children			
None	6·77	98·8	1972
One child			
1 son	4·08	19·22	7161
0 sons	3·57	21·28	6234
Two children			
2 sons	8·28	18·95	6262
1 son	9·26	22·31	10,755
0 sons	7·07	24·67	3422
Three or more children			
3+ sons	5·43	27·30	12,158
2 sons	5·44	23·72	16,158
1 son	7·32	25·88	10,527
0 sons	6·87	33·67	2089
Total	6·33	25·62	76,738

Note: Due to missing observations, for some of the background characteristics the sum of the number of women in each category may not add to the total.
[a]Includes spontaneous abortions and still-births.

women and the experience of natural fetal loss. This is congruent with the assumption that the probability of fetal loss decreases with increases in height.

The rate of natural fetal loss is highest among women living in households with a low standard of living, but their rate of induced abortions is lower than that of households with medium and high standards of living. Concerning religious affiliation, women belonging to faiths other than Hindu, Muslim and Christian have a higher rate of induced abortions, but the rate of natural fetal loss is higher among women belonging to the Muslim faith.

Differences in the rate of induced abortion are observed, with rates peaking at over 8 per 100 women in the 30–34 and 35–59 year age groups. In the case of natural fetal loss, the rate increases with increases in age of the women. The age at first union of the women shows a similar pattern, with the rate of induced abortion increasing as the age of first union increases, and the highest rate being observed among women whose age at first union is 23 years or above. Conversely, the rate of natural fetal loss is highest among women whose age at first union is below 16 years. The rates of induced abortion and natural fetal loss are highest among women whose average pregnancy interval is less than 12 months. As the average pregnancy interval increases, the rates of induced abortion and natural fetal loss decrease. The rate of induced abortion is highest among women who have two living children with one son, while the rate of natural fetal loss is highest among women with no living children followed by women who have three or more living children with no son.

To further examine the role of different risk factors, a multivariate analysis was carried out to study the net effect of each variable after controlling for all other variables simultaneously. Two separate models are fitted for induced abortion and natural fetal loss. The independent variables are entered into the model as dummy variables. In the multivariate analysis, instead of considering the states separately, dummies have been included for various regions by combining states. North region includes New Delhi, Haryana, Himachal Pradesh, Jammu & Kashmir, Punjab and Rajasthan; South region includes Kerala, Tamil Nadu, Karnataka and Andhra Pradesh; Central region includes Madhya Pradesh and Uttar Pradesh; West region includes Goa, Maharashtra and Gujarat; East region includes Bihar, Orissa and West Bengal; and North-east region includes Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland and Tripura. This is the same as the classification used in the NFHS-2 national report.

In addition to the risk factors, the negative binomial regression model includes a variable that reflects the amount of exposure over which the events of induced abortion and natural fetal loss are observed. The exposure variable considered in the analysis is marriage duration. For women who are not sterilized, it measures from age at first union, and for women who are sterilized it is the duration between age at first union and date of sterilization.

The results from the negative binomial regression model for the number of induced abortions per woman are given in Table 5. The number of induced abortions among urban women is found to be higher than for their rural counterparts. The odds of undergoing induced abortions are also significantly higher among educated women than illiterate women. The effect of work status and tobacco and/or alcohol consumption on the rate of induced abortions is not statistically significant when

other variables are controlled. On the other hand, women who experienced domestic violence have 1·6 greater odds of having undergone an induced abortion. By caste or tribe, the odds of undergoing an induced abortion is significantly higher among women who do not belong to scheduled caste, scheduled tribe or other backward castes as compared with scheduled caste women. On the other hand, scheduled tribe women are less likely to undergo induced abortions as compared with scheduled tribe women. By religion, women from 'other religions' (other than Hindu and Christian) are more likely to undergo induced abortions than Muslim women. Similarly, the odds of induced abortion are higher among Hindu women than Muslim women. The odds of undergoing induced abortion are significantly higher among women in the age group 30–34 as compared with women in the age group 45–49. The results also suggest that the rate of induced abortion is significantly different according to age at first union. The chance of undergoing induced abortion is maximum among women whose age at first union is in the age group 19–22 as compared with women whose age at first union is below age 16.

Even after controlling for other possible risk factors, women who had pregnancies closely spaced are more likely to experience induced abortion than women who had more than four years on average between pregnancies. The results suggest that differentials in the rate of induced abortions are found to be not significant, when other variables are controlled. However, the likelihood of undergoing induced abortion is significantly higher in the North-east region as compared with the North region. The sex composition of living children suggests that the rate of induced abortion is significantly higher among women with two or fewer living sons as compared with women with more than two living sons. Similarly, within the different combinations of living children, the odds of undergoing induced abortion are also found to be significantly higher among women with zero living sons.

The results of negative binomial regression for natural fetal loss (see Table 6) indicate that place of residence and education of women are not significant factors, when other variables are controlled. Though the effects are not significant, a negative relationship is noticed between natural fetal loss and place of residence, as well as education of women. The habit of consuming alcohol and/or tobacco increases the chance of experiencing natural fetal loss. The odds of experiencing natural fetal loss significantly increases if the women have experienced domestic violence since age 15.

It is also observed that compared with women aged 45–49, the odds of experiencing natural fetal loss are significantly lower among women aged less than 30 years. Considerably lower rates of natural fetal loss are observed among women whose age at first union is above 16 years than women whose age at first union is below 16 years. As expected, the average pregnancy interval shows a negative relationship between average pregnancy interval and rate of natural fetal loss. The odds of experiencing natural fetal loss are significantly higher among women whose average pregnancy interval is less than 4 years as compared with women whose average pregnancy interval is higher than 4 years. The effect of region on the rate of natural fetal loss is found to be statistically significant, with women in regions other than the North-east being likely to have a lower natural fetal loss as compared with women in the North region. Also, women who have fewer than three living sons,

Table 5. Regression coefficients for number of induced abortions among currently married women aged 15–49, India

Background characteristic	Coefficient	Standard error	Significance level	Odds Ratio
Place of residence[1]				
Urban	0·5388	0·0560	0·0000	1·7139
Education[2]				
Literate, <middle complete	0·6181	0·0605	0·0000	1·8554
Middle school complete	0·8970	0·0723	0·0000	2·4522
High school and above	0·8864	0·0755	0·0000	2·4265
Work status[3]	0·0590	0·0489	0·2280	1·0608
Tobacco chewing/smoking/drinking habit[4]	−0·0821	0·0763	0·2820	0·9212
Experienced domestic violence since age 15[5]	0·4650	0·0461	0·0000	1·5919
Height (cm)[6]				
145–150	0·0112	0·0736	0·8790	1·0113
150–155	0·0522	0·0710	0·4620	1·0536
155+	0·1183	0·0718	0·0990	1·1256
Missing	−0·0917	0·1031	0·3740	0·9124
Standard of living index[7]				
Medium	0·3250	0·0663	0·0000	1·3840
High	0·6544	0·0798	0·0000	1·9240
Caste/tribe[8]				
Scheduled tribes	−0·3326	0·1283	0·0100	0·7171
Other backward castes	0·1278	0·0734	0·0820	1·1363
None of them	0·1432	0·0705	0·0420	1·1540
Religion[9]				
Hindu	0·2270	0·0738	0·0020	1·2548
Christian	0·1097	0·1201	0·3610	1·1159
Other	0·4168	0·1067	0·0000	1·5172
Current age[10]				
15–19	−0·4891	0·1966	0·0130	0·6132
20–24	−0·1637	0·1048	0·1180	0·8490
25–29	0·1833	0·0924	0·0470	1·2011
30–34	0·4341	0·0874	0·0000	1·5436
35–39	0·3447	0·0861	0·0000	1·4116
40–44	0·2155	0·0846	0·0110	1·2404
Age at first union[11]				
16–18	0·2145	0·0555	0·0000	1·2393
19–22	0·3606	0·0642	0·0000	1·4341
23+	0·3156	0·0848	0·0000	1·3711
Average pregnancy interval (years)[12]				
<1	3·4338	0·1707	0·0000	30·9937
1–2	2·4351	0·0600	0·0000	11·4165
2–3	1·5766	0·0571	0·0000	4·8384
3–4	1·0612	0·0644	0·0000	2·8897

Table 5. *Continued*

Background characteristic	Coefficient	Standard error	Significance level	Odds Ratio
Region[13]				
South	0·0111	0·0708	0·8750	1·0112
West	0·0459	0·0744	0·5380	1·0470
Central	0·1062	0·0682	0·1190	1·1121
North-east	1·0167	0·0919	0·0000	2·7640
East	0·0846	0·0800	0·2900	1·0883
Number of living children[14]				
No living children	1·4190	0·1384	0·0000	4·1330
1 son (1 living child)	0·8452	0·1097	0·0000	2·3285
0 sons (1 living child)	0·7125	0·1135	0·0000	2·0391
2 sons (2 living children)	0·7654	0·0879	0·0000	2·1499
1 son (2 living children)	0·8545	0·0797	0·0000	2·3501
0 sons (2 living children)	0·7145	0·1030	0·0000	2·0432
2 sons (3 or more living children)	0·0644	0·0696	0·3540	1·0665
1 son (3 or more living children)	0·3016	0·0730	0·0000	1·3520
0 sons (3 or more living children)	0·2731	0·1302	0·0360	1·3140
Constant	−11·2299	0·1549	0·0000	0·0000
Delta	0·4147	0·0268		

Reference categories: [1]Rural, [2]Illiterate, [3]Not working, [4]Not smoking/chewing tobacco/drinking, [5]No, [6]<145 cm, [7]Low, [8]Scheduled caste, [9]Muslim, [10]45–49, [11]<16, [12]4+ years, [13]North region, [14]3+ sons (3+ living children).

irrespective of number of living children, experience a significantly higher rate of natural fetal loss as compared with women with three or more living sons.

Conclusions

This paper examines induced and natural fetal loss among currently married women in India. Slightly fewer than 1 in 10 pregnancies in India result in fetal loss, with approximately 7% of all pregnancies ending in natural fetal loss. Since fetal loss can have considerable effects on the physical and social well-being of women, these numbers indicate an important area in need of improvement in women's lives. While there may be underlying biological conditions in the fetus, the results showed significant variations in the effects of behavioural, social, economic and demographic factors on induced and natural fetal loss.

Among pregnancies resulting in natural fetal loss, demographic characteristics important to family planning were found to be some of the more important predictors of natural fetal loss. Specifically, short pregnancy intervals, especially pregnancy intervals of less than 2 years, were much more likely to result in natural fetal loss. This points to the importance of family planning education for both women and men

Table 6. Regression coefficients for number of natural fetal losses[a] among currently married women aged 15–49, India

Background characteristic	Coefficient	Standard error	Significance level	Odds Ratio
Place of residence[1]	−0·0198	0·0264	0·4530	0·9804
Education[2]				
Literate, <middle complete	−0·0017	0·0275	0·9510	0·9983
Middle school complete	0·0107	0·0381	0·7780	1·0108
High school and above	0·0231	0·0371	0·5330	1·0234
Work status[3]	−0·0160	0·0219	0·4630	0·9841
Tobacco chewing/smoking/drinking habit[4]	0·0978	0·0302	0·0010	1·1027
Experienced domestic violence since age 15[5]	0·2262	0·0224	0·0000	1·2538
Height (cm)[6]				
145–150	0·0195	0·0329	0·5530	1·0197
150–155	−0·0461	0·0331	0·1640	0·9550
155+	−0·0593	0·0353	0·0930	0·9424
Missing	−0·1220	0·0501	0·0150	0·8852
Standard of living index[7]				
Medium	−0·0095	0·0253	0·7090	0·9906
High	−0·0185	0·0359	0·6060	0·9816
Caste/tribe[8]				
Scheduled tribes	−0·1786	0·0450	0·0000	0·8364
Other backward castes	0·0304	0·0295	0·3030	1·0308
None of them	−0·0277	0·0315	0·3790	0·9727
Religion[9]				
Hindu	−0·0613	0·0320	0·0550	0·9405
Christian	−0·0619	0·0612	0·3120	0·9400
Other	−0·1349	0·0615	0·0280	0·8738
Current age[10]				
15–19	−0·6960	0·0612	0·0000	0·4986
20–24	−0·4207	0·0453	0·0000	0·6566
25–29	−0·1633	0·0405	0·0000	0·8493
30–34	−0·0127	0·0392	0·7460	0·9874
35–39	−0·0077	0·0413	0·8520	0·9923
40–44	0·0001	0·0430	0·9990	1·0001
Age at first union[11]				
16–18	−0·0390	0·0246	0·1120	0·9617
19–22	−0·0800	0·0311	0·0100	0·9231
23+	−0·0871	0·0468	0·0630	0·9166
Average pregnancy interval (years)[12]				
<1	3·6801	0·0751	0·0000	39·6518
1–2	2·5141	0·0334	0·0000	12·3561
2–3	1·6846	0·0326	0·0000	5·3902
3–4	1·0827	0·0340	0·0000	2·9525

time in which the women could have experienced the cumulative effects of multiple pregnancies. Interestingly, advanced maternal age does not increase the odds of experiencing natural fetal loss.

Slightly less than 2% of pregnancies result in induced abortion. While more factors influenced induced abortions, a short pregnancy interval was the single most important factor to increase the likelihood that a pregnancy would end in an induced abortion. There is a positive relationship between education, standard of living and age and the likelihood of a pregnancy having ended in induced abortion. Additionally, urban women are more likely to have had an induced abortion compared with their rural counterparts. These factors point to the importance of access to resources for women to be able to access abortion services.

There are differences in the important factors that influence natural fetal loss and induced abortion. In some cases, such as measures that address access to resources, there is an opposite relationship between these factors and the two forms of fetal loss. On the other hand, pregnancy spacing was the single most important factor predicting natural fetal loss and induced abortion. This points to the importance of family planning and the need for specific information on the risks of close spacing of pregnancies to the health of the mothers and risks of fetal loss. Additionally, the presence of domestic violence in the home was also found to be an important predictor of both natural fetal loss and induced abortion. Reproductive health education needs to incorporate domestic violence education to reduce fetal loss outcomes in the future. Despite these two important similarities, the similarities in factors are limited and different approaches would be needed to address the two forms of fetal loss.

The implications of the results should be taken in a broader perspective within the framework of reproductive health. Policies and programmes that seek to address fetal loss in general need to focus on the importance of spacing and domestic violence. Programmes to reduce induced abortion fetal loss and natural fetal loss should focus on the factors specific to those situations. The recommendations suggested here broaden the scope and sharpen the focus of ongoing community-based reproductive health programmes in many parts of India.

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Annexure 97

Smokeless Tobacco Use and Risk of Stillbirth

A Cohort Study in Mumbai, India

Prakash Chandra Gupta and Sreevidya Subramoney

Background: Maternal cigarette smoking has been causally associated with an increased risk for stillbirth. Preliminary reports suggest an increased risk for stillbirth with smokeless tobacco use during pregnancy.

Methods: We conducted a population-based prospective cohort study to investigate this association by using a house-to-house approach to recruit 1217 women who were between 3 and 7 months' gestation. Of these, 96% were contacted after delivery to determine the pregnancy outcome. Demographic and maternal variables which were apparently associated either with stillbirth or with smokeless tobacco use (OR ≥ 1.5) were included as potential confounders. Stillbirth was defined as any delivery of a dead fetus after 20 completed weeks of gestation. We used time-to-event methods to analyze the risk of stillbirth.

Results: Overall occurrence of stillbirth among singleton deliveries in this population was 4.1%. Smokeless tobacco use was reported by 17% of women; 8.9% of smokeless tobacco users had a stillbirth compared with 3.1% among nonusers (life-table adjusted hazard ratio = 3.1; 95% confidence interval = 1.7–5.6). After adjustment by the Cox proportional hazards procedure for age, educational and socioeconomic background, working status of mother, parity, prenatal care variables, and place of delivery, the risk for stillbirth in users was 2.6 (95% confidence interval-1.4–4.8). Most women used mishri (a pyrolyzed tobacco product often used as dentifrice), and there was a dose–response relationship between the daily frequency of use and stillbirth risk. The risk of stillbirth associated with smokeless tobacco use was greater in earlier gestational periods.

Conclusions: Smokeless tobacco use during pregnancy increases stillbirth risk, with a risk at least as great as that associated with maternal cigarette smoking.

(*Epidemiology* 2006;17: 47–51)

Perinatal mortality is one of the most sensitive indices of maternal and child health. Each year, approximately 8 million perinatal deaths occur globally, 98% in the developing countries; of these, 60% are stillbirths. Rates of perinatal and neonatal mortality in developing countries have decreased more slowly than rates of infant mortality.[1]

In western countries, maternal cigarette smoking has been shown to be causally associated with an increased risk for stillbirth; the relative risk ranges from 1.2 to 1.6.[2] While cigarette smoking is prevalent among women in developed countries, the use of smokeless tobacco is prevalent among women in many developing countries.[3] Smokeless tobacco use also is becoming increasingly common among young girls globally.[4]

Particularly high prevalence of smokeless tobacco use among women (between 15% and 60%) has been reported in several states in the northeastern, eastern, and western regions of India.[5,6] In the Mumbai Cohort study,[7] of 59,527 lower-middle and lower-class women age 35 years and older, 58% reported current tobacco use, virtually all of which was smokeless.

Evidence on stillbirth risk with smokeless tobacco use is sparse.[8,9] A hospital-based cross-sectional study[8] on 1388 singleton births in Pune, India, reported that the rate of stillbirth in tobacco chewers was 3 times higher than that in nonusers. A multicenter hospital-based case–control study in India[9] reported a 1.5 times higher risk of perinatal death (95% CI = 1.3–1.7) in tobacco users. We report on the effect of smokeless tobacco use during pregnancy on stillbirth in a cohort of nonsmoking pregnant women in the city of Mumbai.

METHODS

A cohort of 1217 pregnant women was interviewed on a house-to-house basis from 8 selected geographic areas of Mumbai City. These geographic areas corresponded to Corporation health post areas. There are about 180 health posts in the city serving the health needs of the population, including maternal and child health needs. We selected 8 health posts on the basis of the following criteria: those registering at least 100 new pregnancies per month, accessibility, and enthusiasm of the health post authorities about participating in the study.

Community Health Volunteers attached to these Health posts (n = 177) regularly monitor and list pregnant women in their respective areas during their house-to-house visits. All pregnant women willing to register for antenatal care with the Corporation Health posts are listed.

Recruitment

A project social worker, accompanied by the Community Health Volunteer, visited all the listed women and screened them for eligibility before interviewing them with a

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pilot-tested, structured questionnaire. Eligible women were defined as those who were between 12 and 28 weeks of gestation and who planned to remain in the study area for delivery. Every woman provided oral informed consent to study participation before enrollment in the study. Community Health Volunteers, working in their areas for several years, were well known in the community and had an established rapport with the community. Thus, there were no refusals for study participation. A second interview at recruitment (10%) by a different social worker was used as a quality control check.

Demographic information and medical and obstetric history (including the date of the last normal menstrual period, and the gestational age in months) was elicited at recruitment. Weight and height of the women were measured using a bathroom weighing scale and an inch tape, respectively. Women's weight before pregnancy generally was not known. Detailed information on all types of tobacco consumption was obtained during this phase. Ultrasound estimates of gestational age were abstracted from antenatal records whenever available. After interview, the women were provided with health education regarding optimal antenatal care and were advised to keep regular contact with the health care system. There was no specific focus on smokeless tobacco use.

Follow-Up

The Community Health Volunteers and the social workers regularly monitored the recruited women. A follow-up interview was conducted for 1167 women (96%) at their residence after the delivery. Women were asked their tobacco habits just before delivery and gestational age at birth. Medical records of delivery were abstracted. We obtained the date of delivery from records and verified this date with the woman. Women were advised on immunization schedules for their infant and the importance of breastfeeding. If the infant was reported dead, the time of death was obtained (born dead or died minutes or hours after birth).

Tobacco Habits

Smokeless tobacco use was categorized as light (1–4 times per day) or heavy (5 or more times per day). Women in the state of Maharashtra (which includes Mumbai City) commonly use *mishri*. Mishri is pyrolyzed and powdered tobacco, the use of which starts as a dentifrice. *Gutka* and betel quid are other commonly-used forms of smokeless tobacco. These include other ingredients such as the areca nut and are generally retained in the mouth for longer periods of time and their juices sucked and swallowed, or spit out. Very few women smoke, and those who do, smoke *bidi* (a small amount of tobacco flakes, approximately 0.2 g, hand rolled in a dry *tendu* leaf tied with a thread).

Outcome Definitions

Any fetus that did not breathe or show any other evidence of life at birth after a minimum 20 weeks of gestation was defined as a stillbirth. Early neonatal deaths and stillbirths are very clearly differentiated in the Maternal and Child Health program in India, which has been operational for several decades; doctors are trained to specifically differentiate the 2 outcomes. In addition, mothers were specifically asked whether the child cried and was well, and breast-fed immediately after birth or was resuscitated or transferred to a special care nursery. Our analyses are restricted to stillbirths, as our perinatal mortality statistics were not complete.

Gestational age at delivery was determined on the basis of ultrasound reports before the completion of 30 weeks of pregnancy whenever available (n = 453). For the rest, we use the number of days from the date of start of the last normal menstrual period to the date of delivery. The agreement of ultrasound with self-reports among women for whom both were available was 70% for preterm deliveries and 95% for term deliveries.

Data Analysis

Of the 1167 women who were followed-up, we excluded 2 bidi smokers, 8 women who gave birth to twins, 21 who had aborted before 20 weeks, and 26 with no date of birth and with secondhand information only. Thus, 1110 women were available for analysis of stillbirth rates. Of these 1110 women, 45 had delivered at home; all these women were interviewed after delivery and included in the study.

Socioeconomic status classification involved calculation of an index for each woman. This index, which is considered standard for urban Indian families,[10] uses the sum of standard scores assigned to categories of the educational and occupational status of the father and the per-capita income of the family. Only 2 women had upper-class socioeconomic status score; these women were included along with the middle class women for all analyses.

Demographic and other variables were individually examined for their association with stillbirth; hazard ratios (HRs) and 95% confidence intervals for the risk of stillbirth were calculated using the Cox proportional hazards procedure, with days of gestation as the timescale. Their association with smokeless tobacco use was also individually examined. Potential confounding variables were those that were apparently associated with either the exposure or the outcome (OR $\geq$ 1.5). HIV status was available for 500 women, all of whom were negative. Only 2 women reported alcohol consumption. Therefore, HIV and alcohol use were not included in the analysis. Additional variables considered but not included in the multivariate model were religion, language, type of accommodation, height of mother, weight of mother, interpregnancy interval, and previous preterm delivery, as none of these variables showed association with stillbirth or with smokeless tobacco use.

Stillbirth rates in smokeless tobacco users and nonusers were compared. We then performed multiple covariate analysis using time-to-event methods as described by Smith,[11] with days of gestation as the timescale. Frequency and type of smokeless tobacco use were similarly analyzed. Stillbirth risk at particular gestational periods was calculated similarly using life table methods (as the ratio of the number of stillbirths during the period to all ongoing pregnancies at the start of that period) and adjusted for potential confounders using the Cox proportional hazards procedure. Survival curves were derived using the life table procedure.

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RESULTS

The response rate among pregnant women in the community was 100%. In 10% rechecks, the intersocial-worker agreement was 100% for tobacco use and over 90% for most other variables. Of the 1217 recruited women, regular tobacco use during pregnancy was reported by 208 (17.1%). Smokeless tobacco use predominated (99% of tobacco users; n = 206), with mishri being the most common (81%). Smokeless tobacco use per day was 1–2 times for 46%, 3–4 times for 21%, and higher for the rest. Reduction or cessation of tobacco use late in the pregnancy was reported by only 5 women; hence they were not analyzed separately.

The variables that qualified as potential confounders (Table 1) include age of mother, working status of mother, number of antenatal care visits, number of Tetanus toxoid doses taken, place of delivery, previous stillbirth and previous cesarean section (all associated with an increased risk of stillbirth). Additionally, educational status, socioeconomic score, and parity, were included as potential confounders, as they were associated with smokeless tobacco use.

Of 1110 women, 46 (4.1%) had stillbirths; 28 among 908 nonusers (3.1%) and 18 among 202 smokeless tobacco users (8.9%). The unadjusted HR of stillbirth in users (calculated by life table methods) was 3.1 (95% CI = 1.7–5.6); after adjustment for potential confounders (Table 1, excluding previous stillbirth and previous cesarean delivery) by the Cox proportional hazards procedure, the risk was 2.6 (1.4–4.8).

The unadjusted hazard of stillbirth with smokeless tobacco use among women who had experienced a previous pregnancy (n = 848) was 2.6 (1.3–5). After adjustment for all potential confounders listed in Table 1 (including previous stillbirth and previous cesarean delivery) the HR among these women was 2.1 (1.03–4.4).

TABLE 1. Association of Smokeless Tobacco Use and Potential Confounders With Stillbirth in Univariate and Multivariate Analyses, Using the Cox Proportional Hazards Model

	Unadjusted HRs (95% CI)	Adjusted HRs (95% CI)
Smokeless tobacco use	3.1 (1.7–5.6)	2.6 (1.4–4.8)
Age of mother ≥30 years	2.7 (1.4–5.3)	2.2 (1.05–4.5)
Age <20 years	1.5 (0.6–3.9)	2.1 (0.7–6.2)
Education <10th grade	1.03 (0.5–2.2)	0.6 (0.3–1.4)
Lower socioeconomic score*	1.5 (0.8–2.9)	1.2 (0.6–2.5)
Working mother	2.02 (0.9–4.8)	1.1 (0.5–2.8)
No of pregnancy ≥5	1.4 (0.6–3.3)	0.7 (0.3–1.9)
No of pregnancy = 1	0.8 (0.4–1.7)	0.9 (0.3–2.1)
Number of antenatal visits 5 or fewer	5.7 (3.2–10.3)	3.4 (1.7–6.9)
No of Tetanus toxoid doses		
No doses	13.5 (6.2–29.8)	4.8 (1.9–11.9)
One dose	4.4 (2.1–9.1)	2.2 (0.97–4.9)
Home delivery	2.9 (1.1–7.2)	1.4 (0.5–3.8)
Previous stillbirth†	1.7 (0.8–3.6)	1.6 (0.7–3.7)
Previous Cesarean delivery†	2.6 (1.2–5.6)	3.2 (1.4–7.3)

*See Methods section for calculation.
†Included only in the model on 848 women with previous pregnancies.

TABLE 2. Association of Type And Frequency Of Smokeless Tobacco Use With Stillbirth

	No. Live Births	No. Stillbirths	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
Nonusers†	880	28	1.0	1.0
Type of smokeless tobacco				
Mishri	153	13	2.7 (1.4–5.3)	2.5 (1.3–5.0)
Gutkha	17	3	4.9 (1.5–16)	5.5 (1.6–19)
No. of times mother used mishri				
1–4	115	8	2.2 (1.01–4.9)	2.1 (0.9–4.7)
5+	38	5	4.3 (1.7–11.3)	3.8 (1.5–10.1)

*HRs adjusted for age, educational status, parity, and antenatal care by Cox proportional hazards procedure.
†Reference category.

Table 2 shows the crude and adjusted risk of stillbirth for the 2 common types of smokeless tobacco, mishri and gutka, and the increase in stillbirth risk with increasing use of mishri. This increased risk remained substantial after adjustment for important covariates by the Cox proportional hazards procedure.

The excess risk of stillbirth associated with smokeless tobacco use was apparent throughout gestation (Figure 1). Table 3 shows the proportion of surviving fetuses, stillbirth rates, and HRs by gestational age. HRs were higher at lower gestational periods.

DISCUSSION

We previously reported an effect of smokeless tobacco use on birth weight,[12] reducing babies' weights by

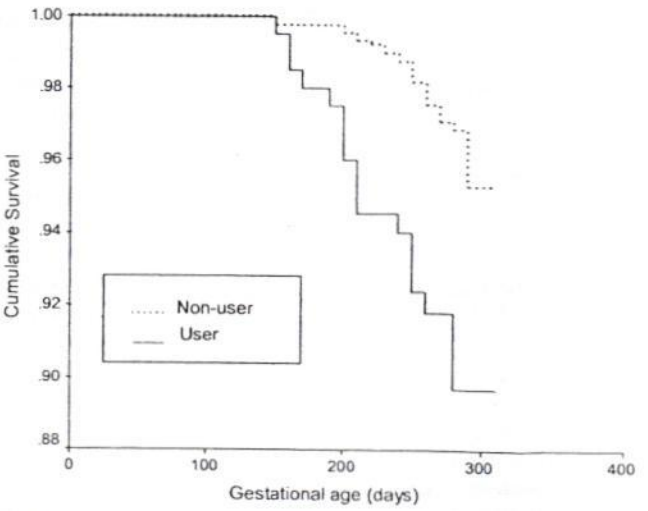

FIGURE 1. Cumulative survival of the fetus in smokeless tobacco users and nonusers by gestational age at birth (for all births ≥20 weeks' gestation).

TABLE 3. Association of Smokeless Tobacco Use With Stillbirth by Gestational Period

Gestational Period (Weeks)	Cumulative Proportion Surviving at End of Period		Stillbirth Rate/1000 Ongoing Pregnancies		Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
	Nonuser	User	Nonuser	User		
20–27	0.9967	0.9653	3.3	34.7	10.5 (2.7–40)	8.2 (2.1–32.5)
28–31	0.9912	0.9453	5.6	20.8	3.7 (0.9–13.9)	3.2 (0.79–12.6)
32–36	0.9756	0.9174	15.8	29.4	1.8 (0.7–5.1)	1.8 (0.6–5.3)
37–44	0.9481	0.9004	18.7	26.7	1.4 (0.1–3.4)	0.7 (0.1–3.3)

*Adjusted for age, educational status, parity, and antenatal care by the Cox proportional hazards procedure.

approximately 100 g. In the present analysis we find that smokeless tobacco use during pregnancy confers an increased risk for stillbirth with a strong dose-related influence and independent of confounding factors. This risk is at least as large as the effect of maternal cigarette smoking. The risk associated with smokeless tobacco use was higher in earlier gestational periods.

Calculation of gestational age for approximately 60% of the women was based on the last menstrual period, which is likely to have resulted in some misclassification error. This imprecision was unavoidable in a population-based study in India, as in many other countries. However, because this error has occurred in both smokeless tobacco user and nonuser groups, it is unlikely to have had a major influence on the calculated relationship between smokeless tobacco use and stillbirth.

Other limitations are the lack of data on infant sex and birth weight for some infants, so that these variables could not be included in the analysis. The possibility of bias owing to differential enrollment of women does not arise in our study, as all women in the selected areas were listed by a house-to-house approach and all listed women were enrolled.

Tobacco in smokeless form contains several carcinogenic and toxic substances.[13] Heavy metals such as lead and cadmium have been found in smokeless tobacco at levels that may present potential risks to the fetus. Exposure to cotinine in fetuses of mishri users has been demonstrated,[14] indicating that nicotine and perhaps other toxic substances can cross the placental barrier.

Smokeless tobacco use during pregnancy has been associated with growth restriction,[12] preterm delivery,[12] and placental morphologic changes.[15] Mediation of increased stillbirth risk through these mechanisms is a possibility. Also, nicotine may have a direct toxic effect by inducing a change in central respiratory control mechanism and eliciting fetal hypoxia-ischemia.[16] Although the reproductive health effects of cigarette smoking have been studied extensively (and smoking during pregnancy is established as a cause of stillbirth), the biologic mechanisms remain to be fully delineated.[2]

It is interesting that use of gutka (containing areca nut in addition to tobacco) conferred a somewhat greater risk of stillbirth than the use of mishri (adjusted HR = 5.5 for gutka compared with 2.5 for mishri). In a case–control study among aborigines in Taiwan[17] (62 subjects with adverse pregnancy outcomes and 124 age-matched controls), chewing of betel quid (including areca nut but not tobacco) was associated with a 2.8-fold higher risk of adverse pregnancy outcomes. However, a prospective study by De Costa and Griew[18] (400 betel chewers and 400 nonchewers) did not suggest an increased risk for perinatal mortality.

The perinatal mortality rate in India and Bangladesh stands at 65–80/1000 total births, in comparison to 20–25/1000 total births in Srilanka and Thailand, and 3–5/1000 total births in the developed countries.[1] With 17% prevalence of smokeless tobacco use and 3 times higher risk of stillbirth in users, about 25% of stillbirths in the study population may be attributable to smokeless tobacco use (calculated as $[i - i_o]/i$, where i is the overall incidence of stillbirth in the population, and i_o the incidence in the nonexposed).

High rates of smokeless tobacco use have been reported among youth (13–15 years) globally including in India,[4] especially so among girls.[19] This may have serious consequences for reproductive health.

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Annexure 78

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Primary care

Smokeless tobacco use, birth weight, and gestational age: population based, prospective cohort study of 1217 women in Mumbai, India

Prakash C Gupta, Sreevidya S

Abstract

Objective To study the effect of using smokeless tobacco during pregnancy on babies' birth weight and gestational age at birth.

Design Population based, prospective cohort study using a house to house approach.

Setting Eight primary health post areas in the city of Mumbai (Bombay), India.

Participants 1217 women who were three to seven months pregnant and planning to deliver in the study area. 1167 women (96%) were followed up.

Main outcome measures Birth weight and gestational age in singleton births.

Results Smokeless tobacco use was associated with an average reduction of 105 g in birth weight (95% confidence interval 30 g to 181 g) and a reduction in gestational age of 6.2 (3.0 to 9.4) days. The odds ratio for low birth weight was 1.6 (1.1 to 2.4), adjusted by logistic regression for maternal age, education, socioeconomic status, weight, anaemia, antenatal care, and gestational age. The adjusted odds ratio for preterm delivery (< 37 weeks) was 1.4 (1.0 to 2.1); for delivery before 32 weeks it was 4.9 (2.1 to 11.8) and before 28 weeks it was 8.0 (2.6 to 27.2).

Conclusions Consumption of smokeless tobacco during pregnancy decreases gestational age at birth and birth weight independent of gestational age. It should receive specific attention as a part of routine prenatal care.

Introduction

Low birth weight and preterm birth are powerful determinants of morbidity and mortality in newborn babies and infants. It has been known for more than 40 years that babies born to mothers who smoke weigh less than babies whose mothers don't smoke. Smoking during pregnancy also increases the risk for preterm delivery.[1] In South East Asia smoking among women may be rare, but use of smokeless tobacco is common.[2] In the Mumbai cohort study in India of 59 527 lower middle class and lower class women aged 35 years and older, 57.5% currently used tobacco, 99.6% of which was smokeless.[3]

There are indications that using smokeless tobacco could be as detrimental to fetal health as cigarette smoking. Of 1388 singleton births in a hospital in Pune, India, tobacco chewers had babies with a consistent birth weight deficit of 100-200 g, independent of maternal weight, socioeconomic status, and gestational age.[4] In 178 deliveries in a Mumbai hospital, the proportion of low birth weight babies in users was 65%, a rate twice as high as that of non-users.[5] The effect on gestational age at birth of using smokeless tobacco has not been reported. We studied a cohort of pregnant women in the city of Mumbai (Bombay), India, to assess the effect of using smokeless tobacco during pregnancy on babies' birth weight and gestational age at birth.

Methods

About 180 government health posts serve the health needs of mothers and children in Mumbai. We conducted this study in collaboration with eight health posts and their community health volunteers (n = 177), who routinely monitor all women in their respective areas for pregnancy.

Recruitment

We screened the women listed by the community health volunteers during house to house visits for eligibility. Two trained social workers interviewed 1217 eligible women after obtaining oral informed consent between June 2002 and November 2002.

Women in the third to seventh month of their pregnancy were eligible if they were planning to remain in Mumbai for the birth (women in India often move to their mother's home to give birth). We used reinterview by a different social worker as a quality control check in 10% of participants (n = 123).

Measurements at recruitment

We gathered information on demographics, tobacco use, and medical and obstetric histories from the women. We used bathroom scales and a tape measure to obtain their weight and height. Most women did not know their weight before pregnancy. The two social workers extracted blood pressure, haemoglobin measurements, and other medical records from the medical reports and created a summary, based on a structured questionnaire format.

Tobacco use

We included as users all women who had used a smokeless tobacco product at least once a day for the past six months. We categorised the frequency of use as light (one to four times per day) or heavy (five or more times per day). Women in the state of Maharashtra, including Mumbai, commonly use mishri (pyrolysed and powdered tobacco), and its initial use is as a dentifrice. Betel quid (paan) with tobacco, gutka, and paan masala are chewed and generally retained in the mouth for longer periods.

Follow up

The community health volunteers and the social workers monitored the women. Interviews took place on delivery, and birth weight and date of delivery were copied from the infant's immunisation card. If medical records of birth weight were not available from the woman they were obtained from hospital records, as was the case in 10% (89) of all available birth weights. For 40 women, information from both sources was available and

in agreement. Blood pressure and haemoglobin measurements were abstracted from antenatal records, and all women gave self reports of high blood pressure or anaemia during pregnancy. Information on induced birth or elective caesarean section was not uniformly obtainable. The women received advice on breast feeding and immunisation schedules.

Outcome definitions

We used as outcomes low birth weight (< 2500 g), preterm birth (< 259 days or 37 weeks), early preterm birth (< 224 days or 32 weeks) and very early preterm birth (< 196 days or 28 weeks).

Data analysis

Of the 1217 recruited women, 208 (17.1%) reported using tobacco regularly during pregnancy. Use of smokeless tobacco predominated (99%, 206 women), mishri being the most common, (80%, 166). Forty six per cent of women (96) chewed tobacco once or twice a day and 24% (49) three or four times a day. Only five women reported that they had stopped using tobacco late in the pregnancy; we did not analyse them separately.

We followed up 1167 women (96%). We excluded two smokers (bidi), eight women who gave birth to twins, 21 who had abortions, and 26 with no date of birth and only secondhand information from neighbours from all analyses. Altogether 1110 women who gave birth after 20 weeks of gestation were therefore available for our analysis of gestational age.

Birth weight was not available in 88 women, 15 (17%) of whom used smokeless tobacco). Forty of these had home deliveries, and for 48 their medical records were not traceable. We excluded 46 stillbirths and two outliers for birth weight (600 g and 4950 g; range 1250-4500 g). Our birth weight analysis therefore included 974 women.

We calculated gestational age as the number of days from the recalled start of the last normal menstrual period to the date of delivery. For 453 women, ultrasound scans before 30 weeks helped date the pregnancy (consistent with self reports in 70% (53 out of 76) of cases for preterm and 95% (359/377) for term deliveries).

Medical reports for haemoglobin (< 100 g/l) and self reports for anaemia were available for 889 women; 99.5% (n = 885) were consistent with self reports, and only self reports were available for the rest. Medical reports for blood pressure (≥ 140/90 mm Hg) and self reports for gestational hypertension were available for 825 (consistent with self reports in 54% (18 of 33) of cases for positive and 99.9% (791/792) for negative self reports; only self reports were available for the rest.

HIV status was available for 500 women; all were negative. Only two women reported alcohol consumption. Calculation of socioeconomic status included the educational and occupational status of the father and the per capita income of the family.[8]

We used the independent samples t test to evaluate the significance of the differences in means and the Mann-Whitney U test for distributions. We calculated relative risks for the outcomes.

We examined differences in the distribution of sociodemographic, biological, and clinical variables among users and non-users of smokeless tobacco. We considered factors that differed significantly between the two groups as potential confounders ($P \leq 0.05$) and entered them into stepwise logistic regression (dichotomised as in table 1), the sociodemographic variable first, followed by the biological and the clinical variable. The final model included only those variables that had independent, significant associations with use of smokeless tobacco. We used SPSS and Epi-Info for statistical analyses.

Table 1 General demographic and other characteristics of participants, by smokeless tobacco use. Values are numbers (percentages) unless otherwise indicated

	Non-user	User	P value (χ^2 test) for difference
Age			
≥20 years	826 (91.0)	181 (89.6)	0.6
<20 years	82 (9.0)	21 (10.4)	
Educational status in years in schooling			
≥10	200 (22.0)	12 (5.9)	0.0001
<10	708 (78.0)	190 (94.1)	
Socioeconomic status			
Middle class*	659 (72.6)	122 (60.5)	0.0001
Low class	249 (27.4)	80 (39.5)	
No of births			
>1	676 (74.4)	172 (85.1)	0.001
1	232 (25.6)	30 (14.9)	
Weight			
≥50 kg	556 (61.2)	138 (68.3)	0.05
<50 kg	352 (38.8)	64 (31.7)	
Height			
≥150 cm	432 (47.6)	105 (52.0)	0.3
<150 cm	476 (52.4)	97 (48.0)	
Antenatal care			
≥5 visits	233 (25.7)	65 (32.2)	0.01
<5 visits	675 (74.3)	137 (67.8)	
History of preterm delivery†			
No	440 (65.1)	108 (62.8)	0.6
Yes	236 (34.9)	64 (37.2)	
Presence of anaemia			
No	644 (70.9)	119 (58.9)	0.001
Yes	264 (29.1)	83 (41.1)	
Gestational hypertension			
No	879 (96.8)	196 (97.0)	0.9
Yes	29 (3.2)	6 (3.0)	
Gestational age at recruitment			
12-20 weeks	342 (37.7)	79 (39.1)	0.6
20-28 weeks	566 (62.3)	123 (60.9)	

*Two women had high socioeconomic status.
†For 848 women with previous pregnancies.

Results

The response rate from the community was 100% as none of the eligible women contacted during the recruitment phase refused to participate. In 123 rechecks (10%) during recruitment the findings of different social workers were 100% in agreement for tobacco use and more than 90% for most other variables.

Women using smokeless tobacco had relatively lower socioeconomic status, weight, and educational status and were less likely to have had optimal antenatal care (a minimum of five antenatal visits are advocated in India for an uncomplicated pregnancy). Proportionately more multiparous and anaemic women (table 1) used smokeless tobacco. We considered these variables as potential confounders in the analyses and also considered the mother's age, a common confounder.

Low birth weight

Babies born to mothers using smokeless tobacco were on average 105 g lighter (2672 g *v* 2777 g, 95% confidence interval for difference 30 g to 181 g; P = 0.006) than those of non-users (median decrease 150 g, P = 0.02). The entire birth weight distribution in users was shifted to the left (fig 1; two tailed P = 0.02), indicating that infants who were already compromised might have been pushed into even higher risk categories.

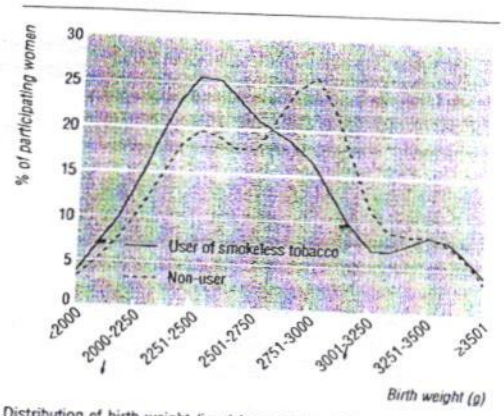

Fig 1 Distribution of birth weight (in g) by smokeless tobacco use of mothers

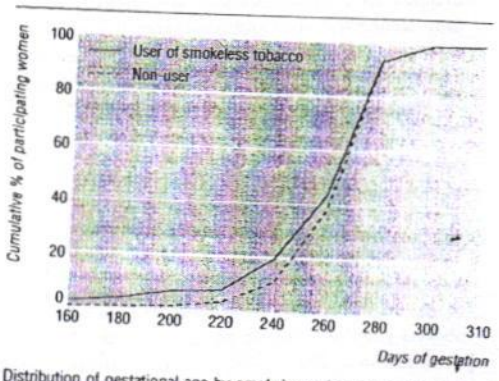

Fig 2 Distribution of gestational age by smokeless tobacco use of mothers (the cumulative percentage for a gestational age is the number of mothers who have given birth up to that gestational age divided by the total number of mothers)

When adjusted for gestational age the birth weight was 87 g lower in users (15 g to 158 g; P = 0.02). A lower birth weight was related to the infant's sex: the reduction was 118 g in baby boys (P = 0.04) and 86 g in baby girls (P = 0.08), and the relative percentage difference (the reduction in birth weight in smokeless tobacco users divided by the mean birth weight) was 4.2 for boys and 3.2 for girls (mean birth weight 2806 g for boys and 2707 g for girls).

The proportion of low birthweight babies was 28.6% (48/168) in tobacco users and 19.9% (160/806) in non-users, giving a crude relative risk of 1.4 (1.1 to 1.9).

The odds ratio for low birth weight remained significant (P < 0.05), with varying confidence intervals, after we adjusted by logistic regression for independent significant confounders (table 2), including gestational age at birth.

The mean decrease in birth weight in light users was 63 g (26 g to 153 g, P = 0.2), and in heavy users 189 g (66 g to 312 g, P = 0.003). The trend of increasing low birth weight with increasing use of smokeless tobacco was highly significant (table 3; χ^2 test 10.3, P = 0.006).

Preterm delivery

Women using smokeless tobacco gave birth an average of 6.2 days earlier than women not using tobacco (271.1 days *v* 264.9 days; 95% confidence interval 3.0 days to 9.4 days; P = 0.0001); preterm deliveries were earlier by 11.6 (4.4 to 18.8) days (P = 0.002). The gestational age distribution in users was shifted significantly to the left and more pronounced at lower gestational ages (fig 2; two tailed P < 0.03).

The proportions of preterm deliveries among women using smokeless tobacco were 26.7% (54/202) and among non-users 18.5% (168/908), giving a crude relative risk of 1.4 (1.1 to 1.9). The crude relative risk for birth before 32 weeks was 3.7 (1.9 to 7.4; 15/202 users *v* 18/908 non-users). The crude relative risk for birth before 28 weeks was 7.2 (2.3 to 22.3; 8/202 users *v* 5/908 non-users).

The odds ratios for preterm delivery remained significant (1.5, 1.009 to 2.2; P = 0.05), after adjustment for age, education, socioeconomic status, and anaemia by logistic regression; the significance level dropped to P = 0.06 after adjustment for weight and antenatal care. The odds ratios for delivery before 32 and 28 weeks remained strong and significant after adjustment for all variables (table 2).

Compared with non-users, light users gave birth an average of 4.9 days earlier (271.1 days *v* 266.2 days; 95% confidence interval 1.2 days to 8.6 days; P = 0.01) and heavy users 8.9 days earlier, (271.1 days *v* 262.2 days; 3.9 days to 13.8 days;

Table 2 Adjusted odds ratios (95% confidence intervals) for low birth weight and preterm delivery in women who used smokeless tobacco

	Low birth weight*	Preterm delivery†		
		<37 weeks	<32 weeks	<28 weeks
Crude odds ratio	1.6 (1.1 to 2.4)	1.5 (1.1 to 2.3)	4.2 (2.1 to 8.5)	8.0 (2.6 to 24.8)
Adjusted odds ratio	1.6 (1.1 to 2.4)	1.4 (1.0 to 2.1)	4.9 (2.1 to 11.8)	8.0 (2.6 to 27.2)
P value	0.05	0.06	0.0001	0.0004

*Adjusted for age, educational and socioeconomic status, weight, anaemia, number of antenatal visits and preterm delivery
†Adjusted for age, educational and socioeconomic status, weight, anaemia and number of antenatal visits.

Table 3 Frequency of smokeless tobacco use, low birth weight, and preterm delivery. Values are numbers of births unless otherwise indicated

Use of smokeless tobacco	Birth weight*		Crude odds ratio	Adjusted odds ratio (95% CI)
	≥2500 g	<2500 g		
Non-users	646	160	1.0	1.0
1-4 times	85	27	1.3	1.5 (0.9 to 2.4)
5 or more times	35	21	2.4	2.1 (1.1 to 4.0)
	Gestational age at birth†			
	≥259 days	<259 days		
Non-users	740	168	1.0	1.0
1-4 times	106	30	1.2	1.2 (0.7 to 1.8)
5 or more times	42	24	2.5	2.2 (1.2 to 3.9)

*Odds ratios adjusted for age, educational and socioeconomic status, weight, anaemia, and preterm delivery
†Odds ratios adjusted for age, educational and socioeconomic status, weight, and anaemia.

P = 0.0001). The trend of increasing preterm births with increasing smokeless tobacco use was highly significant (table 3; χ^2 12.7, P = 0.002).

Discussion

Smokeless tobacco use in pregnant women reduces birth weight and increases the number of low birthweight babies. It shortens the gestational period and increases the number of preterm deliveries. These adverse outcomes are dose dependent and similar to those associated with maternal smoking. Smoking during pregnancy reduces birth weight by an average of 250 g; the adjusted relative risks for low birth weight range from 1.5 to 3.5[7 8] and for preterm delivery from 1.2 to over 2.[8]

Limitations

Confounding due to weight gain and over-reporting of gestational hypertension could not be eliminated, which limits the conclusions of our study. Recorded birth weights may not have been highly accurate, but a systematic bias is unlikely. Although menstrual dating of babies' gestational age in 59% of women (n = 657) was subjective, the findings were consistent with those from women for whom ultrasound results were available. The adjusted odds ratio for preterm birth based only on ultrasound estimates (393 non-users *v* 60 users) was 2.1 (1.0 to 4.1).

In a study from the United States, the association between smoking and preterm delivery before 33 weeks' gestation was stronger than for later preterm delivery.[9] In our study we observed a similar stronger association for early preterm births, independent of possible confounders. Preterm births in settings where the neonatal care infrastructure is less developed can imply a higher perinatal mortality. A greater risk of low birthweight has been observed consistently in women using smokeless tobacco during pregnancy: a preliminary study reported an odds ratio of 3.2 (1.5 to 6.9) with use of mishri,[10] and a hospital based study on tobacco chewers observed a reduction in birth weight of 493 g with of use.[11]

Unexpected finding

Unexpectedly, the prevalence of smokeless tobacco use in our sample (17.1%) was rather low compared with the 57.5% reported earlier from Mumbai.[3] This could be because our study included different age groups (< 35 years *v* ≥ 35 years), fewer Marathi speaking women (30% *v* 75%), and women of higher educational attainment (which is inversely associated with smokeless tobacco use; only 24% of women in our cohort were illiterate), representing different cohorts. With a prevalence of 17% and a relative risk of 1.6, 9.3% of low birthweight and preterm deliveries in this population could be attributed to smokeless tobacco use. For babies born before 32 weeks and 28 weeks, the attributable fractions were 37% and 50%.

Tobacco in smokeless form contains several carcinogenic and toxic substances.[12] Exposure to cotinine has been shown in fetuses of mishri users,[13] which indicates that nicotine and other toxic substances can cross the placental barrier.

Outlook

High rates of smokeless tobacco use in young people have been reported worldwide, including in India,[14] and more so among girls.[15] Increasing use of smokeless tobacco could worsen the fragile situation for mothers and babies in developing countries and should therefore receive specific attention as a part of routine prenatal care.

What is already known on this topic

Maternal cigarette smoking reduces birth weight and increases risk of preterm delivery

Smokeless tobacco is being marketed as a less harmful form of tobacco use

Use of smokeless tobacco by women is common in the developing world

Reports show an association of low birth weight with maternal use of smokeless tobacco

What this study adds

Maternal use of smokeless tobacco decreases birth weight and gestational age

Infants of users have a greater risk of having low birth weight (< 2500 g) and being delivered preterm (< 37 weeks of gestation), independent of confounders

Maternal smokeless tobacco use is associated with high risks for early preterm delivery, independent of confounders

Maternal use of smokeless tobacco use should receive specific attention as a part of routine prenatal care

We thank the health department of the Brihanmumbai Municipal Corporation, particularly the community health volunteers, the staff at the health posts, and the women who participated in the study for their help and cooperation in conducting this study. We also thank Sushama Kadam and Nutan Kiratkar for data collection in the field (interviewing pregnant women).

Contributors: PCG conceptualised the study, designed the field methods, monitored each step of the study, guided analysis and interpretation of the data, revised the article critically for important intellectual content and approved the final version to be published. SS has designed and piloted questionnaires for data collection, coordinated with municipal health authorities, trained field workers, monitored the data collection in the field, did programming for data entry, has analysed and interpreted the data, drafted the article and revised it critically, and was actively involved in the finalisation of the article for publication. Sushama Kadam and Nutan Kiratkar collected data in the field (interviewing pregnant women). PCG is the guarantor.

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Ethical approval: The study conforms to the guidelines laid down by the Indian Council of Medical Research for research on human subjects.

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The influence of maternal cigarette smoking, snuff use and passive smoking on pregnancy outcomes: the Birth To Ten Study

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Summary

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This article describes the patterns and effects of maternal snuff use, cigarette smoking and exposure to environmental tobacco smoke during pregnancy on birthweight and gestational age, in women living in Johannesburg and Soweto in 1990. A cohort of 1593 women with singleton live births provided information about their own and household members' usage of tobacco products during pregnancy. The women completed a questionnaire while attending antenatal services. Data on gestational age and birthweight were obtained from birth records. Women who smoked cigarettes or used snuff during pregnancy accounted for 6.1% and 7.5% of the study population respectively.

The mean birthweight of non-tobacco users was 3148 g [95% CI 3123, 3173] and that of the smokers 2982 g [95% CI 2875, 3090], resulting in a significantly lower mean birthweight of 165 g for babies of smoking mothers ($P = 0.005$). In contrast, women using snuff gave birth to infants with a mean birthweight of 3118 g [95% CI 3043, 3192], which is a non-significant ($P = 0.52$) decrease (29.4 g) in their infants' birthweights compared with those not using tobacco. A linear regression analysis identified short gestational age, female infant, a mother without hypertension during pregnancy, coloured (mixed racial ancestry), and Asian infants compared with black infants, lower parity, less than 12 years of education and smoking cigarettes as significant predictors of low birthweight, while the use of snuff during pregnancy was not associated with low birthweight. The snuff users, however, had a significant shorter gestational age than the other two groups of women. The birthweight reduction adjusted for possible confounders was 137 g [95% CI 26.6, 247.3 ($P = 0.015$)] for cigarette smokers and 17.1 g [95% CI −69.5, −102.7, $P = 0.69$] for snuff users respectively, compared with the birthweight of non-tobacco users. Among women who did not smoke cigarettes or use snuff, exposure to environmental tobacco smoke did not result in significant effects on the birthweight of their infants.

In conclusion, infants of cigarette smokers had significantly lower birthweights than those of non-tobacco users or snuff users who are exposed to nicotine during pregnancy. Passive smoking did not affect birthweight significantly in this population.

Keywords: *maternal cigarette smoking, snuff use, environmental tobacco smoke, pregnancy outcomes.*

Introduction

Maternal cigarette smoking during pregnancy leads to many complications; the most common being retardation of intrauterine growth resulting in a reduced fetal weight and size.[1,2] The health effects of smokeless tobacco during pregnancy have received far less attention with limited publications describing this practice.[3,4] Characterisation of this latter association is

important for several reasons. Millions of women in Africa and Asia use smokeless tobacco,[5] and are seldom advised to stop during pregnancy. Women who use smokeless tobacco are exposed to nicotine, but not to the combustion products in tobacco smoke, such as carbon monoxide and cyanide, which may contribute to fetal hypoxia and reduced birthweight.[6]

In South Africa, 10.7% of women aged 15 years and older smoked regularly, but only 5.3% of black women were found to do so. However, the women using smokeless tobacco (mostly snuff) were found to be predominantly black (13.2%).[7]

Snuff consists of ground dried tobacco leaves of the tobacco species *Nicotina tobacum* and frequently contains additives. Many women, especially those from a rural background, prefer smokeless tobacco manufactured at home. Snuff use by black women fulfils an important social role in terms of relaxation with friends and family, and for ceremonial and medicinal purposes.[8] A number of commercial brands are marketed in South Africa. Dry snuff is usually inhaled through the nose or more commonly placed in the lower labial vestibule.[9] The Tobacco Products Control Act was passed in South Africa in 1993, resulting in a decrease in cigarette use.[7] However, this is contrasted by an increase in snuff consumption of about 30% from 1.1 to 1.5 million kg between 1992 and 1995.[10,11] The snuff containers have escaped the regulations of carrying health warnings that have been placed on cigarettes. Furthermore, snuff containers are not required by law to report their nicotine contents.[12]

Little is known about the effects of the exposure to different tobacco products during pregnancy on the birth characteristics of South African children. The Birth To Ten Study (BTT) is a longitudinal birth cohort study of determinants of growth, development and health of children born to women resident in the Greater Johannesburg Metropolitan area, including Soweto. The data contain information on antenatal exposure to tobacco products, and provide an opportunity to investigate the impact of this exposure on birth outcomes in Johannesburg and Soweto.

Methods

Study population and data collection

The BTT study was initiated in 1990 when infants born during a 7-week period in the Greater Johannesburg/Soweto area were entered into the study.[13] A pre-enrolment phase involved identifying the cohort of women attending antenatal services at 26–32 weeks of pregnancy. Once the cohort enrolment period began, efforts were made to identify and trace every birth that occurred in the Johannesburg/Soweto area. This included placing an interviewer in all public delivery centres during the enrolment period, accessing the records of public and private delivery services, birth notification records as required by local ordinance, mortuary records, and retrospective tracing of women and their infants who later attended postnatal health services in the area. As many women temporarily moved to the city to deliver their infants, the final definition of the cohort was based on birth, as well as on continuous residence in the defined area for 6 months after delivery.

Pairs of mothers and infants with complete data on their tobacco-use patterns and the infants' birth outcomes were included in this study. Trained interviewers interviewed mothers by questionnaire at antenatal visits and in a few cases shortly after delivery. Demographic data, healthcare provision, current and previous pregnancies, social support for the mothers, planned feeding methods for their infants, their use of tobacco products and alcohol, and their exposure during pregnancy to smoking in the household were obtained. Details of the outcome of the pregnancy were obtained from the official birth notification forms completed at each birth. Notification forms contain the following information: mother's identity, age, marital status, employment and parity; date, place, time and type of delivery; and infant's sex, birthweight, estimated gestational age (usually based on date of last menstrual period, palpation, or an ultrasound scan when available).

Asset index

The income of families of infants entered into the cohort study could not be determined. An asset index based on amenities available in the home and environment was developed, using 'an iterated principal factor analysis'. This method was suggested by the World Bank.[14] An asset index was constructed from 13 items that had a loading on the first factor >0.3 or <–0.3. The items with positive loadings >0.3 on factor 1 were: a water-closet system inside the home, hot and cold running water indoors, a separate bathroom, washing machine, employing a domestic worker, having a motor vehicle and telephone at home, living in a flat,

Table 1. Sociodemographic and other characteristics of the 1593 women who used no tobacco, compared with those who used snuff or smoked cigarettes during pregnancy

	All subjects	Non-tobacco users (NT)	Smokers (S)	Snuff users (ST)	Overall *P*-value	Pair-wise comparisons		
						NT : ST	ST : S	NT : S
Numbers (%)	1593	1376 (86.4)	97 (6.1)	120 (7.5)				
Maternal age [mean (SD)]	25.6 (5.7)	25.1 (5.6)	27.6 (5.7)	28.9 (6.1)	<0.0001	<0.0001	0.1041	<0.0001
Asset index								
% in poorest tertile	33.0	33.7	8.3	45.0	<0.0001	0.0031	<0.001	<0.0001
% in middle tertile	34.0	34.7	19.6	37.5				
% in wealthiest tertile	33.0	31.6	72.2	17.5				
Population group								
% Black (n = 1253) (row percentage)	78.7	81.5 (89.5)	12.4 (1.0)	100.0 (9.5)	<0.000	<0.0001	<0.0001	<0.0001
% Coloured (n = 157) (row percentage)	9.9	7.9 (69.4)	49.5 (30.6)	0.0				
% Asian (n = 82) (row percentage)	5.2	5.2 (87.8)	10.3 (12.2)	0.0				
% White (n = 101) (row percentage)	6.3	5.4 (73.3)	27.8 (26.7)	0.0				
% who had ≥12 years' schooling	25.9	27.9	19.6	8.3	<0.0001	<0.0001	0.0154	0.0774
% who earned money during pregnancy	38.6	35.8	68.0	46.7	<0.0001	0.8669	<0.0001	<0.0001
% unmarried	64.6	65.5	49.0	67.5	0.0005	0.0740	0.1013	0.0003
% with insufficient money for basic needs	17.4	16.8	15.6	25.4	0.0003	0.0207	0.2504	0.0006
% who belonged to a medical aid	20.6	19.8	50.6	6.8	0.0206	0.1780	0.3317	0.0105
% whose partner helped with child care	65.7	65.1	79.8	59.0	0.0025	0.7856	0.0498	0.0007
% who had people to help with problems	81.5	82.9	77.1	68.9	<0.0001	0.0180	0.0016	<0.0001
% who discussed problems with others	85.7	86.8	75.3	81.5	0.0038	0.6534	0.0059	0.0011
% who had had a break-up with partners	15.1	13.8	25.8	20.7	0.0017	0.0436	0.3821	0.0016
% who exclusively breast fed	70.7	72.8	39.6	71.7	0.0130	0.2674	0.0043	0.0084
% who bottle and breast fed	22.0	21.4	31.3	24.2	0.0004	0.0002	0.1817	0.1496
% who exclusively bottle fed	7.2	6.0	29.2	4.1	0.0030	0.1085	0.2641	0.0016

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Table 2. Pregnancy exposures, experiences and outcomes of women who used no tobacco, compared with those who used snuff or smoked cigarettes during pregnancy

	All subjects	Non-tobacco users (NT)	Smokers (S)	Snuff users (ST)	Overall *P*-value	Pair-wise comparisons		
						NT : ST	ST : S	NT : S
% who used contraception	60.9	59.9	57.7	74.2	0.0074	0.0190	0.0106	0.6701
% with an unwanted pregnancy	59.0	58.6	78.7	47.4	<0.0001	0.0488	<0.0001	0.0001
% with a partner who smoked	53.7	51.8	71.6	60.5	0.0005	0.0740	0.1013	0.0003
% with members of household who smoked	59.1	57.1	75.3	68.1	0.0003	0.0207	0.2504	0.0006
% who used any alcohol	10.3	8.0	46.3	7.6	<0.0001	0.8669	<0.0001	<0.0001
Gravidity [mean (SD)]	2.2 (1.3)	2.1 (1.3)	2.7 (1.6)	2.9 (1.6)	<0.0001	<0.0001	0.3931	0.0002
Median (range)	2.0 (1–8)	2.0 (1–8)	2.0 (1–8)	3.0 (1–8)				
Parity [mean (SD)]	2.1 (1.2)	2.0 (1.2)	2.4 (1.4)	2.7 (1.5)	<0.0001	<0.0001	0.2067	0.0010
Median (range)	2.0 (1–8)	2.0 (1–8)	2.0 (1–7)	2.0 (1–8)				
% who had vaginal bleeding	6.6	6.0	12.9	8.4	0.0226	0.2862	0.2864	0.0081
% who had high blood pressure	5.5	5.1	11.7	5.0	0.0227	0.9948	0.0749	0.0062
% admitted to hospital	7.6	8.0	17.8	4.4	0.0015	0.1717	0.0019	0.0015
% who had assisted deliveries	9.5	9.1	14.3	11.7	0.4461	0.4112	0.6922	0.3007
Birthweight (g) [mean (SD)] [95% CI]	3135.3 (474.8) [3112, 3158]	3147.6 (473.9) [3122, 3172]	2982.35 (535.2) [2874, 3090]	3118.2 (410.9) [3043, 3192]	0.0176	0.5170	0.0733	0.0052
% low birthweight (≤2.5 kg)	8.7	8.3	16.5	7.5	0.0194	0.7607	0.0391	0.0060
Gestational age (weeks) [mean (SD)] [95% CI]	38.3 (1.6) [38, 38]	38.3 (1.5) [38, 38]	38.7 (2.4) [38, 39]	37.9 (1.4) [37, 38]	<0.0001	0.0026	<0.0001	<0.0001
% small-for-gestational-age infants (≤10th percentile)	7.3	7.0	14.3	4.2	0.0152	0.2466	0.0102	0.0111
% preterm (<36 weeks)	2.8	2.4	9.9	1.7	0.0001	0.6302	0.0085	<0.0001

a self-owned house, and the children having toys. The following items have a negative loading <–0.3 on factor 1: number of occupants per room, a tap and a toilet outside the home only. Infants entered into the BTT study were classified into three categories, those with the highest asset index, the middle group, and those with the lowest asset index.

Birth outcomes

The birth outcomes studied were birthweight (low birthweight ≤2.5 kg), gestational age (preterm <36 weeks) and size according to the gestational age (small-for-gestational-age ≤10th percentile).

Analyses

After data processing, the participants were categorised as non-smokers (NS), cigarette smokers (S) and those using smokeless tobacco, most frequently in the form of snuff (ST). The statistical analyses were performed using the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). Categorical data were compared using the chi-squared test, and continuous data using the Wilcoxon ranks sum test for independent samples. The non-parametric Kruskal–Wallis test was used for the variables in Table 4 that were not symmetrically distributed, as well as the small number of women ($n = 269$) in the group with high exposure to environmental tobacco smoke (ETS) compared with the other groups. Linear regression analyses were performed to identify those variables that independently influenced birthweight. Two forms of exposure to tobacco products were considered. The first analysis was carried out for all the participants with the cigarette smoking variable included after the exclusion of those who used snuff. The second analysis was performed for the black mothers with the smokeless tobacco use variable, snuff use, entered after the cigarette smokers were excluded. Snuff use was reported only by black mothers.

The variables included in the regression model as continuous ones were gestational age, asset index, mother's age and parity of current pregnancy. The dichotomous variables entered were: the infant's sex (boy, girl); mother with hypertension during pregnancy (yes, no); population group white (of European descent) (yes, no); population group black (of African descent) (yes, no); population group coloured (of mixed racial descent, i.e. Koi, San, European, African and/or Malayan) (yes, no); population group Indian (of Indian descent) (yes, no); ≥12 years or <12 years of education; alcohol consumption (yes, no); wanted pregnancy (yes, no); worked for an income during pregnancy (yes, no); living with partner (yes, no); during the last 6 months there was insufficient money for basic needs, such as food, clothes or rent (yes, no); the mother was admitted to hospital during the pregnancy (yes, no). For the first regression analysis, cigarette smoking (yes, no) was entered, and for the second analysis, snuff use (yes, no) was entered. Linear regression models were fitted by entering variables that showed some indication in univariate analyses that they might be possible confounders for the relationship between tobacco use and birthweight.

Results

Complete data sets with antenatal and delivery data were available for 1593 mothers with live born singletons between April and June 1990 (Table 1). Most mothers were black (78.7%), while 9.9% were of mixed racial ancestry (coloured), 6.3% were white, and 5.1% Asian. Unmarried mothers accounted for 64.6% of the study population. During their pregnancy, 38.6% of the mothers earned money, while only 20.6% had medical insurance. Most mothers would have used the public health sector for their antenatal care.

The prevalence of tobacco use in this sample was low; most mothers (86.4%) used no tobacco, 6.1% used snuff, and 5.7% smoked cigarettes. None of the women used both cigarettes and snuff. Significant sociodemographic differences were present among the groups. The snuff users were black and from lower socio-economic circumstances. A quarter had insufficient money for basic needs, were more frequently unmarried, and had less formal education than the other groups. On average, the women who smoked during pregnancy had higher socio-economic standing, more of them earned money during the pregnancy and had health insurance, and they were more likely to be married and receive support from their partners than the other two groups. The non-smokers were less likely to have earned money during their pregnancy; and were more likely to receive support from others than those who used tobacco products.

Women who smoked were found to be least likely to plan breast feeding their infants – they intended to bottle feed more frequently than the other groups of women. Women who smoked had more unwanted

Table 3. Results of a linear regression analysis of the determinants, including either tobacco smoke[a] or snuff use in the African population on birthweight in 1990

	Birthweight differences in all women (excluding snuff use) Adjusted $R^2 = 0.2300$			Birthweight differences in African women (excluding tobacco smokers) Adjusted $R^2 = 0.1525$		
	Differences in birthweight (g)	*P*-value	[95% CI]	Differences in birthweight (g)	*P*-value	[95% CI]
Intercept	−2046.3	<0.0001	[−2734, −1357]	−1397.4	0.0007	[−2203, −591]
Gestational age in weeks of gestation[b]	123.0	<0.0001	[108, 137]	113.5	<0.0001	[96, 130]
Asset index (continuous variable)[b]	5.6	0.1048	[−1, 12]	3.2	0.3657	[−3, 10]
Infant's gender: boy/girl	−67.8	0.0042	[−114, −21]	−73.4	0.0034	[−122, −24]
Mother with hypertension: yes/no	161.7	0.0027	[56, 267]	119.9	0.0598	[−4, 244]
Mother's age (continuous variable)[b]	0.2	0.9429	[−6, 6]	−2.0	0.5608	[−8, 4]
Population group						
White compared with African	10.7	0.8921	[−143, 164]			
Coloured compared with African	−163.7	0.0019	[−266, −60]			
Asian compared with African	−435.4	<0.0001	[−573, −297]			
Parity (continuous variable)[b]	54.0	0.0002	[25, 82]	55.6	0.0002	[26, 84]
Level of education: ≥12 years: yes/no	−60.0	0.0456	[−118, −1]	−82.3	0.0117	[−146, −18]
Used alcohol during pregnancy: yes/no	86.8	0.1039	[−17, 191]	61.4	0.3810	[−76, 198]
Wanted pregnancy: yes/no	−15.2	0.5472	[−64, 34]	−12.2	0.6405	[−63, 38]
Mother worked during pregnancy: yes/no	17.8	0.5237	[−37, 72]	−12.0	0.6861	[−46, 70]
Mother lived with partner: yes/no	12.1	0.6852	[−46, 70]	22.8	0.4677	[−38, 84]
Smoked tobacco: yes/no	−137.0	0.0150	[−247, −27]	–	–	–
Used snuff: yes/no	–	–	–	−17.1	0.6948	[−103, 69]
Had sufficient money for basic needs: no/yes	58.7	0.0624	[−3, 120]	41.9	0.1873	[−20, 104]
Mother admitted to hospital during pregnancy: yes/no	0.6	0.9851	[−57, 58]	−17.0	0.6002	[−80, 46]

[a]When tobacco was entered into regression, all snuff users ($n = 100$) were excluded. When snuff use was entered for all black women, all smokers ($n = 12$) were excluded.
[b]For each one unit by which this continuous variable differed, the birthweight difference in g is given. For the dichotomous variables, the average difference in birthweight in g is provided for the two categories of the variables.
CI, confidence interval.

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Table 4. Comparison of the characteristics and pregnancy outcomes of women who did not smoke, but were exposed to a varying amount of environmental tobacco smoke (ETS) ($n = 1376$)

	All non-smokers (NS) $n = 1376$	NS women not exposed to ETS (NSO) $n = 559$	NS women exposed to one smoker at home (ES) $n = 470$	NS Women exposed to more than one smoker at home (EMS) $n = 269$	Kruskal–Wallis test (General linear model)	Pair-wise comparisons: Wilcoxon ranks sum test		
						P-value NSO : ES	*P*-value ES : EMS	*P*-value NSO : EMS
Mean age of mother (SD)	25.1 (5.6)	25.7 (5.8)	25.2 (5.4)	23.8 (5.1)	0.0001	0.3456	0.0009	<0.0001
[95% CI]	[24, 25]	[25, 26]	[24, 25]	[23, 24]				
Mean asset index (SD)	−0.15 (4.91)	0.44 (5.18)	−0.10 (4.82)	−1.54 (4.21)	<0.0001	0.2383	<0.0001	<0.0001
[95% CI]	[−0, +0]	[0, 0]	[−1, +0]	[−2, +1]				
Mean birthweight (g) (SD)	3147.6 (473.9)	3152.1 (469.2)	3141.6 (468.1)	3136.9 (483.0)	0.8923	0.6272	0.9195	0.8125
[95% CI]	[3122, 3172]	[3113, 3191]	[3099, 3184]	[3078, 3194]	(0.8921)			
Gestational age (weeks) (SD)	38.3 (1.5)	38.4 (1.4)	38.2 (1.6)	38.2 (1.5)	0.1138	0.1614	0.4685	0.0482
[95% CI]	[38, 38]	[38, 38]	[38, 38]	[38, 38]	(0.1054)			
Small-for-gestational-age (SGA) (≤10th percentile)	7.4%	8.2%	6.4%	7.5%	Chi-square 0.5372	Chi-square 0.2657	Chi-square 0.5451	Chi-square 0.7396

CI, confidence interval.

pregnancies, were more often exposed to ETS, and used alcohol more frequently during their pregnancy than the other groups (Table 2). Complications during pregnancy, like vaginal bleeding, hypertension or being admitted to hospital were higher in cigarette smokers than in the other groups. Significant differences in mean birthweight, small-for-gestational-age (<10th percentile) and preterm infants (<36 weeks' gestation) were found among the three groups of women. The mean birthweight of non-tobacco users was 3148 g [95% CI 3123, 3173] and that of the smokers 2982 g [95% CI 2875, 3090], resulting in a significantly lower mean birthweight of 165 g for babies of smoking mothers, despite having significantly longer gestational ages. In contrast, women using snuff gave birth to infants with a mean birthweight of 2982 g [95% CI 2875, 3090], which is a non-significant decrease (29.4 g) in their infants' birthweights compared with those not using tobacco. Cigarette smokers had more small-for-gestational-age and preterm infants than the other two groups of women.

Table 3 provides the results of the linear regression analyses. The first regression with all the women entered and smoking as the tobacco exposure (excluding snuff users), found that lower birthweight was significantly associated with the following variables: shorter gestational age, female infant, mother with hypertension during pregnancy, coloured and Asian infants compared with black infants, lower parity, <12 years of education and smoking tobacco. When the regression analysis was performed for black mothers with snuff use as the only tobacco exposure, the latter was not found to be associated with birthweight. Low birthweight was also found to be associated with shorter gestational age, female infants, low parity, and <12 years of education.

A logistic regression analysis was performed with small-for-gestational-age as the outcome variable. The same associations for the tobacco exposure variables were found as that of the linear regression with low birthweight as the outcome. Tobacco smoke was independently associated with small-for-gestational-age, while snuff use was not associated (data not shown).

A comparison of the characteristics and pregnancy outcomes of women who did not smoke, but were exposed to zero, one or more cigarette smokers in the home is shown in Table 4. The mothers who were exposed to two or more cigarette smokers in the home were younger and poorer (lower asset index) than the other two groups. There was no significant difference

between the mean birthweights of infants born to mothers exposed to ETS and those who were not.

Discussion

These data report the patterns and impact of different forms of tobacco exposure during pregnancy in South African women and their infants. Smoking tobacco was independently associated with low birthweight in Johannesburg and Soweto. Previous studies have found a remarkably constant 175–200 g difference in birthweight between cigarette smokers' and non-smokers' infants.[15,16] The difference in this study (165 g) was slightly below this range. In this setting, snuff use during pregnancy had minimal effects on fetal growth, suggesting that the amount of snuff used was less harmful, and lower blood nicotine levels are present than have been reported in India and Sweden.[3,4] Gupta and Sreevidya[3] found that smokeless tobacco use during pregnancy was associated with an average reduction in birthweight of 105 g [95% CI 30, 181] and delivery before the 37th week of pregnancy. In Johannesburg and Soweto, the mean birthweight of infants of snuff-using mothers was 29.4 g less than that of those black women who did not use snuff, and 17.1 g less after correcting for other possible confounding variables in the linear regression analyses.

We could not record the amount of snuff used by the women in this study. It is possible, however, that their levels of snuff use may have been below the critical level of nicotine intake that will harm the unborn infant. However, a recent study by Ayo-Yusuf *et al.*[17] estimated, through laboratory analyses, that the typical amount of snuff used by South Africans would be sufficient to develop nicotine dependence. This could be equivalent to the amount of nicotine supplied by smoking a packet of 20 cigarettes per day. In this study, mean gestational age among snuff users was significantly reduced compared with non-tobacco users and cigarette smokers (Table 2). However, the preterm rate of <36 weeks' gestation in snuff users was significantly lower than in non-tobacco users. Snuff use is usually initiated for cultural reasons and is considered to have medicinal properties.[8] This is also encouraged, as it is socially more acceptable for black women than smoking, and less expensive than cigarettes. The increasing use of smokeless tobacco by women of childbearing age supports the need for intensified action to control snuff use in South Africa.

Previously published studies of passive smoking in pregnancy indicate a small decrease in birthweight among women who have been exposed to ETS. The size of the effect found is a 28 g reduction in birthweight according to a pooled estimate from 16 studies.[18] Mainous and Hueston,[19] however, found a threshold effect of the level of exposure to passive smoking and low birthweight. In this study, the 15.1 g decrease in birthweight between the women not exposed and those exposed to more than one cigarette smoker in the home was non-significant. This could suggest that the critical threshold of exposure to ETS resulting in low birthweight, as identified by Mainous,[19] might not have been experienced by these women.

Caution is required in interpreting our results, as the pregnant mother's status of tobacco use could not be confirmed by objective measures, such as cotinine or carbon monoxide measurements. In addition, conscious misreporting of tobacco use by pregnant women may play a role, as most South African women are aware that cigarette smoking is detrimental to the health of their unborn child.[20] However, misclassification of tobacco users as non-users will bias outcomes towards no effect, and no information on daily consumption levels was obtained. Therefore, we could not look for dose–response effects. Other unrecorded factors that may affect birthweight are the mother's pre-pregnancy weights, weight gain during pregnancy and her nutritional intake before and during pregnancy. These women were recruited during their third trimester and consequently, the impact of tobacco products on early fetal loss cannot be excluded. The availability of other obstetric outcomes and their relationship to tobacco use would also have been useful.

The profile of the women who used tobacco products during pregnancy identifies two target groups for intervention. The cigarette smokers seem to be the group with higher socio-economic status, a higher marriage and unemployment rate, and with a remarkably high rate of unwanted pregnancies. Their high rate of alcohol use and unwanted pregnancies suggests there are other life-style factors that could also impact on the well-being of their unborn children.

The group of snuff users represents women who are black, mostly poor, with limited health insurance, and less formal education. This group comprises about 10% of the black pregnant women. Snuff use is socially acceptable and would not be perceived as harmful to the unborn child. It is unlikely that public sector ante-

natal services mention smokeless tobacco use as a possible threat to a woman during pregnancy.

This study has identified the need to reduce tobacco smoking during pregnancy in South Africa, particularly in the coloured community where the smoking rate is extremely high and poor pregnancy outcome.[21] A further long-term detrimental effect of smoking during pregnancy is the evidence of an elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy.[22] The health perceptions relating to snuff use should also be addressed. Even if the effects of snuff use were not shown to have an impact on pregnancy outcomes in this study, smokeless tobacco use is harmful to the unborn infant[3, 4] and to the mother's own health. Smokeless tobacco could also cause cancer and a number of non-cancerous oral conditions. Nicotine may also play a role as a cofactor in smokeless tobacco carcinogenesis.[23] Ideally, all women and particularly pregnant women, should eliminate all exposure to tobacco products and nicotine.

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Conflict of interest

In 1995, the National Council Against Smoking accepted a donation from a manufacturer of nicotine replacement products.

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Effect of Swedish snuff (*snus*) on preterm birth

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Objective To compare the effects of Swedish snuff and cigarette smoking on risks of preterm birth.

Design Population-based cohort study.

Setting Sweden.

Population All live, singleton births in Sweden 1999–2006.

Methods Odds ratios (OR) with 95% confidence intervals (CI) were used to estimate relative risks for preterm birth in snuff users (n = 7607), light smokers (1–9 cigarettes/day; n = 41 436) and heavy smokers (ten or more cigarettes/day; n = 16 951) using non-tobacco users (n = 503 957) as reference.

Main outcome measures Very (<32 weeks) and moderately (32–36 weeks) preterm birth.

Results Compared with non-tobacco users, snuff users had increased risks of both very (adjusted OR 1.38; 95% CI 1.04–1.83) and moderately (adjusted OR 1.25; 95% CI 1.12–1.40) preterm birth. Compared with non-tobacco users, light smokers had increased risks of both very (adjusted OR 1.60; 95% CI 1.42–1.81) and moderately (adjusted OR: 1.18; 95% CI: 1.12–1.24) preterm birth, and heavy smokers had even higher risks. Among smokers, but not among snuff users, the risk was more pronounced for spontaneous than induced preterm birth.

Conclusions The use of Swedish snuff was associated with increased risks of very and moderately preterm birth with both spontaneous and induced onsets. Swedish snuff is not a safe alternative to cigarette smoking during pregnancy.

Keywords Pregnancy, premature birth, smokeless, snuff, tobacco.

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Introduction

Preterm birth is a leading cause of neonatal and infant mortality as well as short- and long-term disability.[1,2] The preterm birth rate has risen in several industrialised countries, including in the United States where the rate has increased from 9.5% in 1981 to 12.7% in 2005.[2]

Smoking during pregnancy is associated with an increased risk of preterm birth, especially of spontaneous onset, but the mechanism is unclear.[3–6] Smokeless tobacco contains and delivers quantities of nicotine comparable to those typically absorbed from cigarette smoking, but does not result in exposure to the products of combustion, for example carbon monoxide.[7,8] There are two main forms of smokeless tobacco: chewing tobacco and snuff. Among the high-income countries, Sweden has the highest per capita consumption of smokeless tobacco, predominantly in the form of *snus*, which is an oral moist snuff. The Swedish snuff contains lower levels of some harmful substances, for example nitrosamines, than many of the brands available in North America and some low-income countries.[7] Globally, the use of smokeless tobacco has increased and the largest increase has occurred in women of childbearing age.[9,10] Possible effects of smokeless tobacco on risk of preterm birth have been investigated in only a few studies with somewhat ambiguous results, indicating lower,[11] unaltered[12] and higher[13] risks of preterm birth (<37 weeks) in women using smokeless tobacco during pregnancy compared with non-tobacco users. One of these studies was based on the Swedish Medical Birth Register, including the first 2 years of registration of snuff use among pregnant women.[13]

Data from the Birth Register are now available for six additional years, which made it possible to estimate the potential effects of Swedish snuff on preterm birth in greater detail. Specifically, we wanted to investigate snuff use in relation to severity and onset (spontaneous or induced) of preterm birth. We also aimed to compare the effects of snuff and smoking, to disentangle the possible effects of nicotine versus tobacco combustion products on preterm birth.

Methods

Study design

Information from the Swedish Medical Birth Register was used to define the study population. Women born in the Nordic countries (Sweden, Norway, Denmark, Finland or Iceland) who delivered a live, singleton infant between 1999 and 2006 were included in the study (n = 610 757). The Birth Register contains data on more than 99% of all births in Sweden and includes demographic data, information on reproductive history and complications that occur during pregnancy, delivery and the neonatal period.[14] By means of each individual's unique national registration number, the Birth Register can be linked with other Swedish data sources.

In Sweden, gestational age is assessed by ultrasound scans in 95% of women, usually around the 17th week of gestation.[15] If no early second-trimester ultrasound scan was available, the last menstrual period was used to calculate gestational age at delivery. We excluded 558 pregnancies with missing information on gestational age at delivery.

In the Birth Register, information about cigarette smoking has been recorded since 1983 and about snuff use since 1999. The information about tobacco use is collected by midwives at the woman's first antenatal visit, which occurs before the 15th week of gestation in more than 95% of the pregnancies.[16] Tobacco use is categorised, as reported by the women, into: noncurrent tobacco user, current snuff user, current light smoker (one to nine cigarettes per day), and current heavy smoker (at least 10 cigarettes per day). In all, 39 767 pregnancies (6.5%) had complete missing information about current tobacco use. For the purpose of this study, pregnancies where maternal smoking was recorded but with missing information about snuff use (n = 41 351) were considered as exposed to smoking only. Conversely, pregnancies where snuff use was recorded but with missing information about smoking (n = 2039) were included as exposed to snuff only. Whenever maternal tobacco use was recorded as absent for one product and information about the other was missing (n = 673), the corresponding pregnancies were included as related to non-tobacco users. As a consequence, in this study we analysed the following mutually exclusive categories of exposure for the pregnancies included in the Register (Table 1): non-tobacco users (n = 503 957); exclusive snuff user (n = 7607); exclusive light smoking (n = 41 436), exclusive heavy smoking (n = 16 951) and current use of both snuff and cigarettes (n = 481).

Births before 37 weeks of gestation were considered preterm and were categorised into very (before 32 weeks) and moderately (32 weeks + 0 days to 36 weeks + 6 days) preterm births. Information about onset of birth is routinely recorded in a standardised manner by the midwife at the delivery ward, and is categorised into spontaneous onset of labour, induced onset of labour, and caesarean birth before the onset of labour. In this study, onset of birth was divided into spontaneous and induced (i.e. induced onset of labour or caesarean birth before onset of labour). All births with a diagnosis of preterm prelabour rupture of the membranes (PPROM, International Classification of Diseases, tenth version [ICD-10] code: O42) were included as a spontaneous onset of birth.

Information on maternal age at birth, early pregnancy body mass index (BMI, categorised into underweight: <20 kg/m^2, normal weight: 20–24.9 kg/m^2, overweight:

Table 1. Rates of very (<32 weeks) and moderate (32–36 weeks) preterm birth by maternal characteristics among Nordic women: live single births in Sweden, 1999–2006

Maternal characteristics	No. of births	Very preterm birth (%)	Moderate preterm birth (%)
Tobacco habit			
Non-use	503 957	0.55	4.01
Snuff use	7607	0.74	4.97
Cigarette smoking			
1–9 cigarettes/day	41 436	0.95	4.97
≥10 cigarettes/day	16 951	1.10	6.05
Snuff and cigarette use	481	0.83	4.99
Missing	39 767	1.58	6.39
Maternal age (years)			
≤19	9744	1.19	5.60
20–24	70 051	0.69	4.94
25–29	194 825	0.61	4.41
30–34	221 763	0.61	3.93
≥35	113 816	0.78	4.31
Parity			
0	275 652	0.85	5.33
1–2	304 312	0.49	3.27
≥3	30 235	0.75	5.16
BMI (kg/m^2)			
≤19.9	46 639	0.57	4.62
20–24.9	287 478	0.54	3.89
25–29.9	128 801	0.61	4.14
≥30	56 807	0.89	4.95
Missing	90 474	1.01	5.24
Education (years)			
≤9	45 107	0.97	5.37
10–11	110 265	0.77	4.72
12	172 764	0.64	4.37
≥13	280 890	0.58	3.91
Missing	1173	1.02	6.05
Living with infants father			
Yes	547 992	0.59	4.11
No	26 937	0.84	5.06
Missing	35 270	1.68	6.61
Total no. of pregnancies	610 199	4040	26 215

25–29.9 kg/m^2 or obese: ≥30 kg/m^2), parity and whether the woman was living with the infant's father were obtained from the Birth Register. Through linkage with the Education Register, information on the number of years of formal education completed as of 1 January 2008, was obtained and categorised as <9, 10–11, 12, or 13 years or more.

The study was approved by one of the Regional Ethical Review Boards in Stockholm, Sweden. The board did not require the women to provide informed consent.

Statistical analysis

SAS PROC GENMOD (SAS Institute Inc., Cary, NC, USA) was used to estimate the association between tobacco habit and risk of preterm birth and onset of delivery. Odds ratios (OR), presented with 95% confidence intervals (CI), were calculated before and after adjustments for maternal characteristics. Women who reported daily use of both snuff and cigarettes and women with missing information on tobacco consumption were excluded from the analysis. Snuff users, light smokers and heavy smokers were analysed separately and non-tobacco users were used as reference group. We considered as potential confounders: maternal age at delivery, early pregnancy BMI, parity, years of formal education and whether the woman was living with the infant's father. The last variable was not associated with any of the outcomes and was excluded from the final model. All analyses were performed using the STATISTICAL ANALYSIS SOFTWARE version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

In the cohort, 1.2% of the women exclusively used snuff, 6.8% were light smokers, 2.8% were heavy smokers and 0.08% used both snuff and cigarettes in early pregnancy. We had no information on tobacco use in 6.5% of the cohort. Among 610 199 births, 5.0% were preterm with 0.7% (n = 4040) very preterm and 4.3% (n = 26 215) moderately preterm (Table 1). Women who used snuff and women who smoked cigarettes during pregnancy had higher rates of preterm birth than women who did not use tobacco. High rates of preterm birth were also seen in the youngest and in the oldest mothers, in women either expecting their first child or their fourth or higher order child, and in women who were underweight or obese in early pregnancy. Rates of preterm birth increased with decreasing length of formal education and were higher for women who were not living with the infant's father than for women who were living with the infant's father.

Women who used snuff at the first antenatal visit had a higher risk of moderately and very preterm birth than non-tobacco users, also after adjusting for maternal age, parity, BMI and years of formal education (Table 2). Cigarette smokers also had higher risks of preterm birth than non-tobacco users, and risks increased with amount smoked (Table 2).

For snuff use, we found that the overall adjusted OR related to preterm birth was 1.27 (95% CI 1.14–1.41). Data from the Swedish Birth Register between 1999 and 2000 have been used in a previous study.[13] When we repeated the analysis after restricting the study population to women giving birth in 2001–2006, snuff users had an OR for preterm birth of 1.24 (95% CI: 1.06–1.39).

Of all preterm births, 70% had a spontaneous, 27% had an induced and 3% had an unknown onset of labour. Compared with non-tobacco users, snuff users had increased risks of both spontaneous and induced preterm birth (adjusted ORs 1.25; 95% CI 1.10–1.41 and 1.33; 95% CI 1.10–1.61, respectively). Smokers also had increased risks of both spontaneous and induced onsets of preterm birth compared with non-tobacco users, but the association was stronger to preterm birth with a spontaneous onset, especially for heavy smokers (Table 3).

Table 2. Tobacco exposure status and risks of very (<32 weeks) and moderate (32–36 weeks) preterm birth

Tobacco habit	Very preterm birth (n = 3408)			Moderate preterm birth (n = 23 648)		
	No. of women	Odds ratio (95% CI)		No. of women	Odds ratio (95% CI)	
		Crude	Adjusted*		Crude	Adjusted*
Non-use	2772	Reference	Reference	20 184	Reference	Reference
Snuff use	56	1.34 (1.03–1.75)	1.38 (1.04–1.83)	378	1.26 (1.13–1.39)	1.25 (1.12–1.40)
Cigarette smoking						
1–9 cigarette/day	394	1.74 (1.56–1.93)	1.60 (1.42–1.81)	2061	1.26 (1.20–1.32)	1.18 (1.12–1.24)
≥10 cigarette/day	186	2.00 (1.73–2.33)	1.90 (1.61–2.25)	1025	1.55 (1.46–1.66)	1.45 (1.35–1.56)

*Adjusted for maternal age, early-pregnancy BMI, parity and years of education.

Table 3. Adjusted odds ratios (OR) for spontaneous and induced onsets of preterm birth (<37 weeks) by tobacco exposure status

Tobacco habit	Preterm birth					
	Spontaneous onset (n = 18 872)			Induced onset (n = 7350)		
	No. of women	Rate (%)	Adjusted OR (95% CI)*	No. of women	Rate (%)	Adjusted OR (95% CI)*
Non use	16 022	3.18	Reference	6260	1.24	Reference
Snuff use	298	3.92	1.25 (1.10–1.41)	125	1.64	1.33 (1.10–1.61)
Cigarette smoking						
1–9 cigarette/day	1713	4.13	1.24 (1.17–1.32)	654	1.58	1.17 (1.06–1.28)
≥10 cigarette/day	839	4.95	1.56 (1.44–1.69)	311	1.83	1.30 (1.14–1.48)

*Adjusted for maternal age, early pregnancy BMI, parity and years of education.

Comment

This large population-based study supports associations between use of Swedish snuff during pregnancy and increased risks of very and moderately preterm birth. We found that snuff was a risk factor for both spontaneous and induced preterm birth. We could also confirm earlier findings of a dose–response association between smoking and preterm birth with a more pronounced smoking-related risk for spontaneous than induced preterm birth.[5]

In contrast to cigarette smoking, which includes nicotine as well as carbon monoxide and a large number of combustion products, Swedish snuff contains nicotine as the sole substance that has been clearly implicated in pregnancy outcome.[7–9] Our finding that both snuff and cigarette smoking are associated with preterm birth suggests that nicotine plays an important role in tobacco-related preterm births. We had no information about the amount of snuff used, and were therefore unable to study dose–response relationships as we could with cigarette smoking.

Preterm births have either a spontaneous onset, presenting with preterm labour or PPROM, or an induced onset, presenting with elective birth for fetal or maternal indications. To our knowledge, our study is the first to evaluate the association between smokeless tobacco and onset of preterm birth. We found that Swedish snuff use was associated with a similar risk increase for spontaneous and induced preterm births, suggesting that nicotine has an impact both on mechanisms associated with preterm spontaneous onset of labour and on pregnancy complications associated with iatrogenic elective preterm birth. In agreement with previous studies, the smoking-related risk was stronger for spontaneous than for induced preterm birth.[5]

The present study included more than 7600 pregnancies exposed to smokeless tobacco use, which is a considerably larger sample than in the former studies, which included between 100 and 800 users.[11–13] A South African study reported a lower risk of preterm birth (<36 weeks) in snuff users compared with non-users, though the mean gestational age for all births was lower in snuff users than in non-users and in smokers.[11] The major reason for this discrepancy could be that the women in the South African study were recruited late in pregnancy; therefore earlier preterm birth may have been overlooked. Also, the intensity of snuff consumption is not clear. The snuff used in South Africa is a dry snuff, either commercial or home manufactured. Dry snuff is usually inhaled through the nose or more commonly placed in the lower labial vestibule. In an Indian study, use of smokeless tobacco was investigated in relation to preterm birth by severity.[12] The authors could only report a tendency (P = 0.06) for a higher risk (OR 1.4) of preterm birth (36 weeks or earlier) in women who used smokeless tobacco during pregnancy compared with non-tobacco users. When analysing very (<32 weeks) and extremely (<28 weeks) preterm births separately, the reported ORs for smokeless tobacco users were 4.9 and 8.0, respectively. We could not confirm these high risks. In the Indian population, chewing tobacco was used, mostly in the form of *mishri*, which is a pyrolysed and powdered tobacco used as tooth paste. Other usage included locally manufactured traditional products mixing tobacco with *betel quid* (areca nut). Chewing betel nut *per se* has been linked to adverse pregnancy outcomes, probably through fetal exposure to arecoline, an alkaloid with effects on feto–placental circulation similar to those of nicotine.[17,18] Differences in toxicants between these types of tobacco and Swedish snuff, socio-demographic and anthropometric differences between the populations, and differences in management during pregnancy may therefore explain some of the differences in risks between the reports. However, the studies from South Africa and India also raise concerns about residual confounding.

In a previous study from the Swedish Birth Register that included 789 snuff users giving birth between 1999 and

2000, an odds ratio of 1.98 was found for preterm birth (36 weeks or earlier) for snuff use compared with non-use of tobacco.[13] When we in the present study assessed 6783 snuff users giving birth between 2001 and 2006, the corresponding association was considerably weaker (OR 1.21). Apart from slight differences in inclusion and exclusion criteria between the two studies, a plausible explanation for this discrepancy between risk estimates is that pregnant snuff users in the most recent years may have decreased their consumption or stopped using snuff in late pregnancy after hearing about the reports on adverse pregnancy outcome among snuff users. However, given the differences in number of exposed individuals between the studies, the previously reported relative risk[13] may have been overestimated.

A major strength of the present study is the nationwide population-based design with information on current tobacco use at the first antenatal visit in 93.5% of the pregnant population. We adjusted for confounding variables such as maternal age, BMI, parity and socio-economic status measured as years of formal education and whether the woman was living with the infant's father. In addition, the relatively homogeneous population of women born in the Nordic countries, the fact that antenatal and obstetric care is free of charge with standardised management routines and that more than 99% of births are delivered in public hospitals, should minimise, but cannot eliminate, the potential for residual confounding by unmeasured socio-demographic factors or differences in management. Another strength of the study is that information about current tobacco use was collected by interviews in early pregnancy, before the onset of potential adverse pregnancy outcomes, which precludes recall bias. Moreover, gestational age was assessed during the second trimester by ultrasound scans in almost all pregnancies.[15] Self-reported information on smoking during pregnancy is valid in Sweden,[19] but we lack validation studies with respect to snuff use. Another limitation is that categories of tobacco use were based on information only from one time-point in early pregnancy. Some women may have stopped using tobacco later in pregnancy, while about 10% of the women who stop smoking in early pregnancy are estimated to resume later in pregnancy.[20]

Use of Swedish snuff seems to be less harmful than cigarette smoking concerning risks for cardiovascular disease and cancer, and the role of Swedish snuff in smoking harm reduction has been discussed internationally.[21] The ban of smoking in public places, a public health measure with known effects on smoking reduction at the population level,[22] may be followed by a global increase in Swedish snuff use because of its promotion by international cigarette manufacturers. Promoting snuff use to reduce smoking might have some beneficial effects, but may also lead to recruitment of new tobacco users, predominantly using snuff.[23] The findings of an association between snuff use and preterm birth plead against promoting snuff as an alternative nicotine source during pregnancy.

In conclusion; the use of Swedish snuff during pregnancy is associated with increased risks of both very and moderately preterm birth. Swedish snuff seems not to be a safe alternative to cigarette smoking during pregnancy.

Disclosure of interests

One coauthor (MR Galanti) has previously worked as epidemiologist at the Centre for Tobacco Prevention of the Stockholm County Council, a governmental unit affiliated to the Department of Public Health Sciences at the Karolinska Institutet. In her role as researcher she has never been involved in any kind of advocacy, policy-making or public statement concerning Swedish snuff (*snus*). All other coauthors report no conflict of interests.

Contribution to authorship

SC had the original idea for the study. All authors contributed to the design of the study. A-KW performed the analyses under supervision of OS. A-KW wrote the first draft of the manuscript. All authors made substantial contribution to the interpretation of results and manuscript revision.

Details of ethics approval

The study was approved by one of the Regional Ethical Review Boards in Stockholm, Sweden: reference number: 2008/1481-31, date of approval: 22 October 2008. The board did not require the women to provide informed consent.

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GASTROINTESTINAL DISEASES

Use of tobacco products and gastrointestinal morbidity: an endoscopic population-based study (the Kalixanda study)

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Abstract The impact of snus (smokeless tobacco or snuff) on gastrointestinal symptoms and pathological findings is largely unknown. The authors aimed to investigate whether the exposure to different forms of tobacco influences upper gastrointestinal symptoms, histology and frequency of *Helicobacter pylori* infection. A random sample ($n = 2,860$) of the adult population of two northern Swedish municipalities Kalix and Haparanda ($n = 21,610$) was surveyed between December 1998 and June 2001 using a validated postal questionnaire assessing gastrointestinal symptoms (response rate 74.2%, $n = 2,122$) (The Kalixanda Study). A random sub-sample ($n = 1,001$) of the responders was invited to undergo an esophagogastroduodenoscopy (participation rate 73.3%) including biopsies, *Helicobacter pylori* culture and serology and symptom assessment and exploration of present and past use of tobacco products. No symptom groups were associated with snus use. Snus users had a significantly higher prevalence of macroscopic esophagitis univariately but snus use was not associated with esophagitis in multivariate analysis. Snus use was associated with basal cell hyperplasia (OR = 1.74, 95% CI: 1.02, 3.00) and with elongation of papillae (OR = 1.79, 95% CI: 1.05–3.05) of the squamous epithelium at the esophago-gastric junction. Current smoking cigarettes was associated with overall peptic ulcer disease (OR = 2.32, 95% CI: 1.04, 5.19) whereas snus use was not. There were no significant association between current *Helicobacter pylori* infection and different tobacco product user groups. Snus significantly alters the histology of the distal esophagus but does not impact on gastrointestinal symptoms or peptic ulcer disease.

Keywords Dyspepsia · Esophagitis · Gastroesophageal reflux symptom · Peptic ulcer disease · Smoking · Snus

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Abbreviations

ASQ	Abdominal symptom questionnaire
BMI	Body mass index
CI	Confidence interval
EGD	Esophagogastroduodenoscopy
GERD	Gastroesophageal reflux disease
GERS	Gastroesophageal reflux symptom
IBS	Irritable bowel syndrome
OR	Odds ratio
PUD	Peptic ulcer disease
SD	Standard deviation

Introduction

Smokeless tobacco or moist snuff, snus in this study, is widely used in Sweden (900,000 users, 21% of males and 4% of females, while 13% of males and 17% of females smoke cigarettes) [1] and also in other Nordic countries. There is a widespread use in India and the marketing is intense, while USA is the biggest market of snus in the world with approximately 12 million users [2, 3]. Results of a national US survey show that nearly 9% of male and 0.4% of the female college students used snus [4]. In Sweden marketing efforts have resulted in higher use among young males and females have tripled their use over 8 years [1].

Swedish snus products are predominantly finely ground moistened tobacco with an alkaline pH between 7.9 and 8.6 [5]. A pinch of approximately 1–2 g is placed under the upper lip, and some nicotine is absorbed through the buccal mucosa, while some is swallowed together with the saliva [2].

Epidemiological and experimental studies have shown that smoking leads to harmful effects on the gastric mucosa [6–9]. The mechanisms, however, are unclear and the effects might be mediated by inhaled nicotine, as well as by other chemical contents of tobacco. Many studies provide conflicting results but the overall evidence supports the hypothesis that nicotine per se is harmful to the gastric mucosa [7, 9].

There is little knowledge regarding the relationship between gastrointestinal symptoms and snus. The nicotine intake is usually higher than in smokers, and a great deal of tobacco juice contaminated saliva is swallowed during use. In a Swedish cross-sectional study of symptoms in 130,000 construction workers, smokers reported "ulcer-like" dyspepsia three times as often as the non tobacco users, while snus users reported significantly fewer symptoms than both smokers and non tobacco users [10].

It has been shown both in studies on patients and in population-based studies that smoking is a risk factor for peptic ulcer disease (PUD) [8, 11], but there are no data concerning snus on this issue. Data from the US show that cigarette smokers have a markedly increased risk for gastric cancer and that use of more than one tobacco product increases the risk in men [12]. Male users of smokeless or chewing tobacco have also been shown in US prospective studies to have higher death rates from all causes compared with non-users (CPS-I and II studies) and also higher death rates from cancer of the gastrointestinal tract overall (CPS-I study), but separate data on the upper gastrointestinal tract were not shown [13].

Although there is extensive exposure to swallowed tobacco juice contaminated saliva, and high serum levels of nicotine and nitrites, there have been no studies in terms of oesophageal or gastric histology or *Helicobacter pylori* infection in snus users.

The aim of the study was to investigate whether smoking cigarettes and snus use are associated with gastrointestinal symptomatology, macroscopic findings on endoscopy or histological signs of inflammation or cancer risk markers in the esophagus or stomach, including the prevalence of *Helicobacter pylori*.

Materials and methods

Setting

The Kalixanda study setting consisted of two neighbouring communities in Northern Sweden (Kalix and Haparanda) with 28,988 inhabitants (December 1998). The distribution of age and sex was similar to the national average in Sweden in both communities; although proportion of unemployment was slightly higher and income and the proportion with a higher education were slightly lower [14].

Participants

By using the computerized national population register, covering all citizens in the two communities by date of birth order, a representative stratified sample was generated. Every seventh adult ($n = 3{,}000$) from the target population (18–80 years of age, $n = 21{,}610$ in September 1998) was drawn. The sampled subjects were given an identification number (1–3,000) in a random order [14].

Study design and logistics

The original study population ($n = 3{,}000$) was invited by mail to take part. The invitation included information of the study design and of the aims of the study and a validated questionnaire, the Abdominal Symptom Questionnaire (ASQ) to be returned by mail [15]. Up to two remainders were sent when necessary; 140 subjects were unavailable at the time for invitation, thus 2,860 of the original study

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population were eligible for inclusion [14]. The overall response rate was 74.2% (n = 2,122) of the eligible study population.

The original study population was divided into five groups according to their given identification number, 1–600, 601–1,200 and so forth, the first subset of study subjects was approached with the mailed ASQ in November 1998 and the study was completed in June 2001 [14]. In order to complete 1,001 esophagogastroduodenoscopies (EGDs), 1,563 responders to the ASQ had to be approached of whom 364 declined, 74 had moved or could not be reached and 124 were excluded according to the study protocol. Thus the overall response rate for those eligible for the EGD was 73.3% [14]. The exclusion criteria were the presence of serious physical or mental disorder, alcoholism, previous upper gastrointestinal surgery and pregnancy [14]. The biopsies for *Helicobacter pylori* culture and concomitant histology were available from 1,000 subjects. At the visit for the EGD, the participants filled in a more comprehensive ASQ, as described previously [14].

The study protocol was approved by Umeå University ethics committee and the study was conducted according to the declaration of Helsinki. Informed consent was obtained from all participants.

Assessments

Abdominal Symptom Questionnaire (ASQ) is a questionnaire assessing symptoms from the upper and lower part of the abdomen, and it has been found to be valid, reproducible and reliable [15]. All participants were asked if they had been troubled by abdominal pain or discomfort at any location or by any of the listed 33 other gastrointestinal symptoms [15]. The extended ASQ filled in at the EGD visit also included the grading of severity and the frequency of each symptom (daily, weekly or last 3 months). The participants' medication use during the previous 3 months was recorded.

Demographic data and history

Demographic data were collected at the clinic visit (sex, age, length and weight, use of different tobacco products, use of alcohol and use of medication). The subjects' level of education (low education = elementary, comprehensive or secondary school, high education = upper secondary school or university) was asked at the clinic visit.

Definition of body mass index

Body mass index (BMI) was calculated and categorized according to World Health Organization recommendations [16].

Definitions of symptom groups

Gastroesophageal reflux symptoms (GERS) were defined as the presence of any troublesome heartburn and/or acid regurgitation over the past 3 months [14, 17].

Dyspepsia was defined as epigastric troublesome pain or discomfort, and/or nausea, early satiety or uncomfortable feeling of fullness after meal. This is consistent with the Rome II definition (except for upper abdominal bloating which was not asked about in the ASQ) [18]. A simple definition of dyspepsia, labelled "epigastric pain or discomfort", based on the Rome I definition of dyspepsia, was also used [19].

Irritable bowel syndrome (IBS) was defined as troublesome abdominal pain or discomfort located at any site plus concomitant bowel habit disturbances (constipation, diarrhoea, or alternating constipation and diarrhoea). This definition has been used previously and shown to produce results reasonably concordant with the Rome criteria in Sweden [20].

Abdominal pain was defined as troublesome pain or discomfort indicated anywhere in the abdomen [14].

No or minor gastrointestinal symptoms were symptoms not fulfilling any of the above symptom classifications, or absence of symptoms in the ASQ.

Smoking cigarettes and snus use

A complete medical history was taken after the blinded upper endoscopy. The participants were asked about their present and past snus use and the current amounts/week and also about their smoking habits and the number of cigarettes per day in a standardized fashion.

Definitions of tobacco user categories

Current snus users were individuals using moist snuff or chewing tobacco (n = 1), without any present or former use of smoked tobacco.

Current smokers were individuals smoking cigarettes without any present or former snus use.

Current users of both were individuals currently both smoking cigarettes and using snus.

Former smokers were former cigarette smokers without present or former snus use.

Former snus users were former snus users without present or former smoking cigarettes.

Former users of both were former cigarette smokers and snus users without present smoking or snus use.

Non-users were individuals who had never used tobacco products.

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Esophagogastroduodenoscopy

The upper endoscopies were provided by three experienced endoscopists in Kalix and Haparanda which gave sole medical cover to the area. Internal validity was assessed by means of consensus sessions [14]. The endoscopists had been participating in regular quality assessment programs over several years. The endoscopists were unaware of the symptoms of the subjects before and during the endoscopy [14].

Definition of gastric and duodenal ulcer

Peptic ulcer was defined as a mucosal break at least 3 millimetres in diameter in either the stomach or duodenum [11].

Definition and classification of erosive esophagitis

The subjects with mucosal breaks in the esophagus were classified as having erosive esophagitis and graded according to the Los-Angeles classification [21].

Histology and *Helicobacter pylori*

Two experienced pathologists (M. V. and M. Stolte), who were unaware of the endoscopy findings, evaluated the biopsies and provided a common report. The biopsies were stained with haematoxylin and eosin. *Helicobacter pylori* was detected by Warthin-Starry silver staining [22].

Histological parameters of the gastric mucosa were assessed by using the updated Sydney System definitions [23].

Chemical-reactive gastritis proposed to be caused by aspirin, NSAIDs, alcohol or bile reflux was defined according to the updated Sydney System definitions [23, 24].

Samples from the antrum and corpus were cultured and analysed as described previously [22].

Current *Helicobacter pylori* infection was defined as a positive culture or histology. There was an overall agreement of 99.3 percent between the two methods [22].

Serology

Helicobacter pylori IgG antibodies were determined by EIA (Pyloriset EIA-G, Orion diagnostica, Espoo Finland) [25]. A positive test in the absence of *Helicobacter pylori* detection by culture or histology was considered indicative of a past infection.

Gastrin-17 (cut off $\geq$ 10 pmol/liter) and Pepsinogen-1 (cut off $<$ 25 µg/l for low and $>$ 100 µg/l for high levels) were analysed using specific EIA tests (Biohit Plc, Helsinki, Finland).

Statistical analysis

Pearson χ^2 test was used for testing comparisons in univariate analysis. The associations of tobacco user categories with GERS, dyspepsia, epigastric pain, abdominal pain, no or minor GI symptoms and IBS were analyzed applying logistic regression models including possible confounders; *Helicobacter pylori* infection, use of aspirin, use of non-steroidal anti-inflammatory drugs, use of acid reducing drugs, high alcohol consumption ($\geq$100 g/week), education level and categorized BMI and adjusting for age and sex and using non-users as the reference group (odds ratio (OR) = 1). The associations of tobacco user categories with esophagitis, gastric ulcer, duodenal ulcer, overall PUD, high Pepsinogen-1 level, high Gastrin-17 level and dichotomized histological variables from the esophagus, stomach and duodenum were analyzed applying multivariate logistic regression models including possible confounders; *Helicobacter pylori* infection, use of aspirin, use of non-steroidal anti-inflammatory drugs, high alcohol consumption, education level, categorized BMI, use of acid reducing drugs and GERS and adjusting for age and sex and using non-users as the reference group (OR = 1).

Associations with PUD were also analyzed using smokers as the reference group (OR = 1). The results were controlled for interactions. Age and gender in all analyses and use of aspirin/NSAIDs, high alcohol consumptin, gastroesophageal reflux and *Helicobacter pylori* infection were the variables tested as possible effect modifiers. Stepwise model improvement was applied in all analyses to determine the most suitable multivariate logistic regression model and all analyses were adjusted at least for categorized (15 year bands) age and sex. The results from crude logistic regression models are also presented. The results are presented as odds ratios (OR) with 95% confidence interval (95% CI). The goodness of fit of the models was judged from the Pearson χ^2 test (acceptable model when $P > 0.05$). A two sided P-value of < 0.05 was regarded as statistically significant. Fisher's exact test was used in appropriate analyses. The STATA 8 program (Stata Corporation. College Station, TX, USA) was used for the analyses [26].

Results

Of the 1,001 subjects endoscoped, 12 did not have data on the snus use or cigarette smoking, leaving 989 subjects for analysis. Of these, 96 (9.7%) were current snus users, 165 (16.7%) were current cigarette smokers, 22 (2.2%) were combined users, 209 (27.7%) were former smokers, 16 were former snus users and 49 former users of both. Overall 432 (43.7%) individuals had never smoked or used

snus. The snus users consumed on average 3.2 cans/week (1 can = 24–50 g), smokers consumed on average 11.5 cigarettes/day and combined snus users/smokers consumed 2.2 cans/week and 6.2 cigarettes/day.

The sex distribution, age groups in 15 year bands, mean BMI, use of aspirin, alcohol consumption and education level in different user and non-user groups are shown in Table 1.

Use of proton pump inhibitors, histamine-2 receptor antagonists and antacids during the last week or during the last 3 months before the EGD was not significantly associated with smoking cigarettes or snus use.

Symptoms

Symptom prevalences in different tobacco user categories are shown in Table 2. Associations with GERS, IBS, dyspepsia, epigastric pain, overall abdominal pain and no or minor symptoms are shown in Table 3. No symptom groups were associated with snus use.

Endoscopy and histology

The prevalences of esophagitis, gastric ulcer, duodenal ulcer and overall PUD, split by tobacco use category, are presented in Table 4 and the associations of different tobacco user categories with esophagitis, gastric ulcer, duodenal ulcer and overall PUD are presented in Table 5.

Esophagus

Snus users had a significantly higher prevalence of macroscopic esophagitis in univariate analyze compared with non-users ($P = 0.04$, Table 4). However, snus was not associated with esophagitis in multivariate analyze adjusting for age and sex (Table 5).

Former snus use was associated with hyperplasia of the basal cell layer 2 cm above the esophago-gastric junction (crude logistic regression model, OR = 4.43, 95% CI: 1.54, 12.74) and logistic regression model ajdusting for GERS, categorized age (15 year bands) and sex (OR = 3.79, 95% CI: 1.28, 11.16). Also former cigarette smoking shows an association with hyperplasia of the basal cell layer in crude model (OR = 1.50, 95% CI: 1.03, 2.17) and in logistic regression model adjusting for GERS, *Helicobacter pylori* infection, categorized age and sex the result is nearly significant (OR = 1.41, 95% CI: 0.97, 2.06). Male sex was also associated with hyperplasia of basal cell layer at this location (OR = 1.39, 95% CI: 1.02, 1.89) as was the oldest age group (≥65 years old

Table 1 Demographic data of tobacco user/non-user groups

Demographic variable	Non-user ($n = 432$)	Current snus user ($n = 96$)	Current smoker ($n = 165$)	Using both ($n = 22$)	Former snus user ($n = 16$)	Former smoker ($n = 209$)	Former user of both ($n = 49$)
Proportion of men	38.2	84.4[a]	34.5	54.5	100.0	50.2	89.8
95% CI	33.6, 42,8	77.1, 91.7	27.2, 41.8	33.7, 75.3		43.4, 57.0	81.3, 98.3
Age 20–34 years	8.3	18.8	11.5	22.7	12.5	4.3	10.2
	5.7, 10.9	11.0, 26.6	6.6, 16.4	5.2, 40.2	0.0, 28.7	1.5, 7.1	1.7, 18.7
Age 35–49 years	25.9	28.1	33.9	22.7	37.5	23.0	24.5
	21.8, 30.0	19.1, 37.1	26.7, 41.1	5.2, 40.2	13.8, 61.2	17.3, 28.7	12.5, 36.5
Age 50–64 years	34.0	42.7	41.8	45.5	25.0	40.7	38.8
	29.5, 38.5	32.8, 52.6	34.3, 49.3	24.7, 66.3	3.8, 46.2	34.0, 47.4	25.2, 52.4
Age ≥65	31.7	10.4	12.7	9.1	25.0	32.1	26.5
	27.3, 36.1	4.3, 16.5	7.6, 17.8	0.0, 21.1	3.8, 46.2	25.8, 38.4	14.1, 38.9
High alcohol consumption (>100 g/week)	7.4	25.0	13.3	27.3	6.3	14.4	20.4
	4.9, 9.9	16.3, 33.7	8.1, 18.5	8.7, 45.9	0.0, 18.2	9.6, 19.2	9.1, 31.7
Use of aspirin	10.7	8.3	9.1	13.6	6.3	12.9	10.2
	7.8, 13.6	2.8, 13.8	4.7, 13.5	0.0, 27.9	0.0, 18.2	8.4, 17.4	1.7, 18.7
Use of PPI	5.1	1.0	3.6	4.6	0.0	6.7	8.2
	3.0, 7.2	0.0, 3,0	0.8, 6.4	0.0, 13.4	0.0, 0.0	3.3, 10.1	0.5, 15.9
Mean BMI (SD)	26.6 (3.8)	26.2 (3.5)	25.8[a] (4.5)	26.5 (3.9)	26.3 (3.2)	26.7 (4.2)	27.5 (4.2)
Proportion of low education 95% CI	57.1	54.7	58.0	56.8	56.3	63.8	59.2
	52.4, 61.8	44.7, 64.7	50.5, 65.5	36.1, 77.5	32.0, 80.6	57.3, 70.3	45.4, 73.0

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95% CI 95 percent confidence interval, *SD* standard deviation, *BMI* body mass index

[a] Significant difference compared with non-users ($P < 0.05$)

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Table 2 Three months period symptom group prevalences split by tobacco user category

Symptom	Non-user ($n = 432$)	Current snus user ($n = 96$)	Current smoker ($n = 165$)	Using both ($n = 22$)	Former smoker ($n = 209$)	Former snus user ($n = 16$)	Former user of both ($n = 49$)
GERS%[b]	39.1	38.5	37.6	50.0	42.6	50.0	34.7
95% CI	34.5, 43.7	28.8, 48.2	30.2, 45.0	29.1, 70.9	35.9, 49.3	25.5, 74.5	21.4, 48.0
Dyspepsia %[b]	34.5	32.3	42.3	59.1	37.8	37.5	26.5
95% CI	30.0, 39.0	22.9, 41.7	34.8, 49.8	38.6, 79.9	31.2, 44.4	13.8, 61.2	14.1, 38.9
IBS%[b]	27.6	20.8	30.3	54.6[a]	35.9	43.8	16.3
95% CI	23.4, 31.8	12.7, 28.9	23.3, 37.3	33.8, 75.4	29.4, 42.4	19.5, 68.1	6.0, 26.6
Epigastric pain %[b]	18.5	16.7	26.7	50.0[a]	20.1	25.0	16.3
95% CI	14.8, 22.2	9.2, 24.2	19.9, 33.5	29.1, 70.9	14.7, 25.5	3.8, 46.2	6.0, 26.6
Abdominal pain %[b]	49.5	42.7	52.1	68.2	56.5	62.5	42.9
95% CI	44.8, 54.2	32.8, 52.6	44.5, 59.7	48.7, 87.7	49.8, 63.2	38.8, 86.2	29.0, 56.8
No GI symptoms %[b]	38.2	39.6	37.0	27.3	30.1	18.8	38.8
95% CI	36.6, 42.8	29.8, 49.4	29.6, 44.4	8.7, 45.9	23.9, 36.3	0.00, 37.9	25.2, 52.4

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95% CI 95 percent confidence interval, *GERS* gastroesophageal reflux symptoms, *IBS* irritable bowel syndrome, *GI* gastrointestinal

[a] Significant difference compared with non-users ($P < 0.05$)

[b] Prevalence

Table 3 Tobacco use and association with gastrointestinal symptoms (OR = 1 for non-users, $n = 432$)

Symptom	Current snus user		Current smoker		Using both		Former snus user		Former smoker		Former user of both	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
GERS	1.22	0.72, 2.06	0.9	0.60, 1.39	2.40	0.89, 6.56	1.89	0.65, 5.51	1.12	0.77, 1.65	0.83	0.40, 1.74
Dyspepsia	1.29	0.76, 2.19	**1.61**[a]	**1.09, 2.19**	**2.78**[a]	**1.06, 7.28**	1.93	0.64, 5.86	1.18	0.81, 1.73	0.84	0.40, 1.77
IBS	0.87	0.49, 1.55	1.12	0.74, 1.70	**3.25**[a]	**1.28, 8.22**	2.60	0.91, 7.41	1.62	1.12, 2.35	0.59	0.26, 1.35
Epigastric pain	1.48	0.77, 2.85	1.49	0.94, 2.35	**5.66**[a]	**2.18, 14.69**	3.15	0.91, 10.96	1.17	0.75, 1.83	1.28	0.52, 3.11
Abdominal pain	1.05	0.64, 1.73	1.06	0.72, 1.57	2.08	0.77, 5.66	2.54	0.87, 7.47	**1.48**[a]	**1.03, 2.12**	0.96	0.49, 1.87
No or minor GI symptoms	0.81	0.49, 1.35	0.97	0.65, 1.46	0.63	0.22, 1.80	**0.27**[b]	**0.07, 0.99**	**0.63**[b]	**0.43, 0.93**	0.79	0.40, 1.57

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OR odds ratio, *95% CI* 95 percent confidence interval, *GERS* gastroesophageal reflux symptoms, *IBS* irritable bowel syndrome, *GI* gastrointestinal

[a] Significant association

[b] Significant negative association

individuals). *Helicobacter pylori* infection did not have any impact on histological changes 2 cm above the esophago-gastric junction.

Snus use was associated with hyperplasia of the basal cell layer (crude logistic regression model, OR = 1.98, 95% CI: 1.19, 3.31 and logistic regression model adjusting for GERS, *Helicobacter pylori* infection, categorized age and sex, OR = 1.74, 95% CI: 1.02, 3.00) and with elongation of papillae (crude model. OR = 2.02, 95% CI: 1.23, 3.35 and logistic regression model adjusting for GERS, *Helicobacter pylori* infection, categorized age and sex, OR = 1.79, 95% CI: 1.05–3.05) of the squamous epithelium at the esophago-gastric junction; both are histological markers of cell turnover due to chronic chemical irritation such as occurs in GERD. GERS was also a associated both with hyperplasia of basal cell layer and elongation of papillae at this location (OR = 1.42, 95% CI: 1.07, 1.88 and OR = 1.66, 95% CI: 1.26, 2.21, respectively). *Helicobacter pylori* infection was negatively associated with both these histological changes (OR = 0.71, 95% CI: 0.53, 0.95 and OR = 0.69, 95% CI: 0.51, 0.92). These results were not confounded by sex or age.

Stomach

Current smoking cigarettes was associated with overall PUD (crude logistic regression model, OR = 2.38, 95% CI: 1.11, 5.11 and logistic regression model adjusting for categorized (15 year bands) age, *Helicobacter pylori* infection, use of aspirin, obesity and sex, OR = 2.32, 95%

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Table 4 Prevalences of gastrointestinal findings split by tobacco user category

Endoscopic finding	Non-user ($n = 432$)		Current snus user ($n = 96$)		Current smoker ($n = 165$)		Using both ($n = 22$)		Former snus user ($n = 16$)		Former smoker ($n = 209$)		Former user of both ($n = 49$)	
	%[c]	95% CI	%[c]	95% CI	%[c]	95% CI	%[c]	95% CI	%[c]	95% CI	%[c]	95% CI	%[c]	95% CI
Esophagitis	13.7	10.5, 16.9	21.9[a]	13.6, 30.2	12.7	7.6, 17.8	18.2	2.1, 34.3	25.0	3.8, 46.2	16.3	11.3, 21.3	18.4	7.6, 29.2
Gastric ulcer	1.6	0.4, 2.8	1.0[b]	0.0, 1.8	3.6	0.8, 6.4	4.6	0.0, 13.2	0.0	–	2.4	0.3, 4.5	0.0	–
Duodenal ulcer	1.9	0.6, 3.2	0.0	–	4.2	1.1, 7.3	4.6	0.0, 13.2	0.0	–	1.4	0.0, 3.0	2.0	0.0, 5.9
Overall PUD	3.5	1.8, 5.2	1.0[b]	0.0, 1.8	7.9	3.8, 12.0	9.1	0.0, 21.1	0.0	–	3.8	1.2, 6.4	2.0	0.0, 5.9

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PUD peptic ulcer disease, *95% CI* 95 percent confidence interval

[a] Significant difference $P < 0.05$

[b] A user of chewing tobacco and using only <5 g/week

[c] Prevalence

Table 5 Tobacco use and associations with gastrointestinal findings (OR[a] = 1 for non-users, $n = 432$)

Endoscopic finding	Current snus user ($n = 96$)		Current smoker ($n = 165$)		Using both ($n = 22$)		Former smoker ($n = 209$)		Former snus user ($n = 16$)		Former user of both ($n = 49$)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Esophagitis	1.13	0.62, 2.08	1.07	0.61, 1.88	1.08	0.33, 3.60	1.09	0.66, 1.78	1.33	0.40, 4.43	0.74	0.32, 1.69
Gastric ulcer	0.93	0.11, 8.08[b]	2.6	0.84, 8.08	2.88	0.32, 26.23	1.49	0.46, 4.87	–	–	–	–
Duodenal ulcer	–	–	2.20	0.77, 6.30	2.12	0.23, 19.46	0.64	0.17, 2.51	–	–	0.93	0.11, 8.11
Overall PUD	0.34	0.04, 2.69	**2.32[a]**	**1.04, 5.19**	2.57	0.49, 13.55	1.00	0.41, 2.44	–	–	0.64	0.08, 5.23

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PUD peptic ulcer disease, *95% CI* 95 percent confidence interval, *OR* odds ratio

[a] Significant association

[b] A user of chewing tobacco and using only <5 g/week

CI: 1.04, 5.19) whereas snus use was not. Snus users had lower odds of PUD than smokers (OR = 0.12, 95% CI: 0.02, 0.99 in logistic regression model adjusting for age and sex and OR = 0.13, 95% CI: 0.02, 1.09 analyzed with all possible confounders), but the odds of snus users was not significantly lower than non-users had. Current smoking and former smoking cigarettes were associated with chemical reactive gastritis in the antrum (crude model OR = 1.34, 95% CI: 0.89, 2.00 and OR = 1.36, 95% CI: 0.94, 1.98, respectivley, and logistic regression model adjusting for *H. pylori* infection, high alcohol consumption, use of aspirin, categorized age and sex, OR = 1.62, 95% CI: 1.02, 2.60 and OR = 1.56, 95% CI: 1.02, 2.55, respectively). Sex was not associated with chemical reactive gastritis in the antrum but age groups older than 34 years were associated (35–49 years OR = 1.78, 95% CI: 1.00, 3.16, 50–64 years OR = 2.10, 95% CI 1.19, 3.68 and ≥65 years OR = 2.52, 95% CI 1.35, 4.69). Use of any tobacco product was not associated with high granulocyte or lymphocyte counts in antrum or corpus and neither with atrophy or intestinal metaplasia at these locations.

Helicobacter pylori and serology

Helicobacter pylori infection prevalence and seropositivity are presented in Table 6. There were no significant associations between current *Helicobacter pylori* infection or seropositivity and different tobacco product user groups. The proportion of cag-A positive *Helicobacter pylori* genotypes did not differ significantly between non-users and different tobacco product user groups.

Gastrin-17 and Pepsinogen-1

Snus use or smoking cigarettes were not associated with abnormal gastrin-17 level but both were associated with high Pepsinogen-1 level (crude logistic regression model for snus OR = 2.13, 95% CI: 1.35, 3.36 and logistic regression model adjusting for GERS, age and sex, OR = 2.01, 95% CI: 1.23, 3.28 and crude model for smoking cigarettes, OR = 2.60, 95% CI: 1.79, 3.77 adjusted logistic regression model OR = 3.01, 95% CI:

Table 6 *Helicobacter pylori* prevalences in tobacco user/non-user groups (culture/histology and serology)

Hp infection and serology in age groups	Non-user (*n*) Prevalence (95% CI)	Current snus user (*n*) Prevalence (95% CI)	Current smoker (*n*) Prevalence (95% CI)	Using both (*n*) Prevalence (95% CI)	Former smoker (*n*) Prevalence (95% CI)	Former user of snus (*n*) Prevalence (95% CI)	Former user of both (*n*) Prevalence (95% CI)
Age 20–49	*n* = 148	*n* = 45	*n* = 75	*n* = 10	*n* = 57	*n* = 8	*n* = 17
Current *Hp* infection	16.2 (10.3, 22.1)	17.8 (6.6, 29.0)	21.6 (12.3, 30.9)	10.0 (0.0, 28.6)	29.8 (17.9, 41.7)	25.0 (0.00, 55.0)	35.3 (12.6, 58.0)
Positive *Hp serology*	21.6 (15.0, 28.2)	26.7 (13.8, 39.6)	25.3 (15.5, 35.1)	20.0 (0.0, 44.8)	36.8 (24.3, 49.3)	25.0 (0.00, 55.0)	35.3 (12.6, 58.0)
Age 50+	*n* = 284	*n* = 51	*n* = 90	*n* = 12	*n* = 152	*n* = 8	*n* = 32
Current *Hp* infection	44.0 (38.2, 49.8)	33.3 (20.4, 46.2)	47.8 (37.5, 58.19)	33.3 (6.6, 60.0)	41.5 (33.7, 49.3)	37.5 (4.0, 71.0)	21.9 (7.6, 36.2)
Positive *Hp serology*	53.2 (47.4, 59.0)	47.1 (33.4, 60.8)	60.0 (49.9, 70.1)	41.7 (13.8, 69.6)	55.3 (47.4, 63.2)	37.5 (4.0, 71.0)	31.3 (15.2, 47.4)
All ages	*n* = 432	*n* = 96	*n* = 165	*n* = 22	*n* = 209	*n* = 16	*n* = 49
Current *Hp* infection	34.5 (30.0, 39.0)	26.0 (17.2, 34.8)	36.0 (28.7, 43.3)	22.7 (5.2, 40.2)	38.3 (31.7, 44.9)	31.3 (8.6, 54.0)	32.7 (19.6, 45.8)
Positive *Hp serology*	42.4 (37.7, 47.1)	37.5 (27.8, 47.2)	44.2 (36.6, 51.8)	31.8 (12.3, 51.3)	50.2 (43.4, 57.0)	31.3 (8.6, 54.0)	32.7 (19.6, 45.8)

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Hp Helicobacter pylori, *95% CI* 95 percent confidence interval

2.04, 4.44, respectively) without changing the Pepsinogen-1/Pepsinogen-2 ratio significantly.

When all *Helicobacter pylori* infected, all with histological mucosal atrophy in the stomach and all proton pump inhibitor users were excluded, both snus use and smoking cigarettes were associated with high Pepsinogen-1 (crude logistic regression model for snus OR = 2.71, 95% CI: 1.47, 5.02 and logistic regression model adjusting for GERS, age and sex OR = 2.47, 95% CI: 1.27, 4.79 and (crude logistic regression model for smoking cigarettes, OR = 3.88, 95% CI: 2.29, 6.56 and adjusted logistic regression model, OR = 5.03, 95% CI: 2.89, 8.80, respectively) but not with abnormal Gastrin-17 levels. Male sex was a confounder (OR = 1.9, 95% CI: 1.26, 2.96) as was age groups older than 34 years (35–49 years OR = 2.25, 95% CI: 1.03, 4.88, 50–64 years OR = 2.90, 95% CI 1.35, 6.25 and ≥65 years OR = 4.67, 95% CI 2.00, 10.90). The mean value of Pepsinogen-1 for snus users was 91.8 µg/l (SD 36.4) and for cigarette smokers 102.8 µg/l (SD 37.9). The difference is not significant.

Discussion

This is the first population-based, endoscopic study on the effects of snus use and smoking cigarettes in the upper gastrointestinal tract. The snus use was associated with histological markers of chronic chemical irritation alike in gastroesophageal reflux disease (GERD) at the esophagogastric junction. Smoking cigarettes, but not use of snus, was associated with overall PUD.

In this study, 19% of men and 5% of women were current snus users, which are consistent with the Swedish average, of 21% of men and 4% of women. In addition the amounts consumed are also comparable to use in Sweden (3 cans/week) [2]. The study population has been shown to be representative of the Swedish general population [14]. We believe that the results are likely to be generalizable to most Western populations including those were snus is used.

Smoking was a significant risk for PUD while snus users had less PUD than expected although the latter observation did not reach statistical significance. The reasons for this difference are uncertain. Snus contains high amounts of nitrate [27], which is associated with an increased nitrite formation in the oral cavity and further to formation of nitric oxide in the stomach [28–30]. In contrast, cigarette smoking seems to be related to reduced levels of nitrite in saliva [31]. Salivary nitrite has marked gastro-protective effects through nitric oxide formation [32]. These effects include elevated gastric mucosal blood flow and increased mucus thickness. Acidified nitrite has bactericidal effects [33], possibly including *Helicobacter pylori*. Snus did not

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impact on *Helicobacter pylori* status significantly in this population even though there was a non-significant trend towards less *Helicobacter pylori* infection along with rising age in snus users. We observed that both snus use and cigarette smoking caused significantly higher levels of Pepsinogen-1 without affecting Gastrin-17 level. Thus, the difference in PUD prevalences seems not to be due to the Gastrin-17-acid axis.

Intravenously infused nicotine has been shown to decrease pancreatic bicarbonate secretion in animals [34]. Similarly, reduced bicarbonate has been causally related to a higher risk of PUD in cigarette smokers [6]. There are no studies examining this effect in snus users, whose serum nicotine levels are similar to or higher than those of smokers. The role of swallowed alkaline tobacco-contaminated saliva against the development of PUD is unclear in snus users.

Snus use was associated with histological findings in the esophagus consistent with GERD. In a human study the frequency of transient lower esophageal sphincter relaxation was increased by the nitric oxide generating solution. The nitric oxide generating solution also increased esophageal acid exposure [35]. Whether swallowed alkaline tobacco-contaminated saliva, comprising tobacco specific nitrosamine compounds [27], has any role in the development of esophagitis is unclear.

Juice from snus contains high amounts of nitrate which can be reduced to nitrite in the oral cavity [28–30]. When saliva, including dietary nitrate, converted to nitrite, meets acidic gastric juice, the nitrite is converted to nitrous acid, nitrosative species and nitric oxide [29, 30, 36]. In healthy volunteers this potentially mutagenic chemistry appears to be focused at the gastric cardia [36]. A study from the UK showed that both acid and nitric oxide alone can induce double-strand DNA breaks in non-dysplastic Barrett's esophagus and thus may contribute to the genetic rearrangements in the progression from Barrett's esophagus to esophageal adenocarcinoma [37].

A recent Swedish study could observe an increased risk for esophageal squamous cell cancer and a slightly elevated risk for non-cardiac stomach cancer among snus users who had never smoked [38]. We could, however, not verify any premalignant mucosal changes in the stomach. A retrospective cohort study showed that snus use was associated with increased risk of pancreatic cancer as was also cigarette smoking [39]. A Swedish review on the possible harmful effects of snus use found that the carcinogenic effect is probably due to the content of tobacco specific nitrosamines [40].

The strength of our study is the population-based study design. The response rate to all parts of the study was high, suggesting that the results are likely to be reliable and representative. The ASQ-questionnaire is valid, reliable and reproducible [15]. Each participant was specifically asked about use of tobacco products in a face to face interview, and therefore underreporting use is less likely. The weakness is that we cannot provide any physiological data, aside from Gastrin-17 and Pepsinogen-1 levels, and due to the cross-sectional study design it is not possible to draw definite conclusions about any causal connections between exposure and different gastrointestinal disorders. The small number of individuals in some sub-groups is a limitation. Some of the analyses attaining levels of statistical significance ($P < 0.05$) could be chance given the number of tests.

The possibility of higher odds of histological changes, as shown by us, and the possible risk of cancer shown in earlier studies [38, 39] must be taken in account when advocating for using snus in smoking quitting programs [41]. There is no reason to believe, with Sweden as a vivid example, that addictive snus on an open market would be used only by ex-smokers. It is also important to note that concomitant smoking cigarettes and snus use seems to be more harmful than snus use only [12].

In conclusion the snus use was associated with histological markers of increased proliferation of the squamous epithelium consistent with GERD at the esophago-gastric junction but snus does not increase the risk for self-reported upper gastrointestinal symptom groups or risk for PUD.

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Annexure 1

Oesophageal subepithelial fibrosis: an extension of oral submucosal fibrosis

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Summary

Fifty-five patients with oral submucosal fibrosis and an equal number of patients with no evidence of the disease were studied. All patients underwent upper gastrointestinal endoscopy and any abnormality was noted. Multiple oesophageal biopsies were obtained from the upper end of the oesophagus and from any endoscopically observed abnormality. The histological changes in the two groups were assessed blindly by an experienced histopathologist. Histological abnormalities were noted in the oesophageal mucosa in 2% of controls and 66% of patients with oral submucosal fibrosis ($p < 0.0001$). In the control group, acanthosis was seen in one patient, while in the patient group atrophy of the squamous epithelium was evident in 52%, hyperkeratosis in 52%, parakeratosis in 30%, dyskeratosis in 14%, acanthosis in 14%, and papillomatosis and mild dysplasia in 2% patients. Subepithelial collagenization was seen in 32 (64%) patients. The oesophageal abnormalities were seen more frequently in patients who had consumed *Pan masala, Gutka*, betel nut, tobacco or a combination of some or all of these, with or without betel leaf, for ≥ 5 years compared to those consuming them for a shorter period of time (91% *vs* 46%, $p< 0.001$). It is concluded that oral submucosal fibrosis is not a disease confined to the oral cavity; the oesophagus may also be involved in about two-thirds of patients.

Keywords: oral submucosal fibrosis; oesophageal subepithelial fibrosis; betel; Indians; chewing tobacco

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Oral submucosal fibrosis (OSMF) is a chronic irreversible disease of unknown aetiology. It is mainly found in Indians[1,2] and affects about 0.2–1.2% of the urban population attending dental clinics in India.[3–5] It has also been seen among Indians living in Kenya, Malaysia, Uganda, South Africa, Fiji and the UK,[6–10] and cases have been reported from ethnic groups in Taiwan, Nepal, Thailand, Vietnam and Sri Lanka.[11–13] The disease leads to fibro-elastic transformation of the lamina propria and epithelial atrophy of the oral mucosa. Later, the oral mucous membrane becomes stiff, leading to trismus. Although the aetiology is not known, it has been postulated that the disease is caused by irritation of the oral submucosa by irritants such as capsaicin in chillies and tannins in betel nuts.[10,14] Genetic and environmental factors have also been blamed for the disease.[15] As the name denotes, the disease mostly affects the oral mucosa and, although involvement of the oesophageal mucosa has occasionally been reported,[1] there is a paucity of reports describing oesophageal involvement. This study was set up to study the prevalence of oesophageal disease in patients with OSMF.

Materials and methods

The study group consisted of 55 patients with OSMF and 55 other patients with no evidence of OSMF who were undergoing upper gastrointestinal endoscopy. Patients with oesophageal disease (eg, gastro-oesophageal reflux disease, carcinoma of the oesophagus, oesophageal stricture or oesophageal varices) were excluded. The diagnosis of OSMF was made on clinical grounds and buccal biopsy in 36 patients and on clinical grounds alone in the remaining 19 patients. OSMF was clinically classified as severe if the patient could not open his mouth to accommodate a paediatric mouthguard with an outer diameter of 20 mm, during upper gastrointestinal endoscopy.

A detailed clinical history was obtained, including the duration of the disease and symptoms, and information on any substance(s) chewed and the duration of consumption. Thereafter, all subjects underwent upper gastrointestinal endoscopy with a forward-viewing endoscope (Olympus model XQ 20 or XP 20, Olympus Optical Corporation, Tokyo). A specially designed mouthguard was used in patients who could not open their mouth fully for even a paediatric mouthguard to be inserted.[16] A careful search was made for any abnormality during endoscopy, especially in the oesophagus. Multiple oesophageal biopsies were obtained from any abnormality noticed during endoscopy, and in all cases from the upper end of the oesophagus, just below the upper oesophageal sphincter. All biopsies were fixed in 10% formalin and sent for histopathological examination.

After routine processing, 3–5 μm sections were cut from paraffin wax embedded sections, stained with haematoxylin and eosin, and evaluated by a histopathologist who was unaware of the clinical diagnosis or endoscopic findings. The sections were examined for histological changes. In the epithelium, evidence of atrophy of the lining squamous epithelium, hyperkeratosis, parakeratosis,

dyskeratosis, acanthosis, papillomatosis and dysplasia was sought. In the subepithelial tissue, evidence of collagenization was sought, which was subjectively graded as mild or severe by the histopathologist. Oesophageal biopsies which were superficial and did not contain subepithelial tissue were not evaluated.

STATISTICS

The two groups were compared by the Student's *t*-test, χ^2-test with or without Yates' correction and the Fischer's exact test.

Results

CONTROLS

The mean age of the controls was 31.2 ± 11.8 years; 45/55 were males. None of these subjects showed any oesophageal abnormality on endoscopy. Oesophageal biopsies were too superficial for proper interpretation in six subjects and were discarded. Of the other 49 subjects, oesophageal biopsy from one subject showed evidence of acanthosis in the epithelial tissue. There was, however, no evidence of collagenization of the lamina propria. No histologic abnormality was seen in the oesophageal biopsies from the other 48 subjects (figure 1).

Figure 1 Oesophageal biopsy from a control subject. Note the normal lamina propria (H&E, orig × 80)

PATIENTS

The mean age of this group was 29.4 ± 10.6 years; 47/55 were males. The age and sex ratio were not significantly different from the control group. One patient was asymptomatic and was found to have OSMF accidentally when he could not open his mouth fully during endoscopic examination to detect the cause of melaena. All patients except one chewed either *Pan masala*, *Gutka*, betel nut, tobacco or a combination of some or all of these, with or without betel leaf. All 54 of these patients consumed betel nut in one form or another. Only two patients smoked cigarettes. The offending substance had been chewed for a mean ± SD of 6.2 ± 6.4 years (range 0.5–25). One 25-year-old man with a history of inability to open his mouth fully for the last year denied the use of any offending agent. This was corroborated by his parents and siblings. The mean ± SD duration of symptoms in the patients was 18 ± 32.8 months (range 0.5–168).

All patients had difficulty in opening their mouths. It was clinically severe in 23 (42%) patients in whom a specially designed mouthguard had to be used for upper gastrointestinal endoscopy. Thirty-nine (71%) complained of burning sensations in the mouth while eating highly seasoned food and 21(38%) patients had ulcers in their mouth. Oesophageal symptoms were noted in seven (13%) patients. Dysphagia was reported by four (7%) patients and odynophagia by two patients. One patient had both dysphagia and odynophagia. Loss of taste sensation was noticed by two patients and occasional bleeding from the cheek by one patient.

None of the patients showed any abnormality during upper gastrointestinal endoscopy. Oesophageal biopsies were too superficial for proper interpretation in five (9%) patients. Of the 50 remaining patients, histological abnormalities were noted in 33 (66%). The difference from the control group was statistically highly significant ($p < 0.0001$). Atrophy of the

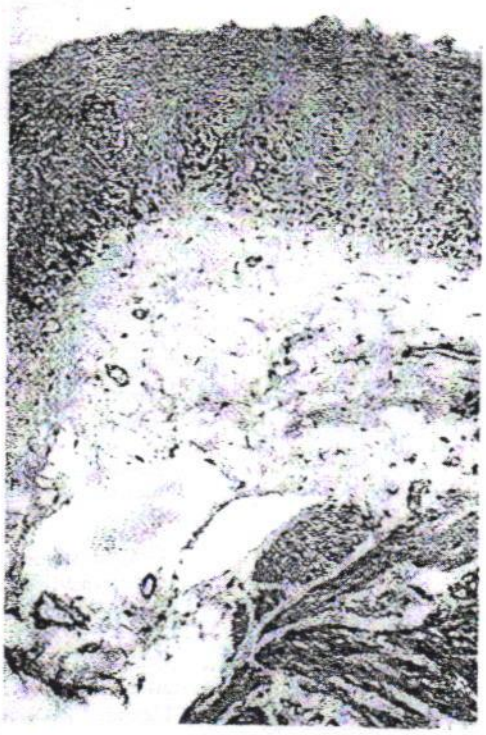

Figure 2 Oesophageal biopsy from a patient with oral submucosal fibrosis showing mild collagenization of the lamina propria (H&E orig × 80)

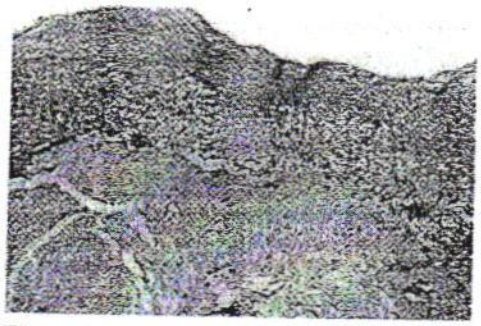

Figure 3 Severe collagenization of the lamina propria in a patient with oral submucosal fibrosis (H&E orig × 80)

squamous epithelium was evident in 26 (52%), hyperkeratosis in 26 (52%), parakeratosis in 15 (30%), dyskeratosis in 7(14%) and acanthosis in seven (14%) patients. Papillomatosis and mild dysplasia were evident in one (2%) patient each. Subepithelial collagenization was seen in 32 (64%) patients; it was mild in 15 (30%) (figure 2) and severe in 17 (34%) patients (figure 3).

Histological abnormalities in the oesophageal biopsies were seen in 13 of 28 (46%) patients with a history of consuming one or more of the offending agents listed above for < 5 years compared to 20 of 22 (91%) consuming them for ≥ 5 years. The difference between the two groups was statistically highly significant ($p < 0.001$). Histological abnormalities were seen in 14 of 20 (70%) patients with clinically severe OSMF compared to 19 of 30 (63%) patients with clinically milder disease. The difference between these two groups was not statistically significant. Of the seven patients with oesophageal symptoms, six had histologically severe collagenization (figure 3), and five had been consuming the offending agent(s) for ≥ 5 years. The other two had consumed the offending agents for 2 and 3 years, respectively. The patient with idiopathic OSMF did not have any histologic abnormality in his oesophageal biopsy.

Discussion

Oral submucosal fibrosis is not an uncommon condition in Indian subjects consuming betel nut, tobacco, *Pan masala* and *Gutka,* with or without betel leaf. The disease is also common in expatriates from the Indian subcontinent in the developed countries, especially in the UK where it has been reported from London and other cities.[8-10] It has been estimated that in the city of Leicester one may find as many as 3000 cases of OSMF. In a study from Durban, with a large (46%) Indian population, a prevalence of 3.4% has been reported.[17] The importance of the disease lies in the fact that it is a preventable precancerous condition of the oral cavity which leads to substantial morbidity especially in the younger population.

While OSMF is predominantly a disease of the oral cavity, fibrosis is also known to extend into the pharynx via the pillars and down to the pyriform fossa. It appears logical that the oesophagus should also be involved because at least some of the material which is chewed or kept in the mouth will go down the oesophagus, leading to irritation of the oesophageal mucosa, which is similar to that of the oral cavity. However, although involvement of the oesophagus has been reported,[1] there are no confirmatory reports to substantiate this. A MEDLINE search revealed only one article on the subject.[18] In this study by Maher *et al,* only the endoscopic appearance of the oesophageal mucosa was evaluated because the oesophageal biopsies obtained were too superficial in nature to be of any value. The authors noted that the mucosa was whitish pale in two of the 30 patients studied, stiff and fibrotic in 19, leathery in four, and firm or gritty in another two cases.

In the present study, we were unable to find any endoscopic abnormality in our OSMF patients. However, histologically, oesophageal involvement could be demonstrated in about two-thirds of patients with OSMF. In the majority of cases the disease in the oesophagus was clinically not apparent and oesophageal symptoms were seen in only seven of the 50 (14%) patients. Of interest was the finding that six out of these seven patients had severe collagenization of the lamina propria of the oesophagus.

Oesophageal subepithelial fibrosis was more common in patients who had consumed betel nut, tobacco, *Pan masala* or *Gutka,* with or without betel leaf, for a longer period. However, 46% of patients had developed the disease after consuming the offending agent(s) for less than 5 years. It therefore appears that, although the chances of developing oesophageal subepithelial fibrosis are high if one of the offending agents are chewed on a long-term basis, even a period of usage as short as a year may be sufficient to cause this condition. This was also evident in a small group of seven patients who had symptoms of dysphagia and odynophagia along with oesophageal subepithelial fibrosis.

One of the patients with OSMF denied consuming any of the known offending agents, which was confirmed by his parents and siblings. There was however, no oesophageal involvement in this patient. Such idiopathic cases of OSMF are known to occur rarely, but the majority of cases occur in people who consume the above-mentioned offending agents.

The implications of oesophageal involvement in patients with OSMF may have far-reaching implications. It is possible that, in at least some of these patients, the lesion will develop into frank carcinoma of the upper oesophagus, as it is well known that OSMF is a premalignant disease.[19]

Although oesophageal subepithelial fibrosis has not been reported earlier in patients with OSMF, ultrastructural abnormalities such as discontinuous, fragmented basement membrane, with reduction of hemidesmosomes, and widened intracellular spaces, have been noted in the oesophageal mucosa of chronic tobacco chewers.[20] With the changes seen on

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light microscopy in about two-thirds of patients with OSMF, the definition of OSMF should be modified to include the involvement of the oesophagus.

While banning tobacco, betel nut, betel, *Panmasala* and *Gutka* is the key to prevention of the disease, this may not be possible in the developing countries because of the lack of political will. However, in the UK, where a large number of immigrants from the Indian subcontinent reside, a blanket ban on import of such articles would go a long way in preventing this precancerous but potentially preventable disease.

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Annexure 103

Effect of occupational exposure to local powdered tobacco (snuff) on pulmonary function in south eastern Nigerians.

Maduka SO, Osim EE, Nneli RO, Anyabolu AE.

Niger J Physiol Sci. 2009 Dec;24(2):195-202.

Abstract

The effect of occupational exposure to local powdered tobacco (snuff) on pulmonary function was studied. Snuff industry workers in Onitsha and Enugu markets were studied and compared with age, weight, and height-matched control not exposed to any known air pollutant. The pulmonary indices studied include forced vital capacity [FVC], forced expiratory volume in one second [FEV1] and ratio of FEV1/FVC as percentage using a vitalograph spirometer and Peak Expiratory Flow Rate [PEFR], using a mini Wright Peak Expiratory Flow Meter. The respiratory and non-respiratory symptoms frequently associated with these workers were also analyzed and dust sampling in both test and control environments was also done. The mean anthropometric parameters, [age, height and body weight] between the two groups were not statistically different. The results obtained showed statistically significant impairment of lung function of workers chronically exposed to snuff. FVC, FEV1 and PEFR in the exposed [test] subjects were significantly decreased in comparison with the control subjects [$P<0.05$]. However, the mean value of FEV1/FVC [%] of the test subjects was 86.8% which was within the normal range and was not significantly different from control. This signified that the test subjects had restrictive pattern of lung function defect. All respiratory symptoms, such as cough, chest tightness had a higher prevalence in test subjects than their control group. The lung function indices of snuff-producing workers proportionately decreased with their length of exposure in the industry. The respirable dust level in the vicinity [indoor] of the snuff-workers [1.11+/-0.35 mg/m3] was significantly [$P<0.001$] higher than in the control environment[0.37+/-0.086 mg/m3]. Although it was not possible to determine all the factors that may be responsible for lung function impairment, the dust sampling result showed that chronic exposure to Nigerian snuff [powered tobacco] dust impairs lung function and the effect is progressive with tim

Annexure 104

Association of snuff use with chronic bronchitis among South African women: implications for tobacco harm reduction.

Ayo-Yusuf OA, Reddy PS, van den Borne BW.

Tob Control. 2008 Apr;17(2):99-104. Epub 2008 Feb 19.

Abstract

OBJECTIVE: Nasal use of snuff is the predominant form of tobacco use among black South African women. This study examines the association between snuff use and chronic bronchitis (CB) among black South African women.

DESIGN: The study investigated a nationally representative sample of 4464 black South African women > or = 25 years old who participated in the 1998 South African Demographic and Health Survey. Data on participants' tobacco use patterns, medical history and other relevant factors were obtained through an interviewer-administered questionnaire. Peak expiratory flow rates (PEFR) were also measured. Data analysis included chi(2) statistics, Student t tests and multiple logistic regression analysis.

OUTCOME MEASURE: CB, defined as reporting a productive cough for > or = 3 months/year for at least 2 successive years.

RESULTS: The prevalence of current snuff use was 16.1% (n = 719). Compared to non-users of snuff, snuff users were not only more likely to present with a history of tuberculosis (TB) (23.3% vs 15.9%; p = 0.06), but they were also more likely to present with CB (5.3% vs 2.8%; p<0.01) and a lower PEFR (275 litres/min vs 293 litres/min; p<0.01). Significant determinants of CB included snuff use > 8 times/day (odds ratio (OR) 2.86, 95% CI 1.17 to 7.02), a history of TB (OR 7.23, 95% CI 4.02 to 13.03), current smoking (OR 2.84, 95% CI 1.60 to 5.04) and exposure to smoky cooking fuels (OR 1.98, 95% CI 1.32 to 2.96).

CONCLUSIONS: These data suggest that snuff use, in the form predominantly used in South Africa, increases the risk of CB. This challenges the idea that snuff may be a much less harmful alternative to smoking in South Africa.

Annexure 105

Economic cost of tobacco use in India, 2004

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ABSTRACT

Objective: To estimate the tobacco-attributable costs of diseases separately for smoked and smokeless tobacco use in India.

Methods: The prevalence-based attributable-risk approach was used to estimate the economic cost of tobacco using healthcare expenditure data from the National Sample Survey, a nationally representative household sample survey conducted in India in 2004. Four major categories of tobacco-related disease—tuberculosis, respiratory diseases, cardiovascular diseases and neoplasms—were considered.

Results: Direct medical costs of treating tobacco related diseases in India amounted to $907 million for smoked tobacco and $285 million for smokeless tobacco. The indirect morbidity costs of tobacco use, which includes the cost of caregivers and value of work loss due to illness, amounted to $398 million for smoked tobacco and $104 million for smokeless tobacco. The total economic cost of tobacco use amounted to $1.7 billion. Tuberculosis accounted for 18% of tobacco-related costs ($311 million) in India. Of the total cost of tobacco, 88% was attributed to men.

Conclusions: The cost of tobacco use was many times more than the expenditures on tobacco control by the government of India and about 16% more than the total tax revenue from tobacco. The tobacco-attributable cost of tuberculosis was three times higher than the expenditure on tuberculosis control in India. The economic costs estimated here do not include the costs of premature mortality from tobacco use, which is known to comprise roughly 50% to 80% of the total economic cost of tobacco in many countries.

Knowledge of the health consequences of tobacco use has led to much greater reductions in tobacco use in developed than in developing countries. The tobacco epidemic is estimated to kill 8 million people annually, with 80% of deaths in developing countries by 2030.[1] Smoking related medical costs account for 6% to 15% of healthcare costs in high-income countries.[2] Evidence from developing countries such as China and Vietnam place this estimate around 4%.[3 4]

With roughly 10% of the world's smokers, India is the second largest consumer of tobacco in the world,[5] second only to China. Tobacco consumption in India is characterised by a large proportion of non-cigarette and smokeless tobacco use. Manufactured cigarettes constitute only 14% of the tobacco consumption in India.[5] The health effects of non-cigarette tobacco use are under-researched probably because they are not popular in most of the developed world. There is reason to believe that the non-cigarette tobacco used in India is also associated with significant adverse health outcomes. Bidis, an indigenous and popular smoked tobacco product in India, delivers nicotine, carbon monoxide and other toxic components of tobacco smoke in equal or greater amounts than conventional cigarettes,[6] making bidi smoking a stronger risk factor than cigarette smoking for cancer of the hypopharynx and supraglottis.[7] Many of the smokeless tobacco products in India such as Khaini, Mawa, Pan, Zarda and Gutkh are also found to be risk factors for cancer.[7] Chewing tobacco in India is also a risk factor for oral cancers and esophageal cancers.[8] A recent nationwide study on smoking and mortality in India estimated that cigarette and bidi smoking causes about 5% of all deaths in women and 20% of all deaths in men aged 30–69 years, totalling 1 million deaths per year in India in 2010.[9]

There has been no comprehensive national level study that estimated the economic cost of tobacco use in India. However, a report submitted to the government of India[10] referred to a study by Rath and Chaudhry[11] that estimated the cost of three major tobacco related diseases in India: cancer, coronary artery disease and chronic obstructive pulmonary disease. Based on a sample from 2 Indian locations—195 patients in Delhi and 500 patients in Chandigarh—they collected data on treatment expenditures (medical and non-medical), institutional expenditures and loss of wages during treatment for 1990–1992, or until death or recovery. Using the consumer price index, they estimated the total direct and indirect cost due to three major tobacco related diseases in India in 1999 to be Rs.277.61 ($6.2) billion, 83.7% of which was due to premature death. Reddy and Gupta[12] updated these costs to 2002–2003, estimating the total cost for the three major tobacco related diseases to be Rs.308.33 ($6.6) billion.

Because tobacco use causes more than just the three diseases listed above, a more comprehensive estimate of the economic burden of tobacco use in India is needed. Moreover, the data needs to be recent and representative to the nation as a whole. This paper estimates the economic burden of tobacco use in India by considering four major categories of tobacco-related disease—tuberculosis, respiratory diseases, cardiovascular diseases and neoplasms—using nationally representative data. This provides the first ever estimate of the economic cost of tobacco in India using nationally representative data. This is also the first time economic costs are estimated separately for smoked and smokeless tobacco. Moreover, the tobacco-attributable cost of tuberculosis, a disease of major importance for India[13] is estimated for the first time in India. Tobacco smoke is known to increase the risk of tuberculosis.[14 15] Recent epidemiological studies in India has also supported this claim.[5]

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METHODS

We use the prevalence-based attributable-risk approach applied to tobacco-related costs by Rice *et al*[16] for estimating the economic burden of tobacco use. This approach measures the value of resources used (direct costs) or lost (indirect costs) from tobacco-caused diseases and deaths during a specified period of time, regardless of the time of tobacco use onset. This method of estimation is designed to measure the aggregate economic burden imposed on society attributable to tobacco use. Using a standard epidemiological formula, it determines the proportion of excess costs that can be attributed to tobacco use and hence preventable. We include only persons aged 35 years and older in the analysis, since relative risks for the diseases considered were available only for this age group.

Data sources

The primary data source for estimating the tobacco-attributable medical cost was the "Morbidity, Health Care and the Condition of the Aged",60th round of the National Sample Survey (NSS) conducted during January to June 2004. It was a nationally representative survey conducted by the National Ministry of Health and Family Welfare (MOHFW). It collected the data on utilisation and expenditures of private and public healthcare services—inpatient hospitalisation during the 365 days prior to the date of interview and outpatient visits during the 15 days prior to interview—from 47 302 rural and 26 566 urban households in India. Expenditures from inpatient hospitalisation were reported for each disease and visit separately. However, expenditures on outpatient visits were reported as total per person regardless of number of visits and ailments. In order to calculate the average expenditure per ailment per outpatient visit we computed average expenditures on outpatient visit for each ailment using only those patients with only one visit and that amount was imputed to the expenditures for the respective ailments of those with multiple visits and ailments. These 15-day averages were multiplied by 24.33 to get annual estimates. NSS self-reported household expenditures were scaled up by a factor of 1.68 to reflect the difference between NSS estimates and India's national healthcare expenditures (expenditures by households, other private and public sources.[17]

The relative risk (RR) of mortality used to estimate the smoking attributable fraction was taken from a prospective 1992–1999 cohort study of 99 570 Mumbai adults aged 35 or older.[18] They reported the RR, adjusted for age and socioeconomic status, separately for smokeless tobacco users and smokers by gender and disease categories. This is the only study that provides cause-specific RR separately for smoked and smokeless tobacco by gender, and thus is relevant in the Indian context where wide disparities in tobacco use exists between genders.[19]

The data source for estimating the prevalence of tobacco use was the second National Family Health Survey (NFHS-2)[20] conducted by the International Institute for Population Sciences in 1998–1999. The NFHS-2 sample represented more than 99% of India's population across all 26 states.

The population figure in India was taken from the estimated mid-year population for 2004 as projected by the US Census Bureau (http://www.census.gov/ipc/www/idb/tables.html), and was estimated to be 175 million males and 170 million females aged 35 and older.

Estimation of the smoking attributable fraction

The smoking attributable fraction (SAF) is the proportion of expenditures on personal health services and morbidity costs that can be attributable to smoked and smokeless tobacco use. Persons were classified into three mutually exclusive categories: (1) never smokers: those who have never used any tobacco, (2) smokeless tobacco users: those who have used smokeless tobacco only and (3) smokers: those who have used smoked tobacco regardless of whether they also used smokeless tobacco or not (15% of adult males and 1% of adult females used smoked and smokeless tobacco). We estimated the SAF separately for smokeless tobacco users and smokers using an epidemiological formula derived from Lilienfeld and Lilienfeld[21] for each of the disease categories by gender and tobacco use type (equation 1).

$$SAF_{tdg} = \frac{PE_{tdg}\,(RR_{tdg} - 1)}{PN_{dg} + \sum_{t=s,c} PE_{tdg}\,(RR_{tdg})}$$

Subscripts t, d and g indicate type of tobacco users, disease category and gender, respectively. PN, PE_c and PE_s denote the percentage of people who are never smokers, smokeless tobacco users and smokers, respectively, with c and s denoting smokeless and smoked tobacco. RR_c and RR_s denote the relative risk of mortality for smokeless tobacco users and smokers, respectively, compared to never smokers.

Estimation of economic cost

We considered three components of the economic cost of tobacco use: (1) direct healthcare expenditures for inpatient hospitalisation or outpatient visits, including surgeon's fees, medicines, diagnostic tests, bed charges, attendant charges, medical appliances and ambulatory services; (2) expenditures incurred for transportation other than ambulance and lodging charge of caregivers; and (3) wage income lost to the whole household due to inpatient hospitalisation or outpatient visits. Items 2 and 3 comprise indirect morbidity costs. A fourth and important component of the economic cost of tobacco is the cost of premature deaths from tobacco use. Data were not available to estimate this component of cost.

Tobacco-attributable direct healthcare expenditures (TAE) are the product of total healthcare expenditure (THE) and the SAF:

$$TAE_{tdg} = THE_{tdg} \times SAF_{tdg} = [PH_{tdg} \times QH_{tdg} + PV_{tdg} \times QV_{tdg} \times 24.33] \times POP_g \times SAF_{tdg}$$

Where PH is the average expenditure per inpatient hospitalisation, QH is the average number of hospitalisations per person in 365 days, PV is the average expenditure per outpatient visit and QV is the average number of outpatient visits per persons for 15 days prior to the date of interview. POP is the population aged > = 35 in 2004.

The tobacco-attributable indirect morbidity cost (TAI) is the product of total indirect morbidity expenditure (TIE) and the SAF:

$$TAI_{tdg} = TIE_{tdg} \times SAF_{tdg} = [(PHI_{tdg} + PHL_{tdg}) \times QH_{tdg} + (PVI_{tdg} + PVL_{tdg}) \times QV_{tdg} \times 24.33] \times POP_g \times SAF_{tdg}$$

Where PHI and PVI are the average expenditure on transportation and caregivers per inpatient hospitalisation and per outpatient visit, respectively; PHL and PVL are the average income lost due to absence from work from inpatient hospitalisation and outpatient visits.

RESULTS

SAFs for smoked and smokeless tobacco

Table 1 shows the prevalence of tobacco use and the relative risks of mortality used in this paper. The prevalence of ever

Table 1 Prevalence of tobacco use and disease-specific relative risk of mortality from tobacco use in India by type of tobacco users and gender for adults aged 35 and older

	Smoked		Smokeless	
	Male	Female	Male	Female
Prevalence* (%)	42.3	4.39	20.65	18.84
Relative risk of death:				
Respiratory diseases	2.12	1.15	1.50	1.04
Tuberculosis	2.30	5.92	1.46	1.40
Cardiovascular diseases	1.54	1.46	1.32	1.15
Neoplasm	2.60	1.85	1.40	1.57

*The prevalence of smokeless tobacco users includes those who only used smokeless tobacco whereas prevalence for smokers includes some who also used smokeless tobacco so that adding smoked and smokeless tobacco user would give prevalence for any tobacco use.

smokers in the age group 35+ for 1998–1999 was 42.3% and 4.4% for males and females while the prevalence of ever smokeless tobacco users was 20.7% and 18.8% for males and females. Prevalence of smoking is less among women in India due to social unacceptability[12] and is largely a cultural phenomenon. The relative risks of mortality were slightly higher for smokers than smokeless tobacco users but did not differ much by gender or disease category, with the exception of tuberculosis, which was especially high for female smokers.

Table 2 shows the SAF of tobacco use by type of tobacco user, gender and disease category computed based on the data shown in table 1 and equation 1. For smokers, the SAFs are substantially lower for women than men for all disease categories partly due to their low smoking prevalence. Cancer and tuberculosis show the highest and the second highest disease-specific SAFs respectively for men, while tuberculosis has the highest disease-specific SAF for women. As for smokeless tobacco users, the SAFs between men and women are not much different. Combining smoked and smokeless tobacco use, the SAFs among men range from 22.8% for cardiovascular diseases to 43.2% for neoplasms. Considering that the SAFs among women are up to 22.6% for tuberculosis and 12.6% for neoplasms, tobacco use contributes to a significant proportion of the burden on Indian women's health despite the low prevalence of tobacco use among them.

The economic costs of tobacco use

Table 3 shows the economic cost of tobacco use for India in 2004 by disease, type of tobacco use and gender separately for inpatient hospitalisation and outpatient visits. The top section of table 3 shows TAEs. The total TAE of treating tobacco related diseases amounted to $1192.5 million, including $833.9 million for male smokers, $73.2 million for female smokers, $188.7 million for male smokeless tobacco users and $96.6 million female smokeless tobacco users. The TAEs were greater for males than females for all disaggregated analyses except that females have higher TAEs for treating cancer attributable to smokeless tobacco use. The TAEs were highest for cardiovascular diseases for males and females regardless of the type of tobacco use. The total TAE from smoked tobacco ($907.1 million) was more than three times that from smokeless tobacco ($285.3 million).

The middle and lower sections of table 3 show the tobacco-attributable indirect morbidity costs for 2004. The total tobacco-attributable transportation and caregiver costs amounted to $91.3 million, including $64.7 million for male smokers, $5.4 million for female smokers, $14.0 million for male smokeless tobacco users and $7.1 million for female smokeless tobacco users. Cardiovascular disease accounts for the largest share of transportation and caregiver costs for males and females. The total value of lost income from tobacco related hospitalisation and outpatient visits amounted to $411.4 million, including $313.8 million for male smokers, $14.5 million for female smokers, $67.8 million for male smokeless tobacco users and $15.3 million for female smokeless tobacco users.

The last row of table 3 presents the total economic cost. Of the total cost of $1.7 billion, smoked tobacco accounts for 77% vs 23% for smokeless tobacco; 87% is attributed to males vs 13% to females. Females contribute more to the cost of smokeless tobacco (31%) than to smoked tobacco (7%). This is reflective of the fact that the prevalence of smokeless tobacco use among women is 19% compared to only 4% for smoked tobacco use.

DISCUSSION

This paper presents the first comprehensive estimate of the economic burden of tobacco use at the national level for India. The total economic cost of tobacco use in India for 2004 amounted to $1.7 billion, which is many times more than the $551 876 that the government of India spent on tobacco control activities in 2006,[1] and is 16% more than the total excise tax revenues collected from all tobacco products in India in the financial year 2003–2004 ($1.46 billion). Tobacco-attributable direct costs ($1.2 billion) account for 4.7% of India's total national healthcare expenditure in 2004 ($25 billion).[17] In comparison, studies from other developing countries such as China[4] and Vietnam[3] found the direct cost of smoking to be 3.1% and 4.3% of the national healthcare expenditure, respectively.

Tuberculosis is a major health risk in India with roughly 1.8 million new cases reported annually,[15] and our findings highlight the important role of tobacco use for this disease. In fact, tuberculosis accounts for $311 million (18%) of the total economic cost of tobacco use in India, including $193 million (16%) of the direct cost and $118 million (24%) of the indirect morbidity cost. This is more than three times the $100 million that was spent on tuberculosis control in India in the year 2006.[13]

Table 2 Disease-specific smoking attributable fractions (SAFs) (%) in India by type of tobacco use and gender for adults aged 35 and older

	Smoked		Smokeless		All tobacco*	
Cause of death	Male	Female	Male	Female	Male	Female
Respiratory diseases	30.04	0.65	6.55	0.74	36.59	1.39
Tuberculosis	33.43	16.73	5.77	5.84	39.21	22.56
Cardiovascular diseases	17.65	1.93	5.10	2.70	22.75	4.62
Neoplasm	38.47	3.26	4.69	9.38	43.16	12.64

*The SAF for all tobacco products equals the SAF for smokers plus the SAF for smokeless tobacco users.

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Table 3 Economic costs of tobacco use in India for 2004 among adults aged 35 and older (US $1000)

	Smoked					Smokeless					All tobacco		
	Inpatient		Outpatient			Inpatient		Outpatient					
Disease	Male	Female	Male	Female	Subtotal	Male	Female	Male	Female	Subtotal	Male	Female	Total
	Tobacco-attributable direct healthcare expenditure												
Respiratory	27 994	548	264 032	3533	296 107	6101	627	57 542	4044	68 314	355 669	8 752	364 421
Tuberculosis	34 604	5442	103 035	18 076	161 157	5978	1899	17 798	6307	31 981	161 415	31 723	193 139
Cardiovascular	102 003	7241	208 625	24 859	342 728	29 508	10 133	60 354	34 788	134 783	400 490	77 021	477 511
Neoplasm	41 380	8317	52 276	5176	107 149	5050	23 936	6380	14 897	50 263	105 086	52 327	157 412
Subtotal	205 980	21 548	627 968	51 644	907 141	46 637	36 595	142 074	60 035	285 342	1 022 660	169 823	1 192 482
	Tobacco-attributable transportation and caregivers expenditure												
Respiratory	1521	29	18 600	346	20 497	332	34	4054	396	4815	24 506	806	25 312
Tuberculosis	1585	239	10 383	1439	13 646	274	84	1793	502	2653	14 035	2265	16 299
Cardiovascular	3598	221	17 954	2188	23 962	1041	310	5194	3062	9607	27 787	5781	33 568
Neoplasm	2733	363	8343	577	12 016	334	1044	1018	1662	4057	12 428	3646	16 074
Subtotal	9437	853	55 279	4551	70 121	1980	1471	12 059	5622	21 132	78 756	12 497	91 253
	Tobacco-attributable lost income due to absence from work												
Respiratory	2061	41	115 432	614	118 148	449	47	25 157	703	26 356	143 099	1405	144 503
Tuberculosis	3337	493	74 019	7670	85 519	576	172	12 786	2676	16 211	90 718	11 012	101 730
Cardiovascular	3936	216	81 334	2913	88 399	1139	303	23 529	4076	29 047	109 938	7508	117 446
Neoplasm	3274	381	30 452	2153	36 261	400	1098	3716	6197	11 411	37 842	9830	47 672
Subtotal	12 608	1132	301 237	13 351	328 327	2564	1619	65 189	13 653	83 025	381 597	29 755	411 352
Total	228 025	23 533	984 484	69 546	1 305 589	51 181	39 686	219 322	79 310	389 499	1 483 013	212 075	1 695 087

One limitation of our study is that we used relative risk of mortality to estimate the attributable morbidity. Risks of morbidity and mortality from tobacco use need not be the same. However, this approach has been widely used in the literature.[4 22–24] Two other approaches have been used to estimate the SAFs for direct medical cost. One was originally developed by Rice and Hodgson (1986),[16] in which the RR of healthcare utilisation for smokers was first estimated and then applied to the calculation of the SAFs for medical cost. The other one was developed in the 1990s by several health economists,[25–27] in which the SAFs was estimated directly from multiple-equation econometric models of the impact of smoking on healthcare expenditures. Due to our data limitations, we could not employ either approach in this study. However, according to a study by Rice and Hodgson,[16] the SAFs for direct medical cost estimated by using the RR of healthcare utilisation approach was 23.5%, while the SAFs for direct medical cost of smoking estimated by using the RR of mortality approach was 19.7%. Therefore, the use of RR of mortality as a proxy for RR of healthcare utilisation is expected to yield an underestimated and conservative SAF for medical costs. Secondly, the relative risks we used were taken from a cohort study of 99 570 persons in Mumbai that is not nationally representative. Longitudinal data on risk factors for healthcare expenditures would be required to apply econometric models to cost estimation. With these data, one could control for different risks, assess the source of payments specifically for tobacco-related diseases and consider the impact of cessation on healthcare expenditure. Unfortunately these data are not available for India.

Our estimates are probably low. We were unable to include the costs of premature mortality from tobacco use, because data on number of deaths by underlying cause of death at the national level in India are currently difficult to acquire. However, the estimates presented here are still important because it is the first time economic costs of tobacco use in India are presented using nationally representative healthcare expenditure data. Even the conservative estimates presented here are huge in comparison with the taxes collected from tobacco or the expenditure on tobacco control incurred by Government of India. The mortality cost has been estimated to account for 84% of total tobacco-related costs in India.[11] Studies from China,[4] Korea,[28] USA,[29] and Germany[30] estimate the cost of premature death to be 58%, 91%, 46% and 64% of the total cost of smoking respectively. If the value of tobacco-attributable deaths adds 84% to the total costs, our estimate of the total economic costs of tobacco use in India for 2004 would be $10.6 billion. It should be also noted that due to the general assumptions used for earnings and employment, the indirect costs especially for women might be under-estimated. Furthermore, our analysis is limited to four categories of tobacco-caused disease. Many more diseases are known to be caused or exacerbated by tobacco use.

The huge healthcare burden attributable to tobacco use in India has many dimensions. More than 70% of the healthcare cost in India is out-of-pocket expenditures. Given that consumption of tobacco in India is more prevalent among the poor,[31] it is likely that much of the tobacco related illness and the associated economic cost would also be higher among them. Hospitalisations for tobacco related diseases force poor people into debt traps and can result in severe impoverishment. There is a higher risk (odds ratio 1.35) of borrowing and distress selling during hospitalisation by individuals who use tobacco in India.[32] Expenditures on tobacco in India displace expenditures on food and education.[33] Thus, high spending on tobacco coupled with the higher healthcare burden of treating tobacco related diseases can push tobacco consumers into a vicious circle of tobacco use, ill health and poverty.

What this paper adds

- The economic cost of tobacco use has been estimated in many countries. However, to date there has not been any comprehensive national level study that estimated the economic cost of tobacco use in India in spite of the fact that India is the second largest consumer of tobacco in the world.
- This study estimates that the economic cost of tobacco use in India, not including the premature mortality cost, amount to $1.7 billion in the year 2004. Of this, smoked tobacco accounted for 77% and smokeless tobacco 23%; 87% is attributed to males and 13% to females.

The economic cost of tobacco use in India reflects an important gender dimension, with 87% costs accounted for by males. Yet, the consequent toll on household income is shared by all the household members. Tobacco control efforts should take heed of these different dimensions of the economic costs of tobacco use.

Current economic costs associated with tobacco use are much higher than the tax revenues generated from tobacco. There is also evidence that the taxes on tobacco in India are much lower than the optimum level possible.[34] Hence, an increase in tobacco taxes could be justified and that money could be used to pay for tobacco induced healthcare expenditures for the poor and for tobacco control efforts to prevent these diseases and lower these costs. An increase in tobacco taxes can also reduce expenditures on tobacco as increased taxes are known to result in decreased tobacco use.[35]

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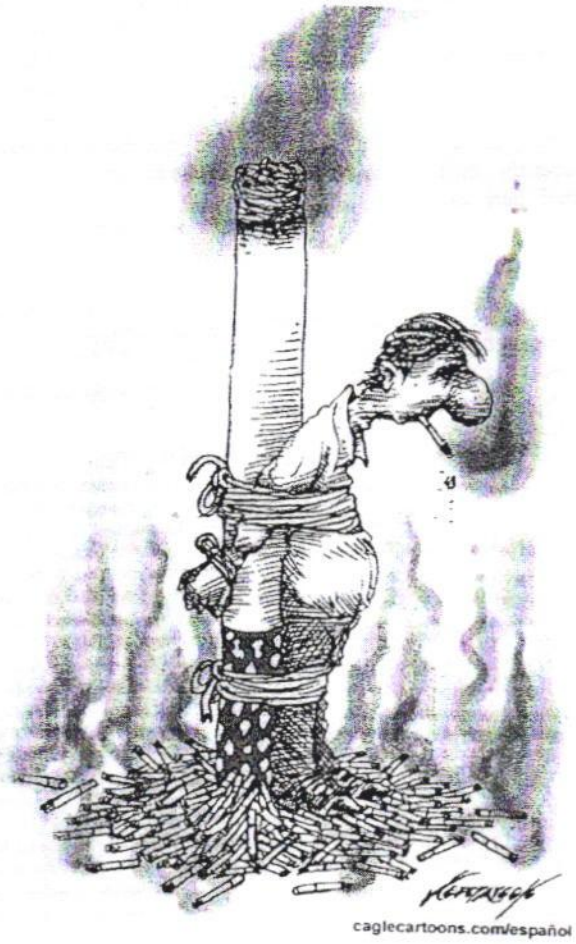
The lighter side



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ARECA NUT SYMPOSIUM

Global epidemiology of areca nut usage

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Abstract

A substantial proportion of the world's population is engaged in chewing areca nut and the habit is endemic throughout the Indian subcontinent, large parts of south Asia and Melanesia. A large variety of ingredients, including tobacco, may be used along with areca nut constituting a betel quid. The composition and method of chewing can vary widely from country to country and these population variations are described in this review. Some populations are known to use areca nut without tobacco providing good opportunities to further research the carcinogenecity of areca nut. Some interesting trends on chewing patterns have emerged from recent data, suggesting a decline in the habit in some countries such as Thailand while the prevalence of areca nut use is rising in India and Taiwan.

Introduction

The usage of areca nut is indigenous to India, Sri Lanka, Maldives, Bangladesh, Myanmar, Taiwan and numerous islands in South Pacific. It is also popular in parts of Thailand, Indonesia, Malaysia, Cambodia, Vietnam, Philippines, Laos, China and in migrant communities from these countries. In populations resident in south and East Asia the use of areca nut is strongly interwoven into local art and craft, folklore, social customs, religious practices and cultural rituals. In this supplement historical and anthropological aspects of areca nut usage are described by Strickland.[1] This paper presents a global perspective of the current usage of areca nut by reviewing available information on its widespread use by population groups to allow an appreciation of the numerous public health problems associated with the use and abuse of this substance.

There are several palms under the genus *Areca* native to South, South-East Asia and Pacific islands. This tropical palm tree bears fruit all year. Areca nut for chewing is obtained from *Areca catechu* (Fig. 1). It is believed that Areca catechu may be native to Ceylon (Sri Lanka), West Malaysia and Melanesia.[2] Areca nut is consumed in large variety of ways and can be used by itself. When ripe it is orange-yellow in colour and the seed (endosperm) is separated from fibrous pericarp (Fig. 2). The nut may be used fresh, or dried and cured before use, by boiling, baking or roasting. In some areas, especially Eastern India and southern Sri Lanka, fermented areca nut is also popular. In Taiwan, areca nut is often used in the unripe stage when it is green, like a small olive (Fig. 3). Areca nut is known colloquially in the Indian subcontinent in Hindi and Bengali as *supari*, in Sri Lanka it is called *puwak*, in Sylheti

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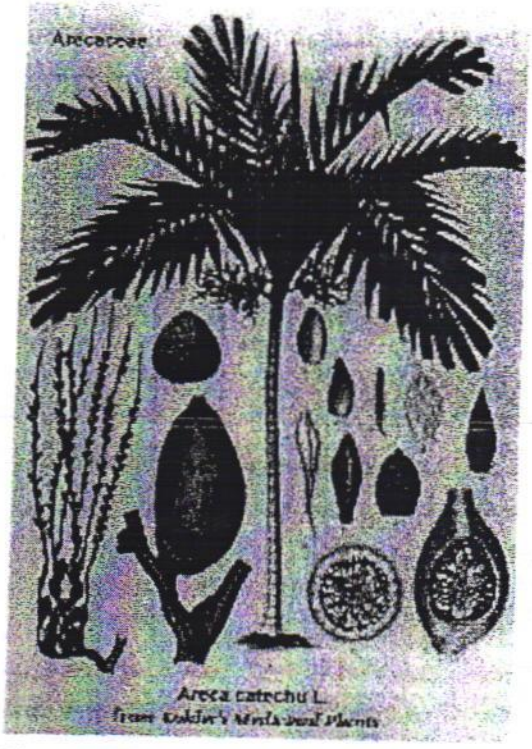

Figure 1. *A diagrammatic illustration of areca palm. Areca nut is obtained from the* Areca catechu *tree.* Source: *1995–2001 Missouri Botanical Garden Library http:/ /ridgwaydb.mobot.org/mobot/rarebooks/*

as *gua*, in Thailand as *mak*, in Sarawak as *pinang* and in Papua New Guinea as *daka*.

Areca nut chewing is practiced is several different ways in various countries and often mixed with several ingredients to make up a betel quid known as *pan* in Hindi. The most popular

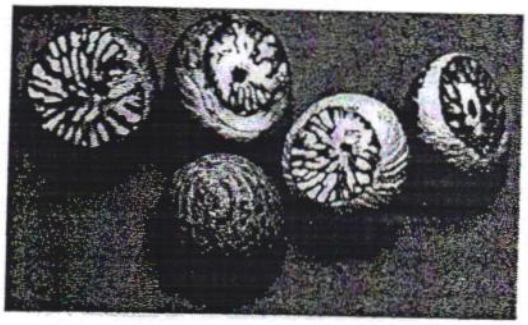

Figure 2. *Areca nut.*

Figure 3. *Unripe nut as consumed in Taiwan.*

accompaniments are the leaf of *Piper betle* (betel leaf), lime, catechu and tobacco. The practice of areca nut chewing in the form of a betel quid is described explicitly in a monograph published by the International Agency for Research on Cancer.[3] The major components of betel quid are illustrated in Fig. 4 and are listed in Table 1.

The most common accompaniment globally is the leaf of *Piper betle*. This has led to areca nut being labelled erroneously as betel nut in the English literature. Apart from the leaf other parts of the betel vine such as stem, inflorescence (flower; pods) or catkins are also consumed with

Figure 4. *A betel quid prepared in the traditional way using betel leaves, sliced areca nut, cut tobacco and slaked lime.*

Table 1. *Constituents of betel quid*

Consituent	Preparation
Areca nut	Sliced fresh ripe nut
	Roasted
	Dried/baked
	Boiled
	Fermented
	Immature
Piper betle	Fresh leaf
	Inflorescence
Lime	From coral
	From shell fish
	From lime stone
Tobacco	Fermented
	Sun dried
	Powdered with molasses with lime
Catechu	Extract of *Acacia catechu*
	Extract of *Acacia suma*
Spices	Cloves
	Cardamom
	Aniseed
Sweetners	Coconut

Modified from Ref 28

the nut. Consumption of the inflorescence (Fig. 5) is common in Melanesia and in parts of Taiwan.

Lime (calcium hydroxide) is often used with areca nut in combination. Lime is obtained in coastal areas by heating the covering of shellfish (sea shells) or harvested from corals. In central areas of a country it is quarried from limestone. In the Asian markets lime is sold as a paste mixed with water (Fig. 6) which is white or pink. In Papua New Guinea lime is available in the powdered form.

Catechu is an extract of the Acacia tree *A. catechu* or *A. suma*. Catechu is often smeared on the betel leaf that is used to wrap areca nut flakes.

Cut tobacco is consumed with areca nut often in the quid mixture. This type of chewing tobacco is made from sun-dried and partly fermented coarsely cut leaves without further processing. Sometimes tobacco is powdered and combined with molasses or boiled before use.

Pan Masala is the generic term used for areca nut-containing products that are manufactured industrially and marketed commercially. These are available in small convenient sachets for individual use. Several trade brands are illustrated in Fig. 7. Pan masalas containing tobacco are referred to as Gutka.

Global epidemiology

Areca nut is used as a masticatory substance by approximately 600 million people worldwide. It is estimated that 10–20% of the world's population chew areca nut in some form, often mixed in betel quid (pan). A challenge facing researchers documenting the prevalence of areca nut use in populations is the difficulty in documenting patterns of areca nut use as separate from betel quid chewing which often contain a variety of ingredients, including tobacco. Thus estimating the population frequency of areca use by itself is often frustrating, as some authors do not record this explicitly in their publications. As areca is often the primary ingredient in betel quid any studies describing population data for betel quid chewing is taken as a valid reference value. While there are no nationwide surveys reported on the prevalence of this habit, data from several

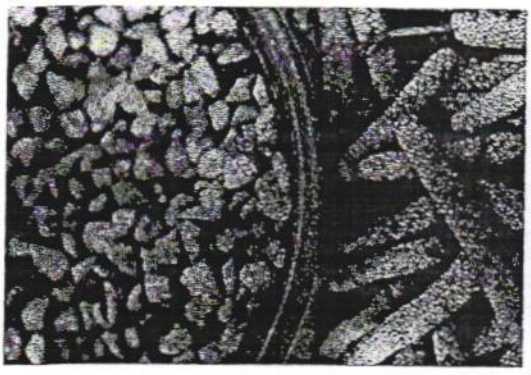

Figure 5. *Inflorescence (flower) of* Piper betle *mostly used in Taiwan and Melanesia.*

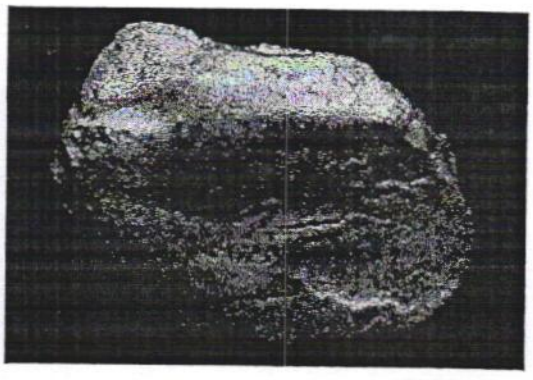

Figure 6. *Slaked lime in paste form.*

Table 2. *Prevalence of areca and/or betel quid chewing among adults in selected populations*

Country	Men		Women		All		Chewing practice		Reference
	n	%	*n*	%	*n*	%	Nut only	Quid	
India, Bombay	40071	34.5	50527	27.2	99598	32.1		x	6
Pakistan, Karachi	2661	3.2	2093	8.2	4754	5.4		x	8
Sri Lanka	316	54	817	42	1133	45.2		x	13
Thailand	986	16	880	19	1816	17		x	15
Taiwan, Kaohsiung	511	28.3	651	1.4	1162	13.3	x		24
Sarawak	195	30	263	63	458	49.3	x		28
Cambodia	366	6.8	953	40.6	1319	31.2			30
China, Xiangtang city	6057	39.3	4989	30.5	11406	35.3	x		32

countries obtained in hospital-based, population-based and school-based surveys are reviewed here.

Data from several published studies arising from a number of population groups studied since 1970 are listed in Table 2. While the range of point prevalence for areca chewing is wide (< 1–54%) some important demographic differences are noted. Strickland[1] has considered these ethnographic differences in detail and the salient points are that in these countries more women than men chew and the prevalence of chewing increases with age. Some particular characteristics relevant to each local population are outlined below.

India

India has the largest areca-consuming population in the world. Much of the data arise from extensive population studies conducted by the TIFR group[4] in the 1960s and 1970s. Data were collected in a series of house-to-house surveys conducted in rural areas from individuals aged 15 years or over with approximately equal proportions of males and females. Interviews were conducted in five districts in India, Gujarat, Andhra Pradesh, Bihar and Kerala, involving 50915 people. The proportion chewing betel quid varied from 3.3% in Sirikakulam in Andhra Pradesh to 37% in Ernakulam in Kerala. Among 50915 people surveyed in five districts, 0.6% of those chewed areca nut alone (supari), compared with 11.6% who chewed betel quid with tobacco. The other large-scale study conducted in India by Malaowalla *et al.*[5] on 57518 industrial workers in Ahmedabad, Gujarat—a population different to the above studies in that these were mostly urban male textile workers—reported pan and supari chewing by 26% of 85% who admitted to an oral habit. In a study of 99598 adults (> 35 years) in Mumbai, some 32.1% reported chewing betel quid with tobacco, whereas only 0.5% reported chewing areca nut or betel-quid without tobacco.[6]

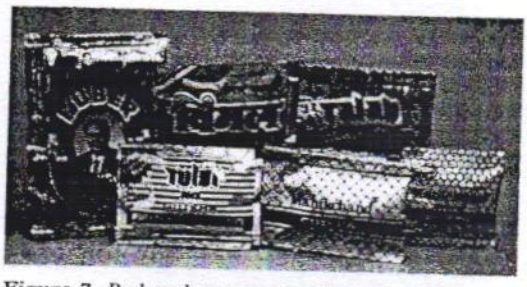

Figure 7. *Packaged areca nut products referred to as pan masala. Those containing tobacco are referred to as gutka.*

Pakistan

Mahmood *et al.*[7] questioned 10749 apparently healthy subjects living in Karachi. He recorded pan use without tobacco in 7.5% and pan with tobacco in 15% of this population. A subcohort of 3562 individuals from this group were re-examined by Jafarey & Zaidi.[8] They reported that at least 30% of these healthy individuals had a pan habit compared with a hospital group of 1192 oral carcinoma patients, among whom 66% had a pan habit. Their description of a pan habit is not explicit, but as tobacco chewers are listed separately the assumption is that this group

reporting pan use chewed predominantly areca nut and betel. Maher,[9] in a recent house-to-house study in a periurban area in Sindh, recorded 35 different items that are consumed as part of betel quid chewing by this population.

Sri Lanka

In Sri Lanka the habit of areca chewing stems from ancient times, and traditionally the nut is chewed with a betel leaf sprinkled with lime (Fig. 4). Tobacco may be added to the quid. Hirayama's early studies in the 1960s[10] indicated that, among a group of healthy control subjects, at least one in five men did not add tobacco to their betel/areca recipe. A higher proportion of women (who did not smoke) were reported to be adding tobacco to the areca/betel quid mixture. Other studies in the 1960s and 1970s confirmed these patterns of chewing.[11,12] Warnakulasuriya,[13] in a large-scale epidemiological study in rural villages in the Central Province of Sri Lanka, reported around 50% of men and women to be chewing betel quid.

In a nationwide survey[14] conducted between 1994 and 1995 approximately 4000 adults over 35 years of age were interviewed on their betel quid chewing habits. The reported prevalence of betel quid chewing was 33.7% among 35–44-year-olds and 47.7% among 65–74-year-olds.

Thailand

The constituents of a betel quid which includes fresh or fermented parts of areca nut as used in Northern Thailand are very similar to those illustrated in Fig. 4. Tobacco is almost always added. A detailed study of several hill tribes (Lahu, Karen, Lisu and Thai) living in Northern Thailand by Reichart *et al.*[15] carried out in 1979–84 suggested a prevalence ranging from 5 to 44% in men and 9 to 46% in women. In the Thai tribe the habit was less predominant and the Meo tribe was the exception, preferring to chew miang—fermented wild tea leaves.

The habit of betel quid chewing in Thailand is declining, the only country in south Asia to record such a trend. In 1955, Young[16] commented on this and Reichart's group[17] substantiated this falling trend by observing that very few villagers below the age of 35 chewed betel, once a universal custom among Thai peasants. The habit of betel chewing in cities such as Bangkok and Chaing Mai has almost vanished.[15] Axell *et al.*[18] reported that only three of 234 subjects (1.3%) attending a hospital unit reported any form of betel or areca use. A decline in frequency and mortality from oral cancer in Thailand is linked to the continuously declining chewing habit among Thais.[19]

Guam

Guamians chew mainly the nut, without the addition of tobacco or lime. Either the fresh immature green areca nut with its husk and skin or areca nut together with a betel leaf is chewed.[20] This practice seems to be ancient and has not changed, but the prevalence data for the chewing habit have not been examined in any systematic survey.

Papua New Guinea (PNG)

In PNG the quid is formed by chewing the kernel of the areca nut, and by adding slaked lime using the inflorescence of betel piper vine (Fig. 5) moistened with saliva, dipped in powdered lime.[21] Together these three form the basis of the quid habit and betel leaf or tobacco are traditionally not consumed[22] Although several descriptive papers refer to the habit of areca chewing among Papuans, mainly from lowland and island areas,[23] no detailed epidemiological studies on the use of areca are available.

Taiwan

Betel quid chewing behaviour is viewed as a predominantly male habit in Taiwan with 21:1 ratio of relative prevalence rates between men (28.3%) and women (1.4%) among Kaohsiung residents.[24] Patterns of chewing among aborigines and Chinese were also reported to be different;[25] an aborigine would wrap a fresh areca nut in a betel leaf while Chinese would sandwich the betel infloescence (fruit) between two halves of the areca nut smeared with lime (Fig. 3). Among the general population in Taiwan, 6% were reported to be current chewers (9.8% for men; 1.6% for women) while among the aborigine people the prevalence was 42.1% (46.5% for men; 38% for women). Analysis of sociodemographic factors suggested that men, older people, less educated people, blue-collar workers, aborig-

ines, smokers and drinkers were more likely to chew areca nut.[25] Lu *et al.*[26] estimated that the age of beginning areca nut chewing in Changhua county was around 12 years, corresponding to the last year in the primary school. During school years from junior high school to vocational school prevalence rates rise from 2% to 10%.[27] Stich *et al.*,[20] examining chewing patterns in the Hualien district in Taiwan, reported that on average a Taiwanese uses 44 areca nuts a day and a significant number of chewers may chew up to 120 nuts a day.

Sarawak and Malaysia

In rural Sarawak, areca nut is essentially an item of local produce. Following a field study Strickland & Duffield[28] reported that 22% of men and 47% of women interviewed in 1996 used areca daily. The habit tended to begin in young adulthood and women were more regular chewers than men. Among indigenous people of Sarawak living in Malaysia, Zain *et al.*[29] reported 37 of 164 (22.5%) were current chewers. Again, the habit was more prevalent in women. However, compared with Sarawak people among Indians working on estates in the same region the habit of quid chewing was more popular and 91 of 147(62%) were identified as habitués. Malay quid chewers are noted not to use tobacco in their quid mixture.

Cambodia

Few epidemiological studies on chewing habits are reported in selected Cambodian populations. Ikeda *et al.*,[30] in the early 1990s, interviewed 1319 individuals in nine villages in Cambodia. Chewing betel quid was reported by 408 subjects (31%). Among these Cambodian chewers 28% reported use of the nut only. Reichart also reported on the popularity of the areca chewing habit among elderly Cambodian women.[31]

China

Zhang *et al.*,[32] in a large-scale epidemiological study, interviewed 11406 subjects in Xiangtan city in Hunan Province in China. The people in Xiangtang were reported to often chew areca nut without tobacco, while bitter and hot pepper were usual additives. Thirty-five per cent of the subjects chewed areca nut. In a pilot study of 100 subjects in Hainan island of the People's Republic of China 95% of the study population chewed areca nut.[33]

Conclusions

There are clearly many differences in the way areca nut is consumed, on its own or often in combination with many other ingredients, including tobacco. In India alone, Pindborg *et al.*,[34] in the 1960s, described 38 different combinations of areca nut and tobacco use according each person's recepe. In some populations the chewing of areca nut begins at a young age and their first experience of areca use is during elementary school years.[35] During the last two decades, with the availability of commercially available products, the pattern of use of areca has changed rapidly and the practice of chewing areca nut has received a boost. More precision is required in defining what is chewed[36] and the risk of carcinogenecity of the betel quid may well relate to the type, duration and frequency of the habit. This review identifies some ethnic groups, mainly in Melenesia, that do not use tobacco in areca/betel quid chewing and there are thus good opportunities for further research into the carcinogenecity of areca nut in these populations. While in some countries such as Thailand areca chewing is declining, there is new evidence that areca usage is increasing in other countries, notably in India and Taiwan, thus increasing the risk of these populations to develop oral submucous fibrosis and oral cancer.

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Early Findings from a Community-Based, Cluster-Randomized, Controlled Oral Cancer Screening Trial in Kerala, India

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BACKGROUND. Oral cancer satisfies the criteria for a suitable disease for screening, and oral visual inspection is a suitable test for oral cancer screening. The efficacy of screening in reducing mortality from oral cancer has not yet been evaluated. The authors describe a cluster-randomized, controlled oral cancer screening trial in southern India and its early results.

METHODS. Apparently healthy subjects age 35 years or older in 13 clusters called *panchayaths* were randomized to either an intervention group (n = 7) or a control group (n = 6). Subjects in the intervention group will receive 3 rounds of screening consisting of oral visual inspection by trained health workers at 3-year intervals. The first round of screening was carried out between October 1995 and May 1998. Participants were visited in their homes and interviewed for sociodemographic details, tobacco-smoking and alcohol-drinking habits, and personal medical history. Those with tobacco or alcohol habits were advised to stop those habits. Subjects in the intervention group were offered screening, and those with lesions suggestive of oral leukoplakia, submucous fibrosis, or oral cancer were referred for examination by physicians. Confirmed leukoplakias were excised whenever possible, others were kept on follow-up, and those with confirmed oral cancers were referred for treatment. Data on oral cancer incidence, stage distribution, survival, and mortality in the study groups are obtained by record linkage with the Trivandrum population-based cancer registry and municipal death registration systems.

RESULTS. There were 59,894 eligible subjects in the intervention group and 54,707 in the control group; 31.4% of the former group reported no tobacco or alcohol habits, compared with 44.1% of the latter. The distribution of age, education, occupation, income, and socioeconomic status were similar in the two groups. Of 3585 subjects in the intervention group referred, 52.4% were examined by physicians; 36 subjects with oral cancers and 1310 with oral precancers were diagnosed. Of the 63 oral cancers recorded in the cancer registry, 47 were in the intervention group and 16 were in the control group, yielding incidence rates of 56.1 and 20.3 per 100,000 person-years in the intervention and control groups, respectively. The program sensitivity for detection of oral cancer was 76.6% and the specificity 76.2%; the positive predictive value was 1.0% for oral cancer. In the intervention group, 72.3% of the cases were in Stages I–II, as opposed to 12.5% in the control

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group. The 3-year case fatality rates were 14.9% (7 of 47 patients) in the intervention group and 56.3% (9 of 16 patients) in the control group.

CONCLUSIONS. Though compliance with referral for confirmatory examination in the first round was lower than the 70% anticipated, intermediate end points, such as stage at diagnosis and case fatality, indicate that the trial is making fairly satisfactory progress. *Cancer* 2000;88:664–73. © *2000 American Cancer Society.*

KEYWORDS: oral cancer, mouth cancer, head and neck cancer, screening, early detection, control, oral visual inspection, randomized trial, leukoplakia, submucous fibrosis.

Oral cancer (ICD C00-C06) satisfies the criteria for a suitable disease for screening[1] in several regions of the world. It has clinically recognizable precancerous lesions (leukoplakia and oral submucous fibrosis) and asymptomatic early invasive lesions. It is a major cancer in populations in South Asia (particularly India), the Western Pacific, and certain regions of Europe and Latin America.[2] Incidence and mortality from oral cancer are reportedly increasing in several Western populations and eastern European populations.[3] Population-based 5-year survival for patients with this group of cancers is approximately 50% in the U.S.;[4] it ranged from 45% to 49% in Europe[5] and approximately 30% in selected developing countries.[6] There has been very little improvement in overall 5-year survival over the last 3 decades;[4] although 5-year survival for localized cancers exceeded 80% in the U.S., it was approximately 60% in selected developing countries.[6] The poor overall survival reflects the advanced stage at diagnosis for the vast majority of these cancers, as 5-year survival seldom exceeds 40% for patients with regional disease and 15% for those who have disease with distant metastasis.

Visual examination of the oral cavity is a simple approach to detecting asymptomatic oral cancers and precancerous lesions. The performance characteristics of this test are satisfactory in terms of sensitivity, specificity, and predictive value;[7–10] therefore, it is a suitable screening test for oral cancer. Precancerous lesions, such as leukoplakia, are likely to regress if risk factors such as tobacco and alcohol habits are stopped. Early stage oral cancers are amenable to single-modality therapy with either surgery or radiation, with minimal posttreatment sequelae and promising long term disease free survival.

Though oral precancers and early cancers can be detected by visual inspection of the oral cavity, to date, no studies have evaluated this approach in terms of reduction in mortality from oral cancer. We initiated a community-based, cluster-randomized controlled intervention trial in Trivandrum District, Kerala, India, in October 1995, to evaluate the mortality reduction associated with screening by visual oral examination provided by trained health workers. The age-standardized incidence rates of oral cancer (ICD 10 C00, C01, C03-C06 categories) were 16.3 per 100,000 males and 7.7 per 100,000 females during 1991–1992 in this region, the fourth highest rates reported in the world.[2] Three rounds of screening at 3-year intervals are planned for this study. We describe the study and findings from the first round of screening, which was completed in May 1998.

MATERIALS AND METHODS

The study participants are apparently healthy resident subjects age 35 years or older, living in 13 clusters called *panchayaths* located in the northern suburb of Trivandrum City, Kerala, India (Fig. 1). *Panchayaths* are municipal administrative units in rural areas of India, with total populations of 20,000–40,000. The number of eligible subjects in each cluster varied from 5177 to 12,147 (mean, 8815). These clusters were allocated to an intervention arm (n = 7) and a control arm (n = 6) by restricted (blocked) randomization. The clusters were grouped into blocks of four, and the allocation into intervention or control arms for a particular block of clusters was chosen at random from the six possible combinations of study groups in blocks of four. The following categories of subjects were excluded from the study: bedridden subjects, those suffering from open tuberculosis or other debilitating diseases, and those diagnosed with oral cancer prior to entry into the study. The study protocol was reviewed and approved by the institutional ethical committee, and informed consent was obtained from participating subjects.

Two health workers (HWs) (1 male and 1 female), hereafter referred to as "intervention HWs," were recruited to enumerate and screen eligible subjects in each panchayath. They were university graduates in biology or social sciences and received a 3-month training period organized by the Community Oncology Division of the Regional Cancer Centre (RCC), Trivandrum, on performance of the following tests:

- To enumerate households and record all their residents;

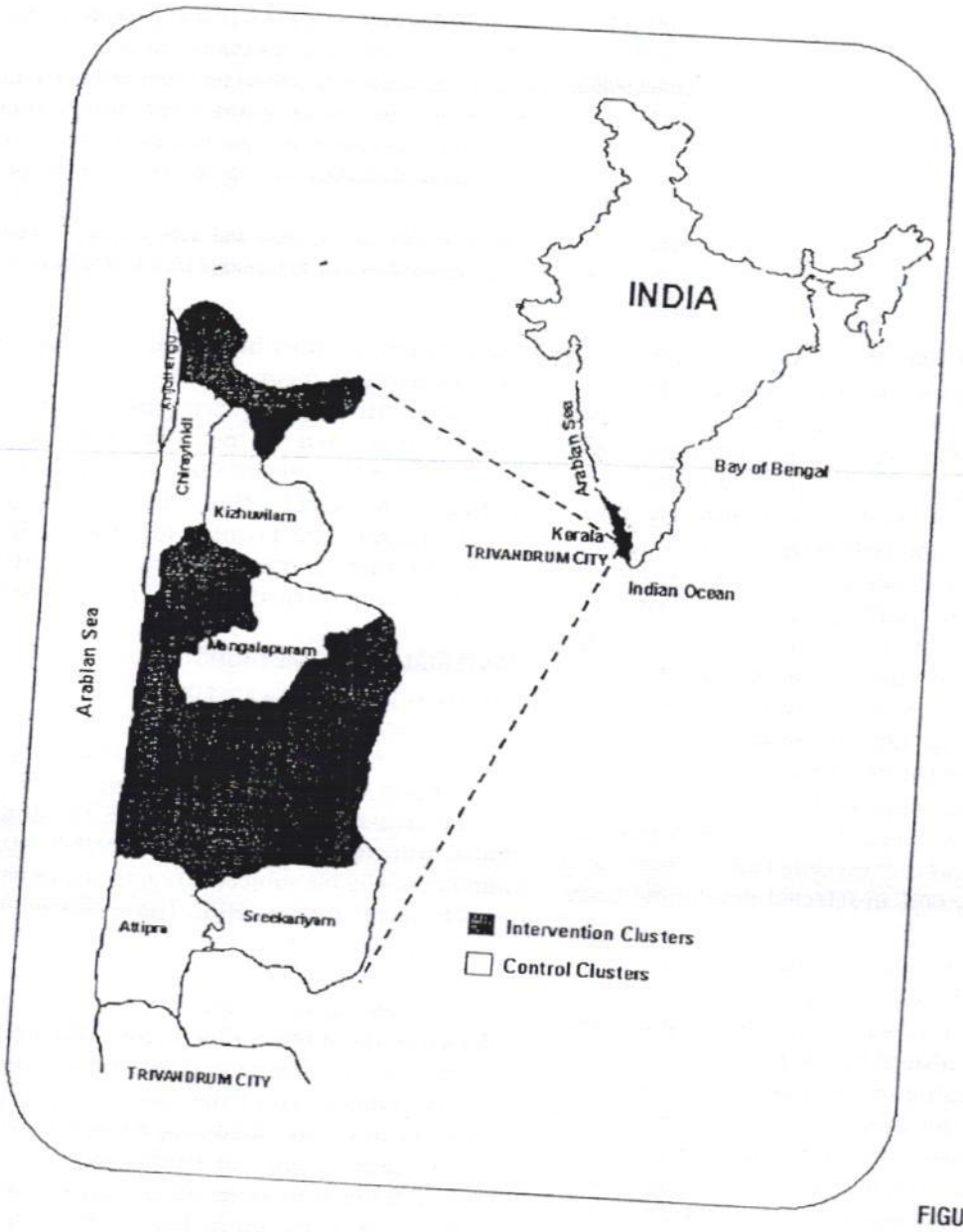

FIGURE 1. A map shows study clusters.

- To interview eligible subjects with respect to socio-demographic factors, personal habits, diet, and medical history, and to record this information on a structured form;
- To measure the height, weight, blood pressure, and respiratory peak flow of eligible subjects;
- To perform an oral visual inspection and to identify anatomic variations, benign lesions, preleukoplakia, homogeneous leukoplakia, ulcerated leukoplakia, verrucous leukoplakia, nodular leukoplakia, erythroplakia, oral submucous fibrosis, and oral cancer.

The faculty for the training sessions consisted of a dental surgeon, a pathologist, a cancer surgeon, a radiation oncologist, a family physician, a social scientist, and a demographer from the Kerala Census Department. The intervention HWs were taught about cancer in general, and oral cancer in particular, in terms of risk factors, natural history, methods of diagnosis, treatment, and prognosis by audio-visual methods. Two simple published manuals on oral visual examination with color photographs and descriptions of various oral lesions were used as the resource manual for training.[11, 12] After the theoretic teaching, they were trained in the field on home visits, enumeration of subjects, interview methodology, performing oral examination in individuals, and recording height,

weight, blood pressure, and respiratory peak flow measurements.

A pair of HWs, hereafter referred to as "control HWs," were recruited from each panchayath randomized to the control arm. They were trained to enumerate and interview the subjects to collect information on sociodemographic factors, personal habits, diet, and medical history, and record the information on a structured form. They were trained in measuring height, weight, blood pressure, and respiratory peak flow measurements, but no training was given to them regarding oral cancer and oral visual inspection.

Information on the households, such as location, house number, address, type of house, facilities in the household (availability of cooking gas, refrigerator, toilets, running hot water, source of water supply, radio, television, vehicles, and telephone), household income, name, age, and personal habits of all subjects in the households in all study clusters, were entered on a household form. The study was then explained to the eligible subjects and they were provided with a pamphlet with printed information on the study in Malayalam (the local language). Each eligible subject was then assigned a unique number based on the panchayath, ward (a subunit of the panchayath), household number, and an assigned individual number. They were then interviewed for details regarding occupation; personal habits, such as pan tobacco chewing, tobacco (bidi, cigarette, cigars, pipe) smoking, alcohol consumption, consumption of vegetables, fruits, and dietary supplements; and personal history of past or current illness. The responses were entered on an individual form. Height, weight, respiratory peak flow, and blood pressure measurements with a mercury manometer were also recorded on the individual's form. A pamphlet describing the harmful aspects of tobacco in Malayalam was distributed to each household. Those with current tobacco or alcohol habits were advised to give them up, and others were encouraged not to initiate these habits.

Oral visual inspection of eligible subjects in the intervention panchayaths was performed in bright daylight with the help of a flashlight. All the intraoral sites were carefully examined and palpated. The neck was also palpated to detect enlarged lymph nodes. The findings were recorded as follows:

- Normal;
- Nonreferable lesions: fissures in the tongue, aphthous ulcer, black patch, tobacco-related blanching, fibroma, hypertrophied papillae, etc.;
- Referable lesions: white patch, ulcerated white patch, verrucous lesion, submucous fibrosis, red patch, suspicious ulcer or growth.

Subjects with referable lesions were given appointments for confirmatory examination by dentists or medical officers in special clinics (at the RCC) or were referred to their own physician or dentist, if they preferred this option. Those attending were examined and the findings documented. Subjects were again advised to stop tobacco and alcohol habits. If the subjects consulted their own physician or dentist, the examining physician was requested to mail feedback to the screening project office regarding the findings and advice given. Oral biopsies were performed in those with clinically confirmed homogeneous leukoplakias, nonhomogeneous leukoplakias (ulcerated leukoplakia, erythro leukoplakia, verrucous leukoplakia, and nodular leukoplakia), oral submucous fibrosis, and cancers. Surgical excision was carried out for leukoplakia wherever possible. Nonsmokers with nonexcisable, nonhomogeneous leukoplakias were randomized to a prevention trial with vitamin A; smokers with large, nonexcisable lesions were given close follow-up. All subjects with oral precancers were regularly reviewed concerning the possibility of surgical excision and to assess any regression or progression. Those with submucous fibrosis were treated symptomatically. Subjects with confirmed oral cancers were referred for treatment with surgery and/or radiotherapy and/or chemotherapy to the RCC, Trivandrum, or a cancer treatment facility elsewhere, if they preferred the latter option.

The intervention and control cohorts are being followed up by the Trivandrum population-based cancer registry to determine the incidence and stage distribution of invasive oral cancer, treatment given, and mortality. A special liaison has been developed with the municipal death registration systems in the study clusters and in Trivandrum City to obtain information on mortality. All deaths occurring among subjects age 30 years or older are abstracted from the death registry and matched against the study data base. Data are recorded using D-Base and analyzed with STATA statistical software (STATA Corporation, College Station, TX).

Short term evaluation of the efficacy of the intervention is based on the following indicators and measures:

1. Participation: the number of eligible subjects screened as a proportion of the total eligible in the intervention arm.
2. Positivity rate: the proportion of screened subjects identified with referable lesions (screen positive) by the intervention HWs.
3. The detection rate for oral precancer and oral cancer is the number of subjects with lesions de-

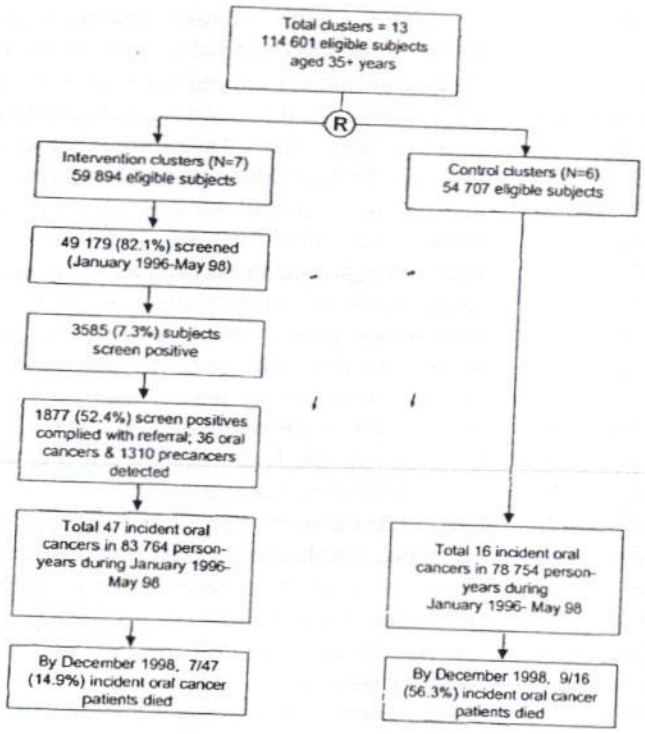

FIGURE 2. The study profile is outlined.

tected per 1000 screened subjects in the intervention group.

4. Compliance with referral: the proportion of screen positive subjects reporting for diagnostic confirmation by dentists or physicians.
5. Sensitivity, specificity, and positive predictive value for detection of oral precancerous lesions: These were calculated in a validation study[10] involving 2069 of eligible subjects (678 men and 1391 women, comprising 231 screen positive and 1838 screen negative subjects) already screened by HWs who were independently examined by physicians (reference test). Sensitivity was given by the proportion of subjects having lesions among those tested positive; specificity was given by the proportion of subjects not having lesions on a physician's examination among those who were screened negative by HWs. Prevalent cancer cases were too few in this sample of subjects to assess sensitivity and specificity for oral cancer.
6. Program sensitivity and specificity for detection of oral cancer: Sensitivity was calculated as the number of screen-detected oral cancers as a proportion of the total oral cancers in the intervention group. Specificity was calculated as the proportion of screen true-negative subjects among the total non-cancer-eligible subjects (see Table 5). Positive predictive value was calculated as the number of screen-detected oral cancers as a proportion of total screen positive subjects.
7. Incidence rate of oral cancers in the study groups per 100,000 person-years: The number of person-years in the intervention and control groups was calculated from the date of study entry to May 31, 1998.
8. Characteristics of oral cancers in the study group: maximum dimension of lesions, regional lymph node involvement, and International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM stage grouping distribution[13] of oral cancers in the study groups.
9. Case fatality for oral cancer cases diagnosed during the study period: the number of deaths among the total number of cases.

The final outcome of the trial will be calculated by a comparison of mortality due to oral cancer in the intervention and control groups.

TABLE 1
Participants in the Intervention Trial

Total	Males in intervention clusters	Males in control clusters	Females in Intervention clusters	Females in control clusters
Total residents	79,234	74,218	93,333	85,415
Eligible individuals	25,453 (100%)	23,356 (100%)	34,441 (100%)	31,351 (100%)
Eligible individuals interviewed	18,639 (73.2%)	14,132 (60.5%)	30,619 (88.9%)	25,516 (81.4%)
Eligible individuals screened	18,605 (73.1%)	–	30,574 (88.8%)	–

RESULTS

The outcome of the first round of screening is shown in the flowchart (Fig. 2). The total number of residents of the study areas, the number of eligible subjects, the number of subjects interviewed, and the number eligible subjects screened are shown according to gender in Table 1. The participation rate for screening was 73.1% for males and 88.8% for females.

The distribution of age, occupation, income, socioeconomic indicators, education, and tobacco and alcohol habits in the intervention and control groups are given in Table 2. The age distribution was similar in both groups. The distribution of income, education, and ownership of, for example, a radio, television, etc., were more or less comparable in both study groups.

The distribution of tobacco and alcohol habits was somewhat different between the study groups (Table 3). Pan tobacco (a combination of betel leaf,

TABLE 2
Characteristics of Participants

Characteristics	Intervention group (n = 59 894)	Control group (n = 54 707)
Age (yrs)		
35–44	37.8%	37.7%
45–54	26.7%	27.6%
55–64	19.8%	19.2%
65–74	10.9%	10.6%
75+	4.8%	4.9%
Occupation		
Manual	83.6%	80.4%
Office related	5.3%	5.7%
Technical/professional	1.7%	2.5%
Education		
Illiterate	17.9%	16.1%
Primary	29.2%	25.7%
Secondary	43.9%	48.8%
University	9.0%	9.4%
Income (in INR/mo)		
Low (<1500)	56.8%	47.6%
Low-middle	27.4%	32.8%
(<3000)	10.0%	12.5%
Middle (<5000)	5.8%	7.1%
High (>5000)		
Household availability of:		
Radio	61.9%	69.7%
Television	41.7%	49.7%
Fridge	16.1%	17.6%
Bicycle	23.1%	16.3%
Scooter	6.4%	8.1%
Car	1.7%	1.8%
Indoor toilet	19.7%	18.1%
Telephone	6.9%	6.0%

lime, arecanut, and dried tobacco leaves) was the most common form of tobacco chewed. Tobacco smoking predominantly involved bidi smoking (a *bidi* is a local cigarette made by wrapping coarse tobacco in a dried temburni leaf), followed by cigarette smoking. The most common alcoholic drinks were a toddy locally brewed from palm vine and an arrack brewed from sugar cane juice. Pan tobacco chewing was more prevalent in the intervention group among both genders when compared with the control group. Smoking and alcohol drinking were rare among females. There was a higher prevalence of smoking and alcohol drinking among males in the intervention group, compared with controls.

Among the 49,179 subjects screened by HWs, 3585 (7.3%) were found to have referable lesions. Of these, 1877 (52.4%) complied with referral for confirmatory examination by dentists or physicians. The compliance among males (49.0%) was lower than among females (54.7%); it was much higher in the age group 55–64 years (59.8%) than in the age groups 35–54 years (47.7%) and 65 years or older (50%). Compliance with

TABLE 3
Prevalence of Habits among Participants

Habits	Intervention males (n = 25,453)	Control males (n = 23,356)	Intervention females (n = 34,441)	Control females (n = 31,351)
No habit	31.4%	44.1%	72.3%	81.8%
Chewing	26.8%	20.5%	26.4%	17.6%
Smoking	55.8%	43.9%	2.4%	1.0%
Drinking	29.8%	22.3%	0.2%	0.2%

referral was lower (48.5%) among those with incomes less than 1500 rupees (less than 36 U.S. dollars) per month as opposed to those with higher incomes (58.7%). It was also lower (47.3%) among screen positive subjects with less severe lesions (suggestive of homogeneous leukoplakia) on screening compared with those who had more severe lesions (suggestive of nonhomogeneous lesions, submucous fibrosis, and suspicious ulcers or growths) (54.6%).

Among the 1877 subjects reporting for confirmatory examination, 531 (28.2%) were found to have normal mucosa, anatomic variations, or benign lesions. The other abnormal findings were homogeneous leukoplakia (n = 634), nonhomogeneous leukoplakia (n= 502), and submucous fibrosis (n = 174), all of which we consider oral precancerous lesions, and oral cancer (n = 36). The detection rate of oral precancerous lesions was 26.6 per 1000 screened subjects.

In a small "validation study" involving a random sample of 2069 subjects, the sensitivity and specificity of detection of oral precancers were 94.3% and 98.3%, respectively, as reported in an earlier article.[10] The positive predictive value for the precancers was 86.6%.

A total of 308 subjects with clinically confirmed oral precancerous lesions were subjected to biopsy. The outcomes of their histologic examinations are shown in Table 4. Invasive cancer was histologically detected in 7.5% of clinically diagnosed nonhomogeneous leukoplakias; some degree of dysplasia was present in 59.7% of the subjects with these lesions. Surgical excision was carried out for 93 subjects with leukoplakia.

A total of 63 patients with oral cancer (47 in the intervention and 16 in the control group; 37 males and 26 females) were registered by the Trivandrum cancer registry from the study groups during the period of the first round of screening (October 1995 through May 1998). A total of 83,764 person-years (35,491 male and 48,303 female person-years) were accrued in the intervention group as of May 31, 1998; 78,754 person-years (33,411 male and 45,163 female person-years) were accrued in the control group. The incidence rate

TABLE 4
Histologic Findings for Subjects with Oral Precancers Subjected to Biopsy

Clinical lesion	Total	Biopsied	Mild dysplasia	Moderate dysplasia	Severe dysplasia	Invasive cancer	Others
Homogeneous leukoplakia	635	71	14	12	0	1	44
Non-homogeneous leukoplakia	519	226	28	88	19	17	74
Submucous fibrosis	175	11	0	6	0	1	4

TABLE 5
Calculation of Program Sensitivity and Specificity for Detection of Oral Cancer

Visual inspection	Oral cancer present	Oral cancer absent	Total
Positive	36	3,549[a]	3,585
Negative	8	45,586	45,594
Not done	3	10,712	10,715
Total	47	59,847	59,894

Sensitivity: 36/47 = 76.6%; specificity: 45,586/59,847 = 76.2%; positive predictive value: 36/3585 = 1.0%.
[a] Includes 1708 non-compliant subjects assumed to be and classified as false-positives.

TABLE 6
Stage Distribution of Oral Cancers in the Study Groups

Stages	Intervention (n = 47)	Control (n = 16)
I	22 (46.8%)	0 (0.0%)
II	12 (25.5%)	2 (12.5%)
III	9 (19.2%)	4 (25.0%)
IV	4 (8.5%)	10 (62.5%)

of oral cancer was 56.1 per 100,000 person-years in the intervention arm and 20.3 per 100,000 person-years in the control group. For males, the incidence rate was 73.3 in the intervention group (n = 26) and 32.9 in the control group (n = 11); the corresponding figures for females were 43.5 (n = 21) and 11.1 (n = 5).

Of the 47 oral cancers in the intervention arm, 36 (76.6%) were screen-detected, 8 (17.0%) were interval cases, and 3 cases were clinically detected from among eligible subjects who were not screened. The detection rate for oral cancer was 0.7 per 1000 screened subjects in the intervention group. Among the screen-detected cancer cases, 21 were males and 15 were females. The intraoral site distribution of cancers in the intervention group was as follows: lip (ICD C00), 0; tongue (ICD C01, C02), 12 (25.5%); gum (ICD C03), 4; floor of mouth (ICD C04), 1; palate (ICD C05), 4; buccal mucosa (ICD C06), 26 (55.4%). The site distribution of cancers in the control group was as follows: lip, 1, tongue, 7 (43.8%), gum, 2, floor of mouth, 1, palate, 0, and buccal mucosa, 5 (31.1%).

The program sensitivity and specificity in detecting oral cancer were 76.6% and 76.2%, respectively (Table 5). These calculations included 1708 screen positive cases who did not comply with referral, were assumed to be false-positive, and were classified as such. The positive predictive value of the visual inspection was 1.0% for oral cancer.

The distribution of the maximum measurable dimension of cancers in the intervention group was as follows: <2 cm: 23 (49.0%); 2–4 cm: 12 (25.5%); >4 cm: 12 (25.5%). The corresponding results for the control group cancer cases were 0 (0.0%), 7 (43.8%), and 9 (56.2%), respectively. Thus, 74.5% of the tumors in the intervention group measured <4 cm, as opposed to 43.8% in the control group. In the intervention group, 36 (76.6%) had no palpable neck lymph nodes, as opposed to 4 (25.0%) in the control group. The stage distribution of oral cancer cases, based on the UICC/AJCC TNM stage grouping,[13] in the two study groups is given in Table 6. In the intervention group, 72.3% of the cases were in Stage I or II, as opposed to 12.5% of cases in the control group ($P < 0.05$). Over the 3-year period, since the inception of the trial, 7 of the 47 oral cancer patients in the intervention group and 9 of the 16 cases in the control groups died, a 3-year case-fatality of 14.9% (7 of 47) and 56.3% (9 of 16) in the respective groups.

DISCUSSION

To our knowledge, our ongoing study is the first controlled intervention trial with the aim of determining whether screening by visual inspection of the mouth can reduce mortality from oral cancer, and whether this approach is sufficiently cost-effective for implementation in routine health care settings in high risk populations. Previous studies have addressed the feasibility and logistics of oral cancer screening or provided information on test characteristics (sensitivity and specificity) of oral visual inspection, participation rate, and compliance with referral.[7–9,14]

Oral visual inspection of asymptomatic subjects has been previously shown to detect oral lesions when provided as part of routine medical care[7,15] and by HWs.[7–9,16,17] Oral examinations performed as part of the clinical examination of 672,000 veteran patients in the U.S. resulted in the detection of 814 oral cancers.[15]

Routine oral examination of 21,318 subjects by 9 physicians and 3 dentists in 9 hospitals of the Gampola region in Sri Lanka resulted in the diagnosis of 9 oral cancers and 29 precancers.[7]

In many developing countries, the health services rely on HWs in the provision of primary health care and, hence, training and utilization of HWs for early detection of common cancers (e.g., the oral cavity, breast, and cervix) have occasionally been proposed.[17,18] In previous cross-sectional studies in Sri Lanka[7,9] and India,[8,16] participation in oral visual inspection by trained HWs ranged from 34% to 78%; compliance with referral varied from 51% to 72%. The sensitivity of mouth examination by HWs to detect lesions varied from 57.7% to 61.4% in the above studies; the specificity ranged from 98.6% to 98.8%.

An oral cancer screening program has been ongoing in Cuba since 1984.[14] Although each dentist in the Cuban Health Services is expected to provide yearly screening with oral visual inspection to an assigned population of approximately 2000 subjects age 15 years or older, in practice, this is carried out mostly as an opportunistic examination of subjects reporting dental problems. The proportion of eligible individuals examined never exceeded 21% in males and 31% in females in any given year up to 1990. Descriptive studies concluded that there was no reduction in incidence of or mortality from oral cancer after the introduction of the screening program, possibly due to inadequate coverage as well as poor compliance with referral and treatment of preinvasive lesions. Nevertheless, two-thirds of the 715 oral cancer cases detected in the program during the years 1984–1990 were <2 cm in size. Staging data based on half of the oral cancer cases registered in Cuba showed that the proportion of Stage I cancers increased from 24% in 1983 to 49% in 1989.

Pan tobacco chewing, *bidi* and cigarette smoking, and alcohol drinking have been established as the major risk factors for oral cancer in this population.[19–21] The differential distribution of the major risk factors between the intervention and control groups is therefore of concern, although somewhat puzzling in the presence of comparable socioeconomic indicators. The most likely explanation is that an information bias, rather than failure of randomization, is responsible. The subjects in the intervention group might have been more motivated and forthcoming about their habits as they were offered active intervention. The interviewers were, of course, aware of the intervention or control status of subjects (another potential source of bias), and one cannot rule out retrospective "correction" of interview data following the physical examination. Risk factors will be accounted for in the final analysis, by stratification.

As any community intervention, clusters were randomized to minimize the potential for contamination between intervention and control groups, where the recruitment process involved house visits, and the eligible subjects were offered screening in their homes. Our analysis suggests an association between clusters and the main risk factors (Table 3). We tend to interpret these differences as being due to information bias, in which case the two groups would experience the same background incidence and, in the absence of intervention, mortality rate. In such circumstances, the study would have 70% power to detect a 30% reduction in mortality from oral cancer at a 5% significance level in the intervention group compared with the control group, by the ninth year of follow-up. Should the risk of the disease be different in the two groups due to a real difference in the prevalence of risk factors, adjustment in the analysis will maintain the level of statistical power. At the end of follow-up, we may have insight regarding the actual differences between the two groups by comparing the cumulative incidence of oral cancer on the long time period.

The participation in screening was acceptably high, particularly so for women (88.7% of eligible females screened vs. 73.1% of eligible males). On the other hand, the proportion complying with referral for confirmatory examination (52.4%) was lower than the 70% anticipated. Of the screened subjects, 7.3% were referred for further examination and 3.8% were examined by physicians. The low compliance with referral in the previously reported cross-sectional studies in South Asia as well as in the current study stresses the need for appropriate educational measures to motivate subjects to comply with interventions, if these are offered in developing countries. We are taking active steps to improve the compliance in the second round.

The findings of histologic examination of biopsy specimens of clinically diagnosed nonhomogeneous leukoplakias underscore the need for routine biopsy of these lesions. One-third of clinically homogeneous leukoplakias revealed dysplasia on histology, stressing the need for close follow-up or even routine biopsy of these cases. Though the numbers of cases of submucous fibrosis subjected to histologic examination is rather small, the finding that more than 50% harbored some degree dysplasia is of considerable clinical interest. Our initial policy was to encourage only subjects with nonhomogeneous leukoplakias to undergo biopsy. We are now taking active steps to encourage also subjects with homogeneous leukoplakia and submucous fibrosis to undergo biopsy in view of the above findings.

Supplementation with retinoids is reportedly associated with regression of oral leukoplakias.[22] However, their efficacy in reducing the incidence of oral cancer in high risk subjects remains unknown. Nonsmoking subjects with nonexcisable, nonhomogeneous oral precancerous lesions in this study are being randomized to receive either vitamin A (200,000 IU per week) or no supplementation. If these lesions, on follow-up, regress to become excisable, surgical excision will be attempted. This approach may increase the proportion of precancerous lesions subjected to excision and may further contribute to the prevention of oral cancers.

The buccal mucosa was the most common intraoral cancer site in the intervention group, as opposed to tongue cancer in the control group. This might be a reflection of the possible differences in the natural history of cancers at these two sites. The reported 5-year survival is low for patients with tongue cancers compared with that for patients with other intraoral cancers.[5,6] It is likely that buccal mucosal cancers have a longer, possibly less aggressive natural history than tongue cancers; if so, buccal mucosal cancers would have a higher likelihood of detection by screening. These findings have some implications for oral cancer screening in view of the marked differences in the intraoral distribution of lesions between geographic regions (due to differences in the relative distribution of established risk factors such as pan tobacco chewing, smoking, and alcohol consumption).[23] It is possible that oral cancer screening may be more efficient in case detection in regions with a high risk of buccal mucosal cancers than in regions with a high proportion of tongue cancers among oral cancers.

Earlier detection of cancer in those screened was clearly evident by the end of the first round of screening, as two-thirds of oral cancers in the intervention group were diagnosed in Stages I–II compared with less than one-fourth in the control group. More than two-thirds in the intervention group had no palpable lymph nodes, as opposed to less than one-third in the control group. These factors seem to be responsible for the difference in the 3-year fatality from oral cancer in the study groups (14.9% in the intervention group as opposed to 56.3% in the control group). Though compliance with referral needs to be further improved, the intermediate end points, such as stage and fatality, indicate fairly satisfactory progress for the intervention trial so far. Active steps are taken to improve compliance of screen positive subjects with confirmatory examination in subsequent rounds of intervention in this study.

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Arecanut and tobacco use among school children in a village in South India – A cross sectional study

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RESEARCH

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Abstract

Background
Areca nut is the fourth most commonly used psychoactive substance in the world after caffeine, alcohol and nicotine. Its use is considered a benign and socially acceptable habit among most Indians. Like tobacco, chewing areca nut also leads to oral and oropharyngeal cancers. Chewing of these substances usually starts early in life leading to a multitude of problems in adulthood. This study was conducted among high school students to determine the prevalence and to assess awareness of health hazards associated with these substances.

Method
This cross sectional study was carried out in Vantamuri village, South India. All consenting school children of 7th, 8th and 9th class were interviewed individually using a pretested questionnaire about their chewing habits. This was followed by a thorough oral cavity examination for all.

Results
Out of 392 participants 62.5% were boys. Mean age of all participants was 14.8 ± 1.13 years. The prevalence of areca nut usage among boys and girls was 27.3% and 6.1% while it was 2.4% for gutka (contains tobacco) amongst boys. Majority of students started chewing between 13 and 14 years. About 49% of users were chewing these substances regularly for more than a year. Addictive tendencies were seen in two users. 43% of users chewed the same product used by their family members (P<0.025). 13.4% of chewers were from divorced or separated parents (P<0.005). About 3/4th of the participants were ignorant of associated health hazards or thought these substances to be harmless. Black staining of teeth was seen in 39.5% of areca nut users (P=0.001). One case of submucous fibrosis was identified among an arecanut chewer.

Conclusion
Awareness level of health hazards was poor among the students. Health education against these substances at an early age may help in curbing this problem.

Key Words
Arecanut, Gutka, children, Awareness, Cross sectional study, India

Background

Globally, arecanut is among the most common addictions following tobacco, alcohol and caffeine.[1] India is the largest producer and consumer of arecanut in the world.[2] Arecanut chewing is considered a benign and socially acceptable habit among most Indians.[3] Its chronic use contributes significantly to the high incidence of oral and oropharyngeal cancer in India. Apart from the carcinogenic potential, arecanut has been shown to be addictive and development of typical dependence symptoms associated with its usage has been described.[4] Acute effects of arecanut chewing include asthma exacerbation, hypertension, and tachycardia.[5] The other adverse health effects include oral leukoplakia, submucous fibrosis and gum disease.[6,7] What is considered benign arecanut use can act as a gateway to tobacco use also very early in life.[4]

Tobacco along with arecanut, slaked lime, catechu and condiments makes gutka. Aggressive advertising and marketing of gutka in small attractive and inexpensive sachets since early 1980s has greatly enhanced the sales of these products.[1,7] Adverse effects of tobacco usage are oral cancer, cardio vascular diseases, Chronic Obstructive Pulmonary Disease to name a few.

Chewing of these products usually starts at an early age (approximately 13 - 15 years) and by adulthood most users are addicted to this habit. The current problem of tobacco usage among 13 to 15 year old school going

children in Karnataka state of South India is estimated to be 4.9%.[8]

Starting the habit at a young age increases the risk of morbidity and mortality in later life. It also significantly increases the risk of cancer in the population.[9]
It is known that the socio demographic predictors of tobacco usage are poorly understood in the society.[10]
In this background, a cross-sectional study was conducted to find out the prevalence of arecanut and gutka usage, correlates of its use, reasons for chewing, awareness about its health hazards and to identify the associated clinically detectable oral lesions.

Method

This study was done in April 2005 in Vantamuri village which is one of the seventeen villages covered by PHC Vantamuri in the field practice area of J.N.Medical College, Belgaum. The village has a population of 4885 and it comes in Belgaum district. The district is situated in north of Karnataka state of South India with a literacy rate of 64.42%.[11] The village has two government high schools and one private high school. After taking consent from school authorities and guardians, all students of 7th, 8th and 9th class (392) of all the three schools present on the days of examination were included in the study. The prevalent forms of substances used among the students of this place were arecanut and gutka.

Each student was interviewed individually using a pretested questionnaire about their chewing habits, age of initiation, frequency of use, source of information about the product, reasons for use, source of money, consumption among family members, awareness about the harmful effects of the product etc. This was followed by an oral cavity examination. A brief education programme followed immediately after the screening to encourage school children to quit their habits. Regular users of arecanut or tobacco were defined as those who chewed during the past 3 months and current users were defined as those who chewed during the week prior to interview. The data was entered in MS Excel and was analyzed using SPSS Inc. Illinois, USA version 11.0. Test of significance was by Chi Square test.

Results

Out of the total 392 student participants, 245(62.5%) were boys. Mean age of all the students was 14.8 years (SD =1.13). Total prevalence of arecanut usage among study participants was found to be 19.4%. The prevalence of gutka usage was low (1.5%) and it was 2.4% among boys and nil among girls (Table1). None of students reported using tobacco in any other forms. Age of starting the habit in majority of arecanut users (34.7%) was 13yrs and majority of gutka users (66.7%) was 13 to 14yrs.

Majority of the boys (65.75%) first came to know about these substances from their friends while most girls (66.7%) came to know about it from their family members. Most boys (44.3%) preferred to chew arecanut or gutka at market place while most girls at their homes (77.8%). Most of the boys (84.9%) and girls (88.8%) were chewing these substances for one or more years.

Most users of both arecanut and gutka were regular users and among them majority were current users (Table2). Among the 67 boys who chew arecanut, 16(23.9%) took 1 or less pack during previous week, 13(19.4%) took 2-4 packs during previous week and 9 (13.4%) took between 1-6 packs every day during previous week. Out of 9 girls who chew arecanut, 4(44.4%) chewed 1-2 packs previous week and 2(22.2%) chewed 3-4 packs previous week. Out of 6 gutka users, 3 took 1 pack each previous week and 2 had taken 2-3 packs each previous week. Addictive tendency towards arecanut and gutka was seen one each among users.

Most students (78.5%) obtained money to buy arecanut or gutka packets from their parents. The students were asked whether their parents knew of their chewing habits. Forty (50.6%) parents/guardians were reported to be unaware that their children were consuming arecanut or gutka. Out of the remaining 39 parents/guardians who knew, 84.6% of them ignored the habit according to the respondents. Out of the 79 children who chew either arecanut or gutka, 34 (43.0%) consumed the same product as their family members (P=0.025). Among the 79 consumers, 11(13.9%) were from divorced or sepearted parents (P=0.005). About three fourth students did not know the harmful effects of these products or were under the impression that it was harmless (Table 3).

Most arecanut users (14.7%) felt mood elation, relief from tooth ache (6.6%), improvement in oral hygiene (3.9%) followed by relief from nausea (1.3%) after chewing. Most gutka users (66.7%) felt relieved of tooth ache followed by mood elation (33.3%) after chewing. Oral cavity examination showed 30(39.5%) out of 76 arecanut chewers and 41(13.0%) out of 316 non arecanut chewers had black staining of teeth and this difference was found to be statistically significant (χ^2 =29, P= 0.001) (Table 4). Oral Submucous Fibrosis (OSMF) was seen in a boy who was chewing arecanut everyday for more than 4 years.

Discussion

Total prevalence of arecanut usage among study participants was found to be almost one in every five children however this study was limited to one village and may not be generalisable. Nonetheless the data are comparable to data from Delhi where 21.3% were reported to be chewing arecanut.[12] However the proportions were much lower than those in other studies from the Mariana Islands and in Karachi.[9, 13] The total prevalence of gutka usage of 1.5% in our study was also much lower than in several other studies.[10, 14, 15, 16, 17]

Age of starting the habit among most arecanut users (34.7%) was 13yrs and most gutka users (66.7%) was 13 to 14yrs.

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The first source of information about arecanut or gutka for majority of boys in this study was friends while for girls it was family members. The role of family members and friends influencing the chewing practices of arecanut and gutka in children was supported by several other studies.[3, 13, 14, 16,18,19,20]

In our study the most preferred place for consuming these substances was market place. These places are favourite spots for students as chewing here ensures no fear of being caught by parents or teachers.[14, 15] The next most preferred place was at home. In our study majority of students (48.8%) were consuming these substances for more than a year. Out of the total students taking arecanut or gutka the majority were current users. Compared to other studies the duration and quantity of consumption of arecanut and gutka was less in our study indicating that substance abuse was a less serious problem in our study area.[13,16,17,21,22] The addictive tendency towards arecanut which was 1.3% in our study was comparable to findings of Oakley et al.[9] However the Karachi study found it to be 40.3%.[21]

The main source of money for purchasing arecanut or gutka in our study was family members. Friends were the source of money only in 2.5% of cases. In Oakley et al study 44% students purchased arecanut out of their own pocket money and 10% from parents.[9] In Karachi study 84.4% of students were using the substances with full knowledge of their family.[21] Significant numbers of children were found chewing the same product consumed by any of their family members. Similar observations were made in several other studies.[14, 19, 21, 23]

Our study also found that significant number of chewers were families of divorced or separated parents. This was similar to results of two studies done in Taiwan wherein students whose parents were separated or divorced had a higher prevalence of arecanut usage.[23,24] In a New Hampshire study, poor familial relations and low school satisfaction were found to be the greatest risk factor for school children trying smokeless tobacco.[25] Knowledge regarding health hazards of arecanut or gutka was very poor among students in our study. Very few knew that it leads to cancer and OSMF. In the Karachi study, 98.6% students knew that arecanut is injurious to health, 42.7% knew that it causes cancer and 3.5% knew that it causes OSMF.[21] Almost half of the students in Parwal et al study knew that gutka usage leads to oral cancer.[15]

Misconceptions like feeling elated, relief from tooth ache & nausea, improvement of oral hygiene was seen in few arecanut users. In Oakley et al study users felt arecanut gives relief from boredom (75%), aids in concentration (53%), elates the mood (51%) and postpones hunger (46%).[9] In Gunaseelan et al study 96% of users felt elated and relaxed after arecanut chewing.[3] Misconceptions like feeling relieved of tooth ache and feeling elated as seen among few gutka users in our study was also seen other studies.[14, 16, 26] In addition to this gutka users in Wardha study felt ease of abdominal complaints and in Delhi study felt relieved of morning motions.[14]

Arecanut chewing was found to be significantly associated with black staining of teeth. This was in contrast to several other studies where in arecanut chewing practice was found to decrease dental decay.[27, 28, 29] The prevalence of OSMF found in our study was much less in comparison to 8.8% detected among Northern Mariana high school children.[9] The boy identified with this condition was chewing arecanuts regularly for more than 4 years. Another research study had found that this condition develops after 8.6 years of betel quid-usage which was much earlier to our observation.[30]

Conclusion

Although the overall prevalence of arecanut and gutka usage among school children in our area was not as high as in other studies, their awareness of hazards associated with usage of these substances was found to be very poor. The fact that most users started chewing at a young age, were regular users, few already developing addictive tendencies should be a cause of concern.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests

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Tables

Table 1. Prevalence of arecanut and gutka (contains tobacco) consumption among high school students.

Product	Boys (n=245)		Girls (n=147)		Total(n=392)	
	No.	(P*)%	No.	(P)%	No.	(P)%
Arecanut	64	26.1	9	6.1	73	18.6
Gutka	3	1.2	-	-	3	0.8
Both	3	1.2	-	-	3	0.8
Total	70	28.6	9	6.1	79	20.1

P* - Prevalence

Table 2. Distribution of substance use according to type of user.

Type of user		Arecanut (n=76)		Gutka (n=6)	Combined (n=82)
		Boys %	Girls %	Boys %	Total %
Regular user	Current user	38 56.7	6 66.7	5 83.3	49 59.8
	Others	27 40.3	2 22.2	0 -	29 35.4
Non regular user		2 3.0	1 11.1	1 16.7	4 4.9
Total		67 100.0	9 100.0	6 100.0	82 100.0

Table 3. Awareness of health hazards associated with arecanut and gutka usage.

Response	Towards arecanut usage		Towards gutka usage	
	No.	%	No.	%
Don't know	206	52.5	237	60.5
Harmless	83	21.2	63	16.1
Cancer	39	9.9	42	10.7
OSMF**	-		1	0.2
Other problems	88	22.4	56	14.3

(n=392)

** Oral Submucous Fibrosis

Table 4. Oral Cavity examination findings of study participants.

Tooth lesions	Arecanut users (n=73)	Gutka users (n=3)	Both users (n=3)	Total users (n=79)	Total non users (n=313)
Black Stains	30	2	-	30	41
Cavity	3	-	1	2	15
Yellow Stains	2	1	1	4	-

P= 0.001.

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Areca (betel) nut chewing habit among high-school children in the Commonwealth of the Northern Mariana Islands (Micronesia)

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Objective To investigate the prevalence of its use by high-school children in Saipan in Micronesia. Usage of the areca nut is indigenous to south Asia and the western and south Pacific. Some serious health effects of areca nut chewing are recognized and the International Agency for Research on Cancer has recently classified regular use of areca nut as being carcinogenic to humans. Information on usage by young people, however, is scarce.

Methods Data on consumption of areca nut were obtained by a self-administered questionnaire. Following an oral mucosal examination using WHO criteria any detectable oral mucosal diseases were recorded.

Findings Of 309 schoolchildren surveyed (mean age 16.3 ± 1.5 years), 63.4% claimed regular use, the highest level recorded in any school population survey. Significant oral diseases detected were oral leukoplakia in 13% and oral submucous fibrosis in 8.8% of children.

Conclusion These findings from Saipan suggest that areca nut chewing starts at a young age in Micronesia. As many users develop dependency this raises important concerns regarding its consequences for oral health.

Keywords Areca/adverse effects; Substance-related disorders/ethnology/psychology; Mouth mucosa/physiopathology; Leukoplakia, Hairy/epidemiology/etiology; Oral submucous fibrosis/epidemiology/etiology; Oropharyngeal neoplasms/epidemiology/etiology; Child; Adolescent; Cross-sectional studies; Micronesia (Federated States of) (*source: MeSH, NLM*).

Mots clés Arec/effets indésirables; Troubles liés substance toxique/éthnologie/pychologie; Muqueuse buccale/pathophysiologie; Leucoplasie chevelue/épidémiologie/étiologie; Fibrose buccale sous-muqueuse/épidémiologie/étiologie; Tumeur oropharynx/épidémiologie/étiologie; Enfant; Adolescent; Etude section efficace; Micronésie (Etats fédérés de) (*source: MeSH, INSERM*).

Palabras clave Areca/efectos adversos; Trastornos relacionados con sustancias/etnología/psicología; Mucosa bucal/fisiopatología; Leucoplaquia vellosa/epidemiología/etiología; Leucoplaquia vellosa/epidemiología/etiología; Fibrosis bucal submucosa/epidemiología/etiología; Neoplasmas orofaríngeos/epidemiología/etiología; Niño; Adolescente; Estudios transversales; Micronesia (Estados Federados de) (*fuente: DeCS, BIREME*).

Arabic

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Voir page 659 le résumé en français. En la página 659 figura un resumen en español.

Introduction

The adverse health effects associated with areca (betel) nut use include oral and oropharyngeal cancer, oral premalignant lesions and conditions (oral leukoplakia and submucous fibrosis), gum disease and addiction (*1*, *2*). Chewing areca nut is widespread in south Asia and in the Pacific region (*3*). A study in Papua New Guinea has reported that areca nut use is highly prevalent among adults in Melanesia (*4*). In Taiwan, China, where the habit is practised widely, particularly in the aboriginal areas (*5*), many reports suggest that this chewing habit starts at a young age (*6–9*).

Guam, the Commonwealth of the Northern Mariana Islands (CNMI), Republic of Palau, the Federated States of Micronesia and the Republic of the Marshall Islands belong to the geographical area of Micronesia which covers a large portion of the central and western Pacific Ocean. Apart from their geographical separation from Melanesia and Polynesia, the Micronesians are distinct in their physical appearance. In addition, each island group represents a unique culture with specific customs.

Together Guam and the CNMI form the Northern Mariana Island chain which extends in a north–south direction

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between the equator and Japan. The CNMI is an unincorporated territory of the USA and consists of 14 principal islands, three of which are inhabited. Saipan, 12.5 miles long and 5.5 miles wide, is the CNMI's largest island and is home to 90% of its population (about 58 000 people in 1995). The indigenous ethnic group are the Chamorro people, who comprise approximately 60% of the population. In the late nineteenth century a migration of islanders from the Caroline Islands (now the Federated States of Micronesia) occurred. The descendants of these immigrants are called Carolinians. Due to the proximity of the CNMI to Asia, there is also a large representation of other racial groups such as Chinese, Filipinos, Japanese and people from the Republic of Korea.

Areca nut use among the inhabitants of Guam has been reported to be widely prevalent (*10*). In Guam, areca nut (pugua) chewing is an old tradition, particularly among Chamorro people (the indigenous people of Guam and Saipan) (http://ns.gov.gu/pugua.html). Most of the chewers in the islands surrounding Micronesia use the soft immature nut, split open and filled with lime (calcium hydroxide) and wrapped with piper betel leaf. Chamorros traditionally chewed the hard mature nut with lime with or without the leaf. The chewing habits among adolescents in Micronesia have not been reported. We conducted a cross-sectional study on high-school students in Saipan with the objective of describing the prevalence, correlates of use, reasons for chewing and reasons for disliking the habit, and to characterize the associated clinically detectable oral mucosal lesions.

Materials and methods

Sample

On Saipan there are three public high schools with a total of 2415 students of whom 1186 are female and 1229 are male. Several small private high schools, all religion-based, were excluded from the study. Permission to undertake the study in the three schools was obtained from the school authorities. Information about the study and consent forms were sent to the parents and legal guardians by schoolteachers and collected prior to the study. Participation was voluntary. All consenting students (with the signed consent of their parent(s) or guardian(s)) who attended the school on the days of the examinations and were physically present in the science classroom in each school at the time of the visits by the research team participated in the study. The mean age of the high-school students was 16 years (range 14–18 years).

During 2004, the three schools were visited by a dentist who acted as a screener and a registered dental hygienist who administered the questionnaire to the participants. The 15-item questionnaire was self-completed by students during class time under the supervision of the dental hygienist. The dentist was blinded as to the responses to the questionnaire. Altogether four visits were made to the schools to collect data.

Questionnaire

Questions on demographic characteristics, areca nut use, daily frequency of use, other ingredients mixed with nut (e.g. leaf and lime), tobacco use (smoking and/or chewing), age of initiation of nut chewing, reasons for use, social influence factors, risk perceptions and reasons for disliking the habit were included in the study questionnaire. The questionnaire (available on request from the authors) was developed on the basis of a previous study undertaken on Asian schoolchildren by one of the authors (*11*). The questionnaire was administered in English as the school classes are taught in English, and this is the spoken language, although many students also speak one of the other two languages, i.e. Chamorro and Carolinian.

The age of initiation of areca nut use was taken as first age of regular nut use. Patterns of nut use were established according to the other ingredients added to the quid. The questionnaire also presented a list of reasons for chewing areca nut which had to be answered with either yes or no. The source of nut was established as: own purchase, from parents, friends, plucked off the trees, or other, to collect information on sharing of the habit with parents or friends. Finally we asked an open question about knowledge and beliefs regarding the adverse health effects associated with nut use and any reasons for not chewing. Information on tobacco smoking or chewing, and alcohol use was also collected.

Clinical examination

All oral examinations were done by one specialist examiner who was familiar with oral mucosal lesions in the local population. The students were seated on a school chair and lighting was provided by a handheld halogen diving light. A sterile mouth mirror was used for retraction of tissue, and where necessary sterile packs of gauze were used. WHO criteria for the detection of oral mucosal lesions were used (*12*), and mouth opening (inter-incisal distance) was measured in millimetres using a sterile metal ruler to establish any limitation of opening to confirm oral submucous fibrosis. The location and description of oral lesions noted were charted, and if a lesion was found, the parent or guardian was informed.

A brief education programme followed immediately after the screening to encourage schoolchildren to quit their habits.

Data analysis

Data were entered on an Excel worksheet, and frequency distributions of areca nut, tobacco and alcohol use by this group of schoolchildren, together with other variables, were estimated. The present focus is on the description of risk factors and the prevalence of oral mucosal diseases in the population under study.

Results

Data were collected on the 309 high-school students who participated in the study. Of these, 153 were male and 156 female and their mean age was 16.3 ± 1.5 years (Table 1). Most children were from the Chamorro tribe (n = 128; 41%) and other ethnic groups included Carolinian (16%), Filipino (14%) and Palauan (9%).

The lifestyle habits as shown by the percentage distributions are described below. A total of 169 students (63.4%) claimed to use areca nut regularly (Table 1). The habit was more prevalent among male students (73% of males versus 54% of females). There were some variations in the prevalence of chewing habits in the three schools visited; the means ranged from 52.8–85.9%. Two students were chain-chewers and 21 (7%) reported chewing more than 20 areca quids per day. The preferred nut was the soft variety and most schoolchildren added powdered lime to the quid mixture. Piper betel leaf was also often consumed with the nut. The mean age of initiation of areca nut chewing was 12.0 years, and 60 students had started the habit at 10 years of age or younger.

Table 1. Age, sex and characteristics with reference to tobacco, alcohol and areca nut use

School	*n*	Mean age	Smokers (%)	Alcohol users (%)	Areca nut chewers (%)	Tobacco/snuff users (%)
1	40	15.4 ± 1.1	25.0	27.5	52.5	22.5
2	78	17.4 ± 1.3	32.1	41.0	85.9	20.5
3	191	16.1 ± 1.4	22.0	20.0	56.5	15.1
All	309	16.3 ± 1.5	24.9	26.2	63.4	17.5

Tobacco use was also widely prevalent among these schoolchildren; almost a quarter of students of both sexes reported smoking tobacco. Tobacco chewing and/or snuff dipping was practised by 17.5%. Alcohol drinking was reported by 26% of high-school students, and the habit was more prevalent among male students (37% of males versus 15% of females).

The percentage distribution of answers on the source of betel nut for individual consumption was examined. The majority (44%) bought areca nut out of their own pocket money. Just over 10% reported being supplied by their parents and there was some sharing of the nut with friends (25%). Some students (9%) had access to the nut from home-grown trees from which they plucked the nuts themselves.

The results from the attitude section of the survey are shown in Table 2, which lists the reasons that users gave for chewing betel nut. Overall, the five most common reasons given were: craving for the nut, boredom, as an aid to concentration, at times of unhappiness and to postpone hunger. Very few used it to refresh their breath or to look mature and none used it to look good.

Among non-users the reasons given for dislike of the habit were stained teeth, offensive breath following chewing and poor appearance due to staining of teeth. Eight out of 160 (5%) who answered the section on beliefs were aware that areca nut could cause oral cancer and one mentioned that the parents did not approve of chewing. Eight mentioned that the quid burned their mouths, probably related to the addition of lime to the nut.

A considerable number of students with associated oral pathological lesions and conditions were noted during the screening examination (Table 3) and a disturbing number of children (12.9%) had oral leukoplakia. These lesions could either be related to tobacco (smoking or chewing) or areca nut chewing, as all students in whom leukoplakia was detected reported indulging in both habits. A condition more specific to areca nut chewing was oral submucous fibrosis with submucosal banding which was found in 27 (8.8%) of schoolchildren; nine had established features (mouth opening < 40mm) and 18 had early features of fibrosis.

Discussion

Areca nut is the fourth most commonly used substance of abuse in the world after tobacco, alcohol and caffeine (*13*). Culturally associated health-risk behaviours, which contribute to morbidity and mortality in later life, often are established during youth, extend to adulthood, are interrelated and are preventable. In this point-prevalence study, 63% of Saipan children in high schools were regular chewers of areca nut. In the neighbouring Republic of Palau, the Youth Tobacco Survey of 2001 (http://www.cdc.gov/tobacco/global/gyts/reports/pdf/palau.pdf) recorded a similar prevalence of chewing among Palau's children. Compared with Taiwan, China (*6, 7, 9*) and Asian migrant schoolchildren (*11*) the prevalence of areca nut chewing recorded in the present study in Micronesia was considerably higher. A high proportion of chewers in Sapian also smoked tobacco and consumed alcohol regularly.

Habituation and addiction to areca nut have been reported in Papua New Guineans (*4, 14*) among aborigines of Taiwan, China (*15*), and among immigrants living in the United Kingdom (*16*). It is likely that children who are regular chewers at school-leaving age will be dependent on the nut and continue the chewing habit into their adult life, unless an appropriate intervention is made.

It was alarming to note the development of oral mucosal lesions in these schoolchildren, associated with the habit of areca nut chewing and tobacco use. Betel chewers' mucosa, oral leukoplakia and oral submucous fibrosis are well characterized as oral lesions caused by chronic use of this substance (*1, 2, 17–19*). Oral submucous fibrosis, a potentially malignant condition leading to considerable disability is specifically caused by areca nut chewing (*20*). The carcinogenicity of the nut has been proven in experimental systems (*21*) and more recently people who chew the nut have been shown to have a significantly increased risk of oral and oropharyngeal cancer (*2*). The International Agency for Research on Cancer has therefore re-affirmed that areca nut is carcinogenic to humans (*2*). Starting the habit at a young age significantly increases the risk of cancer in the population as many of these carcinogens

Table 2. Reasons for chewing areca nut given by high-school students*

Reasons for chewing	School			All
	1	2	3	
Craving	9	33	50	92
Boredom	7	26	42	75
Aid to concentration	8	22	23	53
When unhappy	6	17	28	51
Postpone hunger	6	15	25	46
Taste	7	19	8	34
Do something with mouth	3	13	13	29
Custom	6	11	12	29
Pleasure	2	12	14	28
Snack	1	10	5	16
Refresh breath	0	0	5	5
Look mature	0	1	1	2
Look good	0	0	0	0
No replies	20	4	81	105

* Multiple responses were recorded.

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Table 3. Oral lesions and conditions related to chewing areca nut

Oral lesions	School 1 ($n = 40$)	School 2 ($n = 78$)	School 3 ($n = 191$)	All (%) ($n = 309$)
Chewer's mucosa	2	19	11	32 (10.3)
Lichenoid lesion	0	6	9	15 (4.8)
Leukoplakia	4	17	19	40 (12.9)
Oral submucous fibrosis	4	13	10	27 (8.8)

take several decades to exhibit their mutagenic action. It is important to note that cessation of the habits can lead to resolution of some oral lesions or a decrease in the severity of oral symptoms (*22*).

Following migration from south Asia and the western Pacific to both Europe and North America the habit has remained prevalent among new settlers (*11*, *23*). The health consequences of areca nut chewing should therefore be recognized in these migrant communities that have settled in other parts of the world.

In a study of cancer trends in Guam from 1971 to 1995, a continued high incidence of oral cancer on Guam, particularly among Chamoru people was reported among habitual users of betel nut (*24*). The authors concluded that it therefore seems reasonable at least to try to discourage the adoption of this habit by young people.

The big challenge therefore is to discover effective strategies to motivate young children not to initiate the habit, and to enable adolescent children to realise the potential health risks of this substance. Among the opinions concerning factors that discouraged areca nut use in this study group it is striking that substantial numbers believed that staining of teeth, leading to poor aesthetics was a social problem among chewers. Young people differ from adults in the ways they perceive and interact and it is of interest to note that dental aesthetics was a factor that discouraged them to chew, a factor not suggested by studies in older adults (*25*). School health education programmes in the future should capitalize on such views of schoolchildren in efforts to emphasize important health-related messages. ■

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Résumé

Chique des noix d'arec par les élèves d'établissement d'enseignement secondaire du Commonwealth des Mariannes du Nord (Micronésie)

Objectif Étudier la prévalence de la chique de noix d'arec chez les élèves des établissements d'enseignement secondaire de Saipan en Micronésie. L'utilisation de la noix d'arec est une pratique locale en Asie méridionale et dans le Pacifique Ouest et Sud. On reconnaît à cette pratique certains effets graves sur la santé et l'Agence Internationale pour la recherche sur le cancer a récemment classé l'usage régulier de la noix d'arec comme cancérogène pour l'être humain. Les données concernant cet usage chez les jeunes sont cependant rares.

Méthodes Des données sur la consommation de noix d'arec ont été recueillies à l'aide d'un questionnaire auto-administré. Après examen de la muqueuse buccale selon les critères de l'OMS, toutes les pathologies détectables de cette muqueuse ont été enregistrées.

Résultats Parmi les 309 élèves soumis à l'enquête (âge moyen 16,3 ± 1,5 ans), 63,4 % ont indiqué un usage régulier, ce qui représente la proportion la plus élevée relevée dans une enquête sur une population scolaire. Les affections bucco-dentaires importantes détectées étaient la leucoplasie orale dans 13 % des cas et la fibrose buccale sous-muqueuse chez 8,8 % des enfants.

Conclusions Les résultats obtenus à Saipan laissent à penser que la chique de noix d'arec débute à un âge précoce en Micronésie. Compte tenu de la proportion élevée d'utilisateurs développant une dépendance, ces résultats suscitent de fortes préoccupations à l'égard des conséquences pour la santé bucco-dentaire de cette pratique.

Resumen

Estudio de la costumbre de mascar nuez de areca (betel) entre los escolares de secundaria de la Mancomunidad de las Islas Marianas Septentrionales (Micronesia)

Objetivo Investigar la prevalencia de ese hábito entre los escolares de secundaria de Saipan, en Micronesia. El mascado de nuez de areca es una costumbre autóctona de Asia meridional y el Pacífico occidental y meridional. Se sabe que ese hábito tiene algunos efectos graves en la salud, y el Centro Internacional de Investigaciones sobre el Cáncer ha clasificado recientemente el uso regular de la nuez de areca como hábito carcinogénico en el ser humano. No obstante, la información disponible sobre la frecuencia de esa práctica entre los jóvenes es escasa.

Métodos Los datos sobre el consumo de nuez de areca se obtuvieron mediante un cuestionario autoadministrado. Tras examinar la mucosa oral utilizando criterios de la OMS, se registraba cualquier signo detectable de enfermedad de la mucosa.

Resultados De los 309 escolares encuestados (edad media: 16,3 ± 1,5 años), un 63,4% declararon consumir regularmente betel, lo que constituye el nivel más alto registrado hasta la fecha en una población escolar. Como enfermedades bucodentales importantes se detectaron leucoplasia oral en un 13% de los niños, y fibrosis submucosa oral en un 8,8%.

Conclusión Estos resultados de Saipan indican que la costumbre de mascar nuez de areca se inicia a edades tempranas en Micronesia. Dado que muchos de los mascadores desarrollan dependencia, las posibles consecuencias para la salud bucodental suscitan gran preocupación.

Arabic

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Areca nut habits amongst children in Tower Hamlets, London

Prevalence, age of onset and demographic relationships of different areca nut habits amongst children in Tower Hamlets, London by P. Farrand, R. M. Rowe, A. Johnston, and H. Murdoch Br Dent J 2001; 190: 150-154

Objective
To examine prevalence and demographic relationships of different areca nut habits amongst children.

Design
Self-administered questionnaire.

Subjects
Children aged between 11 and 15. Of 800 questionnaires distributed, 704 were fully completed (88%).

Setting
Two secondary schools in the London district of Tower Hamlets.

Measures
Demographic, areca nut habits used, age first used, still using, frequency of use.

Results
Users of any areca nut habit were exclusively from the South Asian population. Of this population, 77% had engaged in a habit, and dependent upon habit between 54 and 92% of these still remained current users. The highest prevalence of current use for boys and girls respectively was for areca nut alone (36%, 43%), followed by mistee pan (35%, 29%), betel-quid (27%, 26%) and pan masala (14%, 16%). Of the current users, 44% engaged in one habit only, 24% two, 20% three and 13% all four. The highest period of risk for starting to use areca nut alone, betel-quid and mistee pan was between ages 5 and 12, whilst for pan masala it was after 10. Boys had a significantly higher risk of beginning use before 10 ($P < .001$) and a higher frequency of use for pan masala ($P < .01$), areca nut alone ($P < .05$) and betel-quid ($P = .06$) than girls. The frequency of using each habit was between 3 and 5 episodes per week, however boys use pan masala approximately 10 times per week.

Conclusion
South Asian children may already be experienced users of areca nut. Greater attention should be directed towards identifying signs of oral submucous fibrosis, oral cancer and other potentially malignant lesions within the South Asian population.

In Brief
- A high proportion of children with a South Asian ethnic origin may already be experienced users of an areca nut habit (areca nut alone, betel-quid, pan masala, mistee pan). The highest period of risk for starting to engage in an areca nut habit is between ages 5 and 12.
- Boys represent a particular cause for concern. They have a higher risk of beginning use earlier and a higher frequency of use than girls, although frequency of use amongst both is low.
- GDPs should pay special attention for signs of potentially malignant lesions and oral cancer in South Asian children. This should accompany health promotion strategies.

Comment

This paper reports the outcomes of a questionnaire investigating self-reports of four variants of areca nut consumption in a large sample of 704, largely Bangladeshi, children aged 11–14 years. Areca nut consumption by itself is the most common habit, consumed by 36% of boys and 43% of girls respectively. The consumption frequency of all variants was low, ranging from three to five weekly episodes, with the exception of pan masala (a proprietary form of betel-quid or paan) which was consumed by boys 10 times per week.

The authors acknowledge that at these levels of consumption there appears little health risk of oral sub-mucous fibrosis from these items alone. The authors were not able to collect data about the addition of tobacco to these products. There has been a developing concern in the UK about the health compromising aspects of consumption of gutkha — which includes tobacco — by children from South Asian communities.[1] This paper helps to contextualise these concerns. Thirty five per cent of boys and 29% of girls reported themselves as current chewers of mistee pan (commercially prepared areca nut 'sweets') which, the authors note, might also include gutkha.

The findings demonstrate the difficulty of understanding complex, traditional behaviours using self-complete questionnaires. Areca nut preparation and consumption in betel quid or paan has traditionally been according to individual preference. As this investigation reports, proprietary variants are now being developed, packaged and sold under a range of trade names. This leads, as the authors recognise, to variation in terminology and content.

Health promotion strategies are recommended. This might include health education within schools. These young consumers could be advised to read the labels of products to find out their contents. The value of this advice is questionable: inadequate labelling information and inappropriate composition of the proprietary variants has been identified.[2] Regulations are available to address these manufacturing deficiencies.[3,4]

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Areca nut and betel quid chewing among South Asian immigrants to Western countries and its implications for oral cancer screening

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Abstract

The South Asian community is the largest and one of the fastest growing minority groups in Canada, according to the 2006 census. These immigrants bring to Canada talents and skills that can promote Canada's economy and cultural diversity, but they also bring lifestyle habits that may lead to serious health issues. Chewing areca nut and betel quid (*paan*, with and without tobacco) is a known risk factor for oral cancer. This habit is common in the Indo-Canadian population, as evidenced by its sales in local Indian markets and restaurants. In this article, we present an overview of the sociocultural beliefs, knowledge and practices regarding betel quid/areca nut chewing, and discuss its implications for oral cancer screening among this immigrant population.

Keywords

betel quid/areca nut chewing; cancer screening; oral health; rural immigrants

Global usage of betel quid and areca nut

Globally, areca nut is among the most common addictions following tobacco, alcohol and caffeine. Its usage is very popular in India, Taiwan and parts of Southern China[1]. Its chronic use contributes significantly to the high incidence of oral cancer in these countries. With increasing immigration of Indians to the Western world, health professionals in the west should be aware of the habit and its consequences and so be prepared to face the challenges associated with the habit and resulting disease.

Studies from the US and UK have reported the persistence of areca nut chewing among immigrants from South Asia, resulting in increased rates of oral cancer in these new settlements[2–7]. Awareness of this practice should help health professionals to understand the relevance of oral cancer screening in this population.

Chewing habits and risk for oral cancer among South Asian immigrants

Areca nut is present in a number of chewing products, for example, *paan* (betel quid), *gutka* and paan masala (Table 1). These products contain lime, area nut and tobacco. Betel quid consists of a mixture of areca nut (with or without tobacco), slaked lime, catechu and several condiments according to taste, wrapped in betel leaf. While areca nut chewing may cause oral submucous fibrosis, its use along with tobacco can cause leukoplakia, which is also a premalignant lesion. Use of other condiments and ingredients in betel quid can cause lichenoid lesions[8], the premalignant potential of which is not known.

In the last few years small attractive and inexpensive sachets of betel quid substitutes have become widely available, are aggressively advertised and marketed and are consumed by the

very young and old alike. These products have higher genotoxic and carcinogenic potential compared with conventional quids[9]. Chewing of these products usually starts at an early age (at approximately 13 to 15 years) and, by adulthood, most users are addicted to the habit[10]. Older adults are not alarmed by the fact that young children are indulging in this habit as they consider it a part of their normal life[10]. However, this practice often leads to addiction and, once the habit is formed, it persists after immigration.

Betel quid substitutes contain both carcinogens and genotoxic agents which have role in multistage progression of oral cancer[11]. Smokeless tobacco contains nitrosonornicotine and 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone; areca nut contains arecoline and 3-(methylnitrosamino) propionitrile, while lime provides reactive oxygen radicals, each of which has a role in oral carcinogenesis[9].

Chewing betel quid without tobacco is an independent risk factor for developing oral cancer[12]. When betel quid with tobacco is consumed with alcohol and smoking the relative risk increases 11-fold[13]. The risk of such interactions may be underestimated in some South Asian communities. For example, Sikhism and Punjabi religious beliefs prohibit alcohol and tobacco use[14]; however, there are reports of alcohol[15] and tobacco consumption among them[16].

Betel quid chewing seriously affects oral and periodontal health with higher oral hygiene index scores, increased periodontal pocket depth and bleeding causing poor oral hygiene[17,18]. There is not enough evidence to suggest that poor hygiene alone in absence of habits and other risk factors has a role in etiology of oral cancer.

It is important, however, to remember that the South Asian community is not homogenous, for it has people from diverse cultures who have distinct beliefs and practices. The extent of areca nut chewing varies among different religious groups and among first and second generation immigrants. A study from Leicester, UK, reported that areca nut chewing was most common among first generation Asian immigrants with the highest prevalence among Jains (28%) and Muslims (23%), followed by Hindus (18%). In second generation Asian immigrants, this practice was highest among Muslims (17%), followed by Hindus (13%) and Jains (12%)[15].

It is interesting that the proportion of individuals chewing areca nut was reduced in generations subsequent to immigration. However it is a concern that the traditional habit of spitting out the contents of betel quid has also changed, and it is now being swallowed in Western countries. This change in habit may increase the risk of hypopharyngeal and esophageal cancer[19].

Sociocultural reasons for chewing areca nut

Four factors form the foundation for the popularity of chewing areca nut and betel quid chewing: social acceptability, religious beliefs, perceived health benefits and addiction.

Areca (betel) nut is regarded by many Indians as a fruit of divine origin. It is considered an auspicious ingredient in Hinduism and is used along with betel leaf in religious ceremonies and when honoring individuals. Among the followers of the Hindu religion, areca nut (*Supari*) is considered a vital ingredient in the food for God (*Bhagwan*). In the absence of idols and other sacred images, the fruit (whole nut without its husk) is used while offering prayers. It is believed that God blesses the fruit which is then distributed to the followers[20,21]. With the religious and health beliefs regarding areca nut being so prevalent in many Indian cultures, areca nut is very commonly offered at important social gatherings and weddings[21].

In addition to its religious connotations, areca nut is regarded by many people in South Asia as good for health, and it is used as a traditional ayurvedic medicine. It is used as an astringent,

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mouth freshener after meals; a taste enhancer, purgative and intoxicant; and for indigestion, impotence and gynecological problems, parasitic intestinal infection and for prevention of pregnancy-related morning sickness[22].

Areca nut is often chewed in a betel quid and is used as a mildly euphoric stimulant because it contains relatively high levels of psychoactive alkaloids. Chewing also increases the capacity to work, causes a hot sensation in the body and heightens alertness. It is also used among the poor to avoid boredom and to suppress hunger[20,22,23]. A study in the United Kingdom (UK) reported that 42% of South Asian immigrants (from Bangladesh) chewed areca nut because it gave them a refreshing feeling and 35% because of its good taste; 29% used it as a snack, and others used it because it helped to relieve stress and was believed to strengthen the teeth and gums[24].

Lack of awareness about areca nut as a risk factor for oral cancer

South Asian communities are generally not aware that areca nut chewing can cause oral cancer and that ceasing its use would reduce the likelihood of developing oral cancer[15,25]. A study in the UK showed that many Bangladeshi adolescents living in East London were unaware of the association between areca nut chewing and oral cancer[24].

Reports also suggest that many shopkeepers selling these chewing products are not aware of any health risks and there are no restrictions placed on sale of these products to minors[2]. Those shopkeepers aware of health risks continue selling these products because it has become a multimillion dollar industry[23].

Oral precancerous lesions in South Asian immigrants

Globalization and increased movement of people across boundaries has resulted in changes in the patterns of oral diseases. Historically, oral submucous fibrosis (a premalignant condition) was endemic and limited to South Asia and some parts of China and Taiwan. But with increasing numbers of South Asian immigrants in Western countries this pattern is changing. There were no case reports of oral submucous fibrosis in South Asian immigrants until the mid-1980s. Interestingly, this time period coincides with increased immigration from South Asia to these countries. Most reports have come from the UK, although there are some case reports from Canada, Germany, France, Australia and South Africa (Table 2). There is also a Canadian report of a child of Indian origin who developed oral pre-cancer at the age of 4 years, possibly due to early exposure to areca nut, as its consumption is socially accepted in the South Asian community at any age[26]. Therefore, the practice of areca nut chewing and the presence of oral precancerous lesions are spreading from South Asia to the Western countries, with the potential of becoming a major public health issue.

Oral cancer rates among South Asians in many countries such as the UK[36,37] and USA[38] are higher than in the general population, and this may be attributable to the continuation of habits among South Asians after migration.

A descriptive study is in progress of oral cancer cases from the British Columbia (BC) Cancer Registry from 1980 to 2006, and our initial results suggest that age-adjusted incidence rates among South Asians are higher than the general population, at 5.63 (95% CI; 2.02–9.63) for South Asian men as compared with 4.32 (95% CI; 3.86–4.78) in the general male population and 4.41 (95% CI; 1.17–7.79) for South Asian women as compared with 2.73 (95% CI; 2.37–3.08) in the general female population (authors' pers. data; 1980–2006). This translates to relative risks of 1.33 and 1.66 for South Asian men and women, respectively, as compared with the BC general population.

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Although South Asian immigrants maintain higher rates of oral cancer as compared with the general population, these rates are still below the oral cancer rates in their home countries (for men, the age-adjusted incidence rate is 12.8 and for women, it is 7.5)[39]. These comparisons need to be interpreted with caution, however, because there are no national cancer registries and the incidence varies among different regions/ states in India.

Our observation that oral cancer frequently occurs in the cheek and gums of South Asians (authors' pers. data; 2006) is also consistent with this risk behavior. This finding has been reported elsewhere[40,41].

Implications for oral cancer screening in South Asian Immigrant communities

Oral cancer is commonly found in India and this elevated risk is also brought to the west by its immigrants. A special report on Indian immigrants from census data suggests that the majority of immigrants from India to Canada come under family class immigration and not as business and independent skilled labor worker class[42]. Many of the Indian immigrants do not have proficiency in either of the Canadian official languages (English and French). Immigrants from India often choose to live on the outskirts of cities because the majority were engaged in agricultural and manufacturing industries. Data available for South Asian immigrants to BC showed that only 24% reported Vancouver as their intended destination, while the majority of Indian immigrants preferred to stay in the outskirts of Surrey and Abbotsford[42]. Few physicians are aware of the habits of betel quid chewing that may be practiced among immigrants living in rural and remote areas.

South Asian immigrants do not feel culturally safe and comfortable with visits to doctors and dentists of a different ethnic background and communication may be limited and sometimes ineffective[43]. Culturally insensitive behavior from the healthcare provider may offend immigrant patients, hampering healthcare delivery.

The concept of screening an otherwise healthy individual for asymptomatic disease is not a concept well understood by many South Asian immigrants[44]. In addition, those practicing potentially harmful oral habits may be less likely to participate in oral cancer screening initiatives; hence, special efforts may be required to reach these individuals. The screening examination provides an excellent opportunity for education about risk behaviors, including areca nut chewing, and interventions to help change such behaviors. Early signs of oral submucous fibrosis include blanching of oral mucosa, rigidity and fibrosis of tissues, restricted mouth opening and loss of cheek elasticity[45] should be examined for while screening patients in this population.

Future strategies

In some of the South Asian communities, areca nut and betel quid (paan) chewing is a routine daily practice and an important component of social life and cultural identity. South Asians are now one of the largest minority groups in Canada with approximately 1 262 900 people, according to census reports[46]. It is important to study risk behaviors, beliefs, knowledge levels and oral health practices in this population. Further research is required to understand in depth the beliefs of people as they relate to this habit; as well as to enquiring into potential barriers and facilitators for participation in oral cancer screening, and discovering what educational messages should be made for health promotion and education among this community. This information is critical to developing and implementing health education programs appropriately targeted to the needs of the South Asian community. Healthcare providers must also be aware of these risk behaviors and alert to the presence of oral precancerous lesions, such as oral submucous fibrosis, that are becoming important clinical findings in many Western countries.

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Table 1

Areca nut chewing: its contents and practice

Local or common name	Content	Habit as practiced
Mawa	A thin shaving of areca nut with tobacco and slaked line, sold in cellophane papers.	Before consumption, the cellophane pouches are rubbed to mix the contents, which are kept in the mouth in the vestibule and chewed slowly.
Paan	Also known as betel quid, has 4 main ingredients: tobacco, areca nuts and slaked line wrapped in betel leaf. May also contain cardamom, coconut, cloves and sugar.	All ingredients are chewed slowly. The contents with the juices are either swallowed or spat out of the mouth.
Gutkha	A powdered mixture of tobacco, areca nut and slaked lime with spices and flavoring agents.	The powder is placed in the mouth and slowly chewed. Contents are usually swallowed
Paan masala	A powdered mixture of areca nut and slaked lime with spices and flavoring agents.	The powder is placed in the mouth and slowly chewed. Contents are usually swallowed.
Khaini	Tobacco leaves mixed with lime.	The dried tobacco leaves are hand-mixed with lime and made into a bolus that is placed in the mouth, either in the vestibule or below the tongue.

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Table 2

Review of cases with oral precancerous lesions among South Asian immigrants[3,4,6,7,15,25,26–35]

Country [reference number]	Year of study	Ethnic group of patients
Canada [26–28]	1985, 1987	Indian
United Kingdom [6, 7, 15, 25, 29–31]	2007, 2006, 1999, 2000, 1984, 2001, 2002	Bangladeshi, Indian, Pakistani
Germany [32]	2006	Indian
Australia [33]	1992	Indian
France [34]	1986	Indian
South Africa [35]	1984	Indian
USA [3,4]	2005, 2006	Bangladeshi

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