SUPREME COURT VOLUME-4

ANNEXURES

SLP (C) No. 16308/2007-Ankur Gutkha Vs Indian Asthama Care Society & Ors-regarding.

British Journal of Cancer (2001) 85(5), 661–667
© 2001 Cancer Research Campaign
doi: 10.1054/ bjoc.2001.1920, available online at http://www.idealibrary.com on IDEAL
http://www.bjcancer.com

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

RK Phukan[1], MS Ali[2], CK Chetia[3] and J Mahanta

[1]Regional Medical Research Centre, Indian Council of Medical Research, Dibrugarh, North East Region, Assam, India; [2]Hospital Tumour Registry, Indian Council of Medical Research, Assam Medical College, Dibrugarh, Assam, India; [3]Department of Statistics, Dibrugarh University, Dibrugarh, Assam, India

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

Received 16 November 2000
Revised 27 April 2001
Accepted 27 April 2001

Correspondence to: J Mahanta

715

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, pre-tested 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(β)) 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.

I16

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 (1.4–7.6)	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).

717

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 (2.2–13.8)	<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				
	Ca/Co	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value
NCh & NAD	22/218	1			
Chadha	16/35	4.5 (1.6–10.3)	0.003	3.8 (1.9–8.5)	0.003
Chadha+NCAD	19/28	6.7 (2.8–14.4)	< 0.001	6.1 (2.6–12.8)	0.004
Chadha+PA	15/23	6.5 (2.4–15.2)	< 0.001	5.3 (2.2–13.1)	0.002
BL+R/GBN	21/53	3.9 (1.4–12.6)	0.008	2.8 (1.3–7.5)	0.06
BL+R/GBN+NCAD	26/41	6.3 (2.5–11.4)	0.002	5.6 (2.2–9.6)	0.004
BL +R/GBN+PA	14/25	5.5 (1.9–10.8)	< 0.001	4.2 (1.8–10.5)	< 0.001
BL+UGBN	22/58	3.8 (1.2–9.6)	0.004	3.1 (1.6–8.5)	0.002
BL+UGBN+NCAD	39/46	8.4 (3.4–14.5)	< 0.001	6.2 (2.4–11.3)	< 0.001
BL+UGBN+PA	20/41	4.8 (1.6–11.2)	0.001	3.6 (1.7–9.5)	< 0.001
BL+R/GBN+D	21/38	5.5 (2.3–11.8)	< 0.001	5 (1.7–10.6)	< 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
BL+R/GBN+D+PA	12/22	5.4 (1.8–10.6)	< 0.001	4.8 (1.7–9.3)	< 0.001
BL+UGBN+D	26/20	12.9 (3.2–18.5)	< 0.001	10.3 (3.6–20.8)	< 0.001
BL+UGBN+D+ NCAD	31/14	21.9 (7.5–32.4)	< 0.001	18.5 (5.6–27.3)	< 0.001
BL+UGBN+D+PA	12//15	7.9 (1.9–14.5)	< 0.001	6.3 (2.5–14.7)	< 0.001
BL+SBN+Z	9//6	14.9 (4.6–22.8)	< 0.001	8.4 (2.6–17.5)	< 0.001
BL+SBN+Z+NCAD	6//3	19.8 (5.3–28.6)	< 0.001	12.1 (4.3–21.4)	< 0.001
BL+SBN+Z+PA	7//4	17.3 (4.2–24.5)	< 0.001	13.6 (4.6–22.5)	< 0.001

	Female				
	Ca/Co	OR (95% CI)	*P* value	Adj OR (95% CI)	*P* value
NCh & NAD	28/149	1			
Chadha	7//6	6.2 (2.4–15.9)	<0.001	5.8 (2.1–12.4)	< 0.001
Chadha+NCAD	4//3	7.1 (2.8–19.7)	< 0.001	6.3 (2.4–14.3)	< 0.001
Chadha+PA	3//3	5.3 (1.5–16.3)	< 0.001	4.4 (1.7–9.5)	< 0.001
BL+R/GBN	10//27	2 (0.7–8.5)	0.04	1.4 (0.3–6.5)	0.24
BL+R/GBN+NCAD	7//20	2 (0.3–10.6)	0.08	1.6 (0.2–9.3)	0.41
BL +R/GBN+PA	6//12	2.7 (1.1–9.5)	< 0.01	1.7 (0.6–8.5)	0.15
BL+UGBN	9//15	3.2 (1.8–11.5)	< 0.001	2.4 (0.9–7.2)	< 0.01
BL+UGBN+NCAD	7//10	3.7 (1.3–10.7)	< 0.001	2.1 (1.3–5.4)	0.04
BL+UGBN+PA	5//9	3 (1.5–8.6)	< 0.001	1.9 (0.4–7.5)	0.09
BL+R/GBN+D	8//8	5.3 (1.7–10.8)	< 0.001	4.2 (1.6–10.5)	< 0.001
BL+R/GBN+D+ NCAD	7//6	6.2 (2.3–14.2)	< 0.001	5.6 (2.3–12.4)	< 0.001
BL+R/GBN+D+PA	5//3	8.9 (2.4–19.8)	< 0.001	7.3 (2.6–10.3)	< 0.001
BL+UGBN+D	12//5	12.8 (4.2–20.8)	< 0.001	10.4 (2.6–18.5)	< 0.001
BL+UGBN+D+ NCAD	9//3	16 (8.3–26.4)	< 0.001	13.5 (3.1–20.6)	< 0.001
BL+UGBN+D+PA	5//2	13.3 (5.4–21.6)	< 0.001	10.6 (3.2–18.2)	< 0.001
BL+SBN+Z	7//4	9.3 (3.6–18.5)	< 0.001	8.4 (3.1–16.3)	< 0.001
BL+SBN+Z+NCAD	3//2	8 (2.4–17.3)	< 0.001	6.5 (2.7–14.6)	< 0.001
BL+SBN+Z+PA	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).

ACKNOWLEDGEMENTS

We thank Dr GG Ahmed, Director, Dr Bhubaneswar Barooah Cancer Institute, Guwahati. Assam. India for permitting us to do our study in his institute. Our sincere thanks to Dr A Nanda Kumar, Dy Director General (Sr Grade). National Cancer Registry Programme (ICMR). Kidwai Memorial Institute of Oncology. Bangalore, India for his kind permission to analyse our work. We also acknowledge the technical help of Mr Muralidhar. Senior Investigator. NCRP (ICMR). Kidwai Memerial Institute of Oncology, Bangalore, during the analysis of our work.

REFERENCES

Bandre TR (1983) *Toxicity studies of food contaminants*. (Ph.D. Thesis). Nagpur University, Nagpur (India)

Bhansle RB, Murti PR, Daftary DK and Mehta FS (1979) An oral lesion in tobacco lime users in Maharashtra, India. *Ind J Oral Pathol* **8**: 47–52

Blot WJ, McLaughlin JK, Devesa SS and Fraument J Jr (1997) Cancer of oral cavity and pharynx. In: *Cancer Epidemiology and Prevention* (D Schottenfeld, JG Searle and J Fraumeni Jr eds) Oxford University Press: London

Borle RM and Gupta DS (1987) Fungal contamination of Arecanut. *Indian J Pathol Microbiol* **30**: 357–360

Breslow NE and Day NE (1980) *The analysis of case-control studies. Statistical methods in cancer research*, Vol. 1, No. 32, IARC scientific publications

Chatterjee A and Deb S (1999) Genotoxic effect of arecoline given either by the peritoneal or oral route in murine bone marrow cells and the influence of N-acetylcysteine. *Cancer-Lett* **139**: 23–31

Chen CL, Chi CW, Chang KW and Liu TY (1999) Safrole-like DNA adducts in oral tissue from oral cancer patients with a betel quid chewing history. *Carcinogenesis* **20**: 2331–2334

Chetia M, Mahanta J and Sharma SK (1996) Toxic effect of tender and fermented ripe betel nuts on root growth and root tip cells of Allium cepa. *J Environ Biol* **17**: 251–256

Jussawalla DJ (1971) Epidemiological assessment of aetiology of oesophageal cancer in Greater Bombay. In: *Monograph No. I International seminar on epidemiology of oesophageal cancer*, Bangalore, India, 4 November, 20–30

Jussawalla DJ (1981) Oesophageal cancer in India. *J Cancer Res Clin Oncol* **99**: 29–33

Jussawalla DJ and Deshpande VA (1971) Evaluation of cancer risk in tobacco chewers and smokers: an epidemiologic assessment. *Cancer* **28**: 244–252

Kinjo Y, Cui Y, Akiba S, Watanabe S, Yamaguchi N, Sobue T, Mizuno S and Beral V (1998) Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. *J Epidemiol* **8(4)**: 235–243

Levin ML (1953) The occurrence of Lung cancer in Man. Acta Unio Int. *Contra Cancrum* **9**: 531–541

Mahanta J, Chetia M and Chelleng PK (1999) The toxic properties of saliva of betel nut chewers on a plant test system (*Allium cepa* L) *J Environ Biol* **20**: 85–88

Munoz N and Day NE (1997) Esophageal Cancer: *Cancer Epidemiology and Prevention*: D Scottenfeld, JG Searle and J Fraumeni. Oxford University Press, London

Nair J, Nair UJ, Oshima H, Bhide SV and Bartsh H (1987) *Endogenous nitrosation in the oral cavity of chewers while chewing betel quid with or without tobacco*. IARC Scientific Publications, **84**: 465–469

Nandakumar A, Anantha N, Pattabhiraman V, Probhakaran PS, Dhar M, Puttaswamy K, Venugopal TC, Reddy NMS, Rajanna, Vinutha AT and Srinivas (1996) Importance of anatomical subsite in correlating risk factors in cancer of the oesophagus-report of a case-control study. *Br J Cancer* **73**: 1306–1311

National Cancer Registry Programme (NCRP) of India (1984–1989) *Annual Reports*, Indian Council of Medical Research, New Delhi

Saikia JR, Schneeweiss FH and Sharan RN (1999) Arecoline-induced changes of poly-ADP-ribosylation of cellular proteins and its influence on chromatin organization *Cancer-Lett* **139**: 59–65

Sharan RN and Wary KK (1992) Study of unscheduled DNA synthesis following exposure of human cells to arecoline and extracts of betel nut in vitro. *Mutation Research* **278**: 271–276

Suri K, Goldman HM and Wells H (1971) Carcinogenic effects of DMSO extracts of betel nut on hamster check pouch. *Nature* (London), **230**: 383

Tuyns AJ, Pequignot G and Jensen OM (1977) Oesophageal cancer in Ille et Villaine in relation to alcohol and tobacco consumption. Multiplicative risk. *Bull Cancer* **64**: 45–50

721

Annexure 61

Int. J. Cancer: 49, 485–489 (1991)
© 1991 Wiley-Liss, Inc.

Publication of the International Union Against Cancer
Publication de l'Union Internationale Contre le Cancer

RISK FACTORS FOR CANCER OF THE OESOPHAGUS IN KERALA, INDIA

R. SANKARANARAYANAN[1,2,6], Stephen W. DUFFY[2], G. PADMAKUMARY[3], S. MURALIDHARAN NAIR[4], Nicholas E. DAY[2] and T.K. PADMANABHAN[5]

[1]*Dept. of Cancer Epidemiology and Clinical Research, Regional Cancer Centre, Trivandrum, 695 011 India;* [2]*MRC Biostatistics Unit, 5 Shaftesbury Road, Cambridge, CB2 2BW, UK;* [3]*Regional Cancer Centre, Trivandrum;* [4]*Medical College, Trivandrum; and* [5]*Cancer Registry, Regional Cancer Centre, Trivandrum, 695-011 India.*

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 termburni 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.

[6]To whom correspondence and reprint requests should be sent, at the Regional Cancer Centre, Trivandrum.

Received: December 27, 1990 and in revised form [illegible]

722

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.

723

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.

ACKNOWLEDGEMENTS

R.S.'s programme at the MRC Biostatistics Unit, Cambridge, UK, was funded by the Commonwealth Scholarship Commission. The authors are grateful to Ms. A. Nayar, Ms. J. Kumary, Ms. P.T. Latha and Mr. R. Nair who were involved in data collection. They also thank Miss Eve Swale, Miss J.K. Jayanthy and Miss B. Suseela Devi for preparation of the manuscript.

REFERENCES

ARMITAGE, P. and BERRY, G., *Statistical methods in medical research.* Blackwell, Oxford (1987).

BRESLOW, N.E. and DAY, N.E., *Statistical methods in cancer research. I. The Analysis of Case-Control Studies. IARC Scientific Publication 32,* IARC, Lyon (1980).

DAY, N.E., MUÑOZ, N. and GHADIRIAN, P., Epidemiology of oesophageal cancer: a review. *In:* P. Correa and W. Haenszel (eds.), *Epidemiology of cancer of the digestive tract,* pp. 21–57, Nijhoff, The Hague (1982).

GHADIRIAN, P., Thermal irritation and esophageal cancer in northern Iran. *Cancer,* **60**, 1909–1914 (1987).

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, *Evaluation of the carcinogenic risk to humans: alcohol drinking. IARC Monograph 44,* pp. 186–194, IARC, Lyon (1988).

JAYANT, K., BALAKRISHNAN, B., SANGHVI, L.D. and JUSSAWALLA, D.J., Quantification of the role of smoking and chewing tobacco in oral, pharyngeal and oesophageal cancers. *Brit. J. Cancer,* **35**, 232–235 (1977).

JUSSAWALLA, D.J. and DESHPANDE, V.A., Evaluation of cancer risk in tobacco chewers and smokers: an epidemiologic assessment. *Cancer,* **28**, 244–252 (1971).

LA VECCHIA, C. and NEGRI, E., The role of alcohol in oesophageal cancer in non-smokers, and of tobacco in non-drinkers. *Int. J. Cancer,* **43**, 784–785 (1989).

LI, J.Y., Epidemiology of oesophageal cancer in China. *Nat. Cancer Inst. Monogr.,* **62**, 113–120 (1982).

LI, J.Y., ERSHOW, A.G., CHEN, Z.J., WACHOLDER, S., LI, G.Y., GUO, W., LI, B. and BLOT, W.J., A case-control study of cancer of the esophagus and gastric cardia in Linxian. *Int. J. Cancer*, **43**, 755–761 (1989).

MUÑOZ, N., GRASSI, A., SHEN, Q., CRESPI, M., GUO QING, W. and ZHANG CAI, L., Pre-cancer lesions of esophageal cancer in high risk populations in Iran and China. *Lancet*, **I**, 876–879 (1982).

ICMR, *Annual Report, National Cancer Registry Project of India (NCRP)*. Indian Council of Medical Research, New Delhi (1982–1985).

MUIR, C.S., WATERHOUSE, J., MACLE, T., POWELL, J. and WHELAN, S., *Cancer incidence in five continents. IARC Scientific publication 88*, IARC, Lyon (1987).

NOTANI, P.N., Role of alcohol in cancers of the upper alimentary tract: use of models in risk assessment. *J. Epidemiol. Comm. Hlth.*, **112**, 187 (1988).

SANKARANARAYANAN, R., DUFFY, S.W., PADMAKUMARY, G., DAY, N.E. and PADMANABHAN, T.K., Tobacco chewing, alcohol and nasal snuff in cancer of the gingiva, in Kerala, India. *Brit. J. Cancer*, **60**, 638–643 (1989).

SIDDIQI, M. and PREUSSMANN, R., Esophageal cancer in Kashmir—an assessment. *J. Cancer Res. clin. Oncol.*, **115**, 111–113 (1989).

THURNHAM, D.I., ZHENG, S.F., MUÑOZ, N. and 4 OTHERS, Comparison of riboflavin, vitamin A and zinc status of Chinese populations at high and low risk for esophageal cancer. *Nutr. Cancer*, **7**, 131–140 (1985).

TUYNS, A.J., Oesophageal cancer in non-smoking drinkers and in non-drinking smokers. *Int. J. Cancer*, **32**, 443–445 (1983).

WYNDER, E.L. and BROSS, I.J., A study of etiological factors in cancer of the oesophagus. *Cancer*, **14**, 389–413 (1961).

YANG, C.S., Research on esophageal cancer in China: a review. *Cancer Res.*, **40**, 2633–2644 (1980).

726

Original Article

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

Subhash C Joshi[*], Sandeep R Saxena[*], VN Satyawali[*], Arun Joshi[**], Pranesh Nigam[***], VK Singh[****], SP Rai[*****]

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.

*Assistant Professor of Medicine, **Associate Professor of Medicine, ***Professor and Head, Department of Medicine, ****Assistant Professor of Statistic, Community Medicine, *****Professor of Surgery, Dr. Sushila Tiwari Memorial Forest Hospital and Uttarakhand Forest Hospital Trust Medical College, Haldwani-263139 (District Nainital), Uttarakhand
Received: 22.04.2008; Revised: 18.07.2008; Re-revised: 07.05.2009; Accepted: 08.05.2009

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.

727

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	

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

728

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 foodstuffs 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.

Acknowledgement

We are grateful to the Secretary, Principal and Medical Superintendent, U.F.H.T. Medical College and Dr. S.T.M. Forest Hospital, Haldwani for their permission to publish this series of cases.

References

1. Indian Council of Medical Research, Bienneal Report. 1988-89. National Cancer Registry. ICMR, New Delhi 1992.
2. Mohandas KM., Gastro-intestinal tumors. In API Text Book of Medicine. Eds, Shah SN, Paul Anand M, Acharya VN et al. 7th edition. The Association of Physicians of India, Mumbai. Ch XVI-Oncology, Sec. 8: pp 1011-1015, 2003.
3. Hormozdiari H, Day HE, Aramesh B, Mohboubi E. Dietary factors and oesophageal cancer in the Capsian Littoral of Iran. Cancer Res 1975; 35: 3493-3498.
4. Wohrendorf J, Chang Claude J, Liaxg QS, Rei YG, et al. Precursor lesions of oesophageal cancer. Lancet 1989; 25: 1239-1241.
5. Nayar D, Kapil U, Joshi YK, Sundaram KR, Srivastava SP et al. Nutritional risk factors in oesophageal cancer. J Assoc Phys Ind 2000; 48: 781-787.
6. Kuppuswamy B., Mannual of socio-economic status scale (urban) Delhi. Manasayan, 32, Netaji Subhash Marg.
7. Thimmayamma BVS. A Hand Book of Schedules and Guidelines in Socio-economic and Diet Surveys. National Institute of Nutrition, Indian Council of Medical Research, Hyderabad. 1987; 18-23.
8. Jussawalla DJ, Yede BB, Natekar MV, Sunny I. Cancer incidence and mortality in Greater Bombay. 1994- a report. Indian Cancer Society, Mumbai. 1997.
9. Ansari MM, Haleem S, Beg MH. Clinico-pathological profile of carcinoma oesophagus in Aligarh. J Ind Med Assoc 1991; 89: 217-219.
10. Chitra S, Ashok L, Anand I, Srinivasan V, Jayanti V. Risk factors for oesophageal cancer in Coimbatore Southern India- A hospital based case control study. Ind J Gastro-enterology 2004; 23: 19-21.
11. Sankaranarayanan R, Duffy SW, Padma Kumary G, Nair SM, Daeg NE, Padmanabam TK. Risk factors for cancer of the oesophagus in Kerala, India. Int J Cancer 1991; 49: 485-489.
12. Prasad MPR, Krishna TP, Pasricha S, Krishnaswamy K, Qureshi MA. Oesophageal cancer and Diet- A case control study. Nutr Cancer 1992; 18: 85-93.
13. Notani PN, Jayant K. Role of diet in upper GI tract cancer. Nutr Cancer 1987; 10: 103-113.
14. Dragsted IO, Strube M, Larsen JC. Cancer protective factors in fruits and vegetables (leafy), Biochemical and biological background. Pharmacol Toxicol 1993; 72: 116-135.
15. Diplock AT. Antioxidant nutrients and disease prevention- A review. Am J Clin Nutri 1991; 53: 189S-193S.
16. Khuroo MS, Zargar SA, Mahagan R, Ranaday MA. High incidence of oesophageal and gastric cancer in Kashmir in a population with special reference to personal and dietary habit. Gut 1992; 33: 11-15.
17. Siddiqui M, Kumar R, Fazili Z, Spiege Cholder B, Preussmann R. Increased exposure to dietary amines and nitrates in a population of high risk of oesophageal and gastric cancer in Kashmir (India). Carcinogenesis 1992; 13: 1331-1335.
18. Siddiqui M, Preussmann R. Oesophageal cancer in Kashmir- An Assessment. J Cancer Res Clin Oncol 1989; 115: 111-117.
19. Schaltter J, Lutz WK. The carcinogenic potential of ethylcarbamate (urethane); risk assessment at human dietary levels. Food Chem Toxicol 1990; 28: 205-211.
20. Yu Mc, Garabrant DH, Peters JM, Mack FM. Tobacco, alcohol, diet, occupation & carcinoma of the oesophagus. Cancer Res 1988; 48: 3843-3848.
21. Phukan RK, Ali NS, Chetia CK, Mohanta J. Betel nut and tobacco chewing potential risk factors of cancer oesophagus is Assam, India. Br J Cancer 2001; 85: 661-667.
22. Nandakumar A, Amantha N, Pattabhiraman V, Prabhakaran PS, Dhar N Puttaswamy K et al. Importance of anatomical subsite in correlating risk factors in the cancer of the oesophagus- report of case control study. Br J Cancer 1996; 73: 1306-1311.

731

DOI:10.1158/1055-9965.EPI-05-0074 Annexure 63

Cancer Epidemiology, Biomarkers & Prevention

Tobacco Use and Stomach Cancer in Mizoram, India

Rup Kumar Phukan, Eric Zomawia, Kanwar Narain, et al.

Cancer Epidemiol Biomarkers Prev 2005;14:1892-1896. Published online August 15, 2005.

732

DOI:10.1158/1055-9965.EPI-05-0074

Special Section

Tobacco Use and Stomach Cancer in Mizoram, India

Rup Kumar Phukan,[1] Eric Zomawia,[2] Kanwar Narain,[1] Nakul Chandra Hazarika,[1] and Jagadish Mahanta[1]

[1]Regional Medical Research Centre, N.E. Region (ICMR), Assam, India and [2]Aizawl Civil Hospital, Mizoram, India

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).

Received 1/27/05; revised 5/30/05; accepted 6/6/05.

Requests for reprints: Jagadish Mahanta, Regional Medical Research Centre, N.E. Region (ICMR), PO Box 105, Dibrugarh 786 001, Assam, India. Phone: 91-373-2381494; Fax: 91-373-2381748. E-mail: icmrrcdi@hub.nic.in

doi:10.1158/1055-9965.EPI-05-0074

DOI:10.1158/1055-9965.EPI-05-0074

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)

DOI:10.1158/1055-9965.EPI-05-0074

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.

925

DOI:10.1158/1055-9965.EPI-05-0074

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	21	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.

736

DOI:10.1158/1055-9965.EPI-05-0074

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.

Acknowledgments

We thank Dr. Lalsangluaia Sailo (Director of Hospital and Medical Education, Government of Mizoram, India) for permitting us to do our study in his state, Dr. D. Baruah (Superintendent of Aizawl Civil Hospital, Mizoram) for permission to carry out our work in his hospital, and M. Chetia (Laboratory Technician, Regional Medical Research Centre, Dibrugarh, Assam, India) for his help during our field work.

References

1. Parkin DM, Bray F, Ferlay J, et al. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153–6.
2. Parkin DM, Muir CS, Whelan SL, et al. Cancer incidence in five continents. Vol. 7. Lyon: IARC Scientific Publications; 2002: p. 1555.
3. Rao DN, Ganesh B. Estimates of cancer incidence in India in 1991. Indian J Cancer 1998;35:10–8.
4. National Cancer Registry Programme. Two-year report of the population based cancer registries 1997–1998. New Delhi: Indian Council of Medical Research; 2002; p. 25.
5. Phukan RK, Zomawia E, Hazarika NC, et al. High prevalence of stomach cancer among the people of Mizoram, India. Curr Sci 2004;87:285–6.
6. Vumson Zo. History. NT Thawagn, Venghlui, Aizawl, Mizoram, editors. India: Vumson Publisher; 1986. p. 26–39.
7. Chaturvedi HK, Phukan RK, Zoramthanga K, et al. Tobacco use in Mizoram, India: sociodemographic differences in pattern. Southeast Asian. J Trop Med Pub Hlth 1998;29:66–70.
8. Mahanta J, Chetia M, Hazarika NC, et al. Toxicity of *tuibur*, a unique form of tobacco smoke extract used in Mizoram, India. Curr Sci 1998;75:381–4.
9. Breslow NE, Day NE. The analysis of case-control studies. Statistical methods in cancer research. IARC Scientific Publication No.5. Lyon (France): IARC; 1980. p. 1.
10. Kneller RW, Mclaughlin JK, Bjelke E, et al. A cohort study of stomach cancer in a high-risk American population. Cancer 1991;68:672–8.
11. Inoue M, Tajima K, Hirose K, et al. Life-style and sub site of gastric cancer-joint effect of smoking and drinking habits. Int J Cancer 1994;56:494–9.
12. McLaughlin JK, Hrubee Z, Blot WJ, et al. Smoking and cancer mortality among U.S. veterans: 26-year follow-up. Int J Cancer 1995;60:190–3.
13. Ji BT, Chow BH, Yang G, et al. The influence of cigarette smoking, alcohol and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. Cancer 1996;77:2449–57.
14. Nomura A. Stomach cancer. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 1996. p. 707–24.
15. Zang ZF, Kurtz RC, Sun M, et al. Adenocarcinomas of the esophagus and gastric cardia: medical conditions, tobacco, alcohol and socioeconomic factors. Cancer Epidemiol Biomarkers Prev 1996;5:761–8.
16. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1997;89:1277–84.
17. Jedrychowski W, Wahendorf J, Popiela T, et al. A case-control study of dietary factors and stomach cancer risk in Poland. Int J Cancer 1986;37:837–42.
18. La Vecchia C, Negri E, Decarli A, et al. A case-control study of diet and gastric cancer in Northern Italy. Int J Cancer 1987;40:484–9.
19. Buiatti E, Pall D, Decarli A, et al. A case-control study of gastric cancer and diet in Italy. Int J Cancer 1989;44:611–6.
20. Boeing H, Frentzel-Beyme R, Berger M, et al. Case-control study on stomach cancer in Germany. Int J Cancer 1991;47:858–84.
21. Agudo A, Gonzalez CA, Marcos G, et al. Consumption of alcohol, coffee and tobacco and gastric cancer in Spain. Cancer Causes Control 1992;3:137–43.
22. Jedrychowski W, Boeing H, Wahrendorf J, et al. Vodka consumption, tobacco smoking and risk of gastric cancer in Poland. Int J Epidemiol 1993;22:606–13.
23. Engeland A, Andersen A, Haldorsen T, et al. Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. Cancer Causes Control 1996;7:497–506.
24. Gajalakshmi CK, Shanta V. Lifestyle and risk of stomach cancer: a hospital-based case-control study. Int J Epidemiology 1996;25:1146–53.
25. Rao DN, Ganesh B, Dinshaw KA, et al. A case-control study of stomach cancer in Mumbai, India. Int J Cancer 2002;99:727–37.
26. Chow WH, Swanson CA, Lissowska J, et al. Risk of stomach cancer in relation to consumption of cigarettes, alcohol, tea and coffee in Warsaw, Poland. Int J Cancer 1999;81:871–6.
27. Correa P, Fontham E, Pickle LW, et al. Dietary determinants of gastric cancer in South Louisiana inhabitants. J Natl Cancer Inst 1985;75:645–54.
28. Wu-Williams AH, Yu MC, Mack TM. Life-style, work place, and stomach cancer by sub site in young men of Los Angeles County. Cancer Res 1990;50:2569–76.
29. Kato I, Tominaga S, Ito Y, et al. A comparative case-control analysis of stomach cancer and atrophic gastritis. Cancer Res 1990;50:6559–64.
30. Tominaga K, Koyama Y, Sasagawa M, et al. A case-control study of stomach cancer and its genesis in relation to alcohol consumption, smoking and familial cancer history. Jpn J Cancer Res 1991;82:974–9.
31. McLaughlin JK, Hrubee Z, Blot WJ, et al. Stomach cancer and cigarette smoking among US veterans 1954–1980. Cancer Res 1990;50:3804.
32. Tricker AR. *N*-nitroso compounds and man: sources of exposure, endogenous formation and occurrence in body fluids. Eur J Cancer Prev 1997;6:226–68.
33. Mirvish SS. Role of *N*-nitroso compounds (NOC) and *N*-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. Cancer Lett 1995;93:17–48.
34. IARC. Monographs on the evaluation of carcinogenic risks to humans. Vol. 83. Lyon (France): IARC; 2002.
35. Kneller RW, You WC, Chang YS, et al. Cigarette smoking and other risk factors for progression of precancerous stomach lesions. J Natl Cancer Inst 1992;84:1261–6.
36. Chao A, Thun MJ, Henley SJ, et al. Cigarette smoking, use of other tobacco products and stomach cancer mortality in US adults: the Cancer Prevention study II. Int J Cancer 2002;101:380–9.
37. Williams RR, Stegens NL, Horn JW. Patient interview study from the Third National Cancer Survey: overview of problems and potentials of these data. J Natl Cancer Inst 1977;58:519–24.
38. Wynder EL, Kmet J, Dungal N, et al. An epidemiological investigation of gastric cancer. Cancer 1963;16:1461–96.
39. Weinberg GB, Kuller LH, Stehr PA. A case-control study of stomach cancer in a coal mining region of Pennsylvania. Cancer 1985;56:703–13.
40. Cogliano V, Straif K, Baan R, et al. Smokeless tobacco and tobacco-related nitrosamines. Lancet Oncol 2004;5:708.
41. IARC. Monograph on the evaluation of carcinogenic risk of Betel-quid and areca nut chewing with or without tobacco. Vol. 85. Lyon (France): IARC; 2004

727

Int. J. Cancer: **114,** 992–995 (2005)

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

Paolo Boffetta[1,2*], Bjarte Aagnes[2], Elisabete Weiderpass[1-4] and Aage Andersen[2]

[1]*International Agency for Research on Cancer, Lyon, France*
[2]*Norwegian Cancer Registry, Oslo, Norway*
[3]*Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden*
[4]*Finnish Cancer Registry, Helsinki, Finland*

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.

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

Grant sponsor: U.S. National Cancer Institute with the Cancer Registry of Norway; Contract number: PH 43-64-499.
*Correspondence to: Gene-Environment Epidemiology Group, International Agency for Research on Cancer (IARC), 150 cours Albert-Thomas, 69008 Lyon, France. Fax: +33-4-72738320. E-mail: boffetta@iarc.fr
Received 13 August 2004; Accepted after revision 1 October 2004
DOI 10.1002/ijc.20811
Published online 11 January 2005 in Wiley InterScience (www.interscience.wiley.com).

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.

739

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.

References

1. Everett SA, Husten CG, Warren CW, Crossett L, Sharp D. Trends in tobacco use among high school students in the United States, 1991–1995. J Sch Health 1998;68:1137–40.
2. Vainio H, Weiderpass E. Smokeless tobacco: harm reduction or nicotine overload? Eur J Cancer Prev 2003;12:89–92.
3. Gupta PC, Ray CS. Smokeless tobacco and health in India and South Asia. Respirology 2003;8:419–31.
4. Critchley JA, Unal B. Health effects associated with smokeless tobacco: a systematic review. Thorax 2003;58:435–43.
5. Winn DM. Epidemiology of cancer and other systemic effects associated with the use of smokeless tobacco. Adv Dent Res 1997;11:313–21.
6. Foulds J, Ramstrom L, Burke M, Fagerström K. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. Tobacco Control 2003;12:349–59.
7. Heuch I, Kvale G, Jacobsen BK, Bjelke E. Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. Br J Cancer 1983;48:637–43.
8. Alguacil J, Silverman DT. Smokeless and other non cigarette tobacco use and pancreatic cancer: a case-control study based on direct interviews. Cancer Epidemiol Biomarkers Prev 2004;13:55–8.
9. IARC. Tobacco habits other than smoking. In: IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol. 37. Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some related nitrosamines. Lyon: IARC, 1985. 37–140.
10. Hoffmann D, Djordjevic MV, Fan J, Zang E, Glynn T, Connolly GN. Five leading U.S. commercial brands of moist snuff in 1994: assessment of carcinogenic N-nitrosamines. J Natl Cancer Inst 1995;87:1862–9.
11. Nilsson R. A qualitative and quantitative risk assessment of snuff dipping. Regul Toxicol Pharmacol 1998;28:1–16.
12. Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. Chem Res Toxicol 1998;11:559–603.
13. Lund KE. Samfuunsskapte endringer i tobakksbruk i Norge i det 20. Århundre. Dr Polit, Thesis. Oslo: University of Oslo, 1996.
14. Magnus K, Hougen A, Andersen A, Pedersen E. A study of disease in migrants and their siblings: development of sibling rosters. J Chronic Dis 1970;23:405–10.
15. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. J Natl Cancer Inst 1977;58:525–47.
16. Farrow DC, Davis S. Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. Int J Cancer 1990;45:816–20.
17. Muscat JE, Stellman SD, Hoffmann D, Wynder EL. Smoking and pancreatic cancer in men and women. Cancer Epidemiol Biomarkers Prev 1997;6:15–9.
18. Prokopczyk B, Hoffmann D, Bologna M, Cunningham AJ, Trushin N, Akerkar S, Boyiri T, Amin S, Desai D, Colosimo S, Pittman B, Leder G, et al. Identification of tobacco-derived compounds in human pancreatic juice. Chem Res Toxicol 2002;15:677–85.
19. Rivenson A, Hoffmann D, Prokopczyk B, Amin S, Hecht SS. Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and areca-derived N-nitrosamines. Cancer Res 1988;48:6912–7.
20. Li D. Molecular epidemiology of pancreatic cancer. Cancer J 2001;7:259–65.
21. Dikshit RP, Kanhere S. Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: a population-based case-control study in Bhopal, India. Int J Epidemiol 2000;29:609–14.
22. Accortt NA, Waterbor JW, Beall C, Howard G. Chronic disease mortality in a cohort of smokeless tobacco users. Am J Epidemiol 2002;156:730–7.
23. Gajalakshmi V, Hung RJ, Mathew A, Varghese C, Brennan P, Boffetta P. Tobacco smoking and chewing, alcohol drinking and lung cancer risk among men in Southern India. Int J Cancer 2003;107:441–7.
24. Merchant A, Husain SS, Hosain M, Fikree FF, Pitiphat W, Siddiqui AR, Hayder SJ, Haider SM, Ikram M, Chuang SK, Saeed SA. Paan without tobacco: an independent risk factor for oral cancer. Int J Cancer 2000;86:128–31.
25. Ahmed F, Islam KM. Site predilection of oral cancer and its correlation with chew and smoking habit—a study of 103 cases. Bangladesh Med Res Counc Bull 1990;16:17–25.
26. Sein K, Maung KK, Aung TH. An epidemiologic study of 70 oral cancer cases at the Institute of Dental Medicine, Yangon, Myanmar, 1985-1988. Odontostomatol Trop 1992;15:5–8.
27. Zaridze DG, Blettner M, Trapeznikov NN, Kuvshinov JP, Matiakin EG, Poljakov BP, Poddubni BK, Parshikova SM, Rottenberg VI, Chamrakulov FS. Survey of a population with a high incidence of oral and oesophageal cancer. Int J Cancer 1985;36:153–8.
28. Elbeshir EI, Abeen HA, Idris AM, Abbas K. Snuff dipping and oral cancer in Sudan: a retrospective study. Br J Oral Maxillofac Surg 1989;27:243–8.
29. Idris AM, Ahmed HM, Malik MO. Toombak dipping and cancer of the oral cavity in the Sudan case-control study. Int J Cancer 1995;63:477–80.
30. Winn DM, Blot WJ, Shy CM, Pickle LW, Toledo A, Fraumeni JF Jr. Snuff dipping and oral cancer among women in the southern United States. N Engl J Med 1981;304:745–9.
31. Stockwell HG, Lyman GH. Impact of smoking and smokeless tobacco on the risk of cancer of the head and neck. Head Neck Surg 1986;9:104–10.
32. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, Bernstein L, Schoenberg JB, Stemhagen A, Fraumeni JF Jr. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988;48:3282–7.
33. Spitz MR, Fueger JJ, Goepfert H, Hong WK, Newell GR. Squamous cell carcinoma of the upper aerodigestive tract: a case comparison analysis. Cancer 1988;61:203–8.
34. Sterling TD, Rosenbaum WL, Weinkam JJ. Analysis of the relationship between smokeless tobacco and cancer based on data from the National Mortality Followback Survey. J Clin Epidemiol 1992;45:223–31.
35. Mashberg A, Boffetta P, Winkelman R, Garfinkel L. Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. Cancer 1993;72:1369–75.
36. Lewin F, Norell SE, Johansson H, Gustavsson P, Wennerberg J, Biorklund A, Rutqvist LE. Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck. Cancer 1998;82:1367–75.
37. Schildt EB, Eriksson M, Hardell L, Magnuson A. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. Int J Cancer 1998;77:341–6.
38. Idris AM, Ibrahim SO, Vasstrand EN, Johannessen AC, Lillehaug JR, Magnusson B, Wallstrom M, Hirsch JM, Nilsen R. The Swedish snus

and the Sudanese Toombak: are they different? Oral Oncol 1998;34: 558–66.

39. Pottern LM, Morris LE, Blot WJ, Ziegler RG, Fraumeni JF Jr. Esophageal cancer among Black men in Washington, D.C. I. Alcohol, tobacco, and other risk factors. J Natl Cancer Inst 1981; 67:777–83.
40. Lagergren J, Bergström R, Lindgren A, Nyrén O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesphagus and gastric cardia. Int J Cancer 2000;85:340–6.
41. Hansson LE, Baron J, Nyrén O, Bergström R, Wolk A, Adami HO. Tobacco, alcohol and the risk of gastric cancer: a population-based case-control study in Sweden. Int J Cancer 1994;57:26–31.
42. Advisory Committee to the Surgeon General. The health consequences of using smokeless tobacco. NIH Publ. No. 86-2874. Bethesda, MD: National Institutes of Health, 1986.
43. Slattery ML, Schumacher MC, West DW, Robison LM. Smoking and bladder cancer: the modifying effect of cigarettes on other factors. Cancer 1988;61:402–8.
44. Goodman MT, Morgenstern H, Wynder EL. A case-control study of factors affecting the development of renal cell cancer. Am J Epidemiol 1986;124:926–41.
45. Muscat JE, Hoffmann D, Wynder EL. The epidemiology of renal cell carcinoma: a second look. Cancer 1995;75:2552–7.
46. Fagerström KO, Schildt E-B. Should the European Union lift the ban on snus? Evidence from the Swedish experience. Addiction 2003;98: 1191–5.

DOI:10.1158/1055-9965.EPI-03-0033

Annexure 02

Cancer Epidemiology, Biomarkers & Prevention

AACR

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

Juan Alguacil and Debra T. Silverman

Cancer Epidemiol Biomarkers Prev 2004;13:55-58. Published online January 26, 2004.

742

DOI:10.1158/1055-9965.EPI-03-0033

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

Juan Alguacil and Debra T. Silverman

Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, Bethesda, Maryland

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-

Received 4/24/03; revised 9/15/03; accepted 9/18/03.

Grant support: National Cancer Institute Grants NO1-CP-51090, NO1-CP51089, NO1-CP51092, NO1-CN-05225, NO1-CN-31022, and NO1-CN-05227.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Debra T. Silverman, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, 6120 Executive Boulevard, EPS 8108, Rockville, MD, 20852. Phone: (301) 435-4716; Fax: (301) 402-1819; E-mail: silvermd@mail.nih.gov.

743

DOI:10.1158/1055-9965.EPI-03-0033

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–

DOI:10.1158/1055-9965.EPI-03-0033

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)	0.17
>1	9	41	1.8	(0.8–4.2)	
No. of years smoked					
≤20	3	24	1.2	(0.3–4.3)	0.16
>20	13	61	1.9	(0.9–3.9)	
Smokeless tobacco					
Ounces/wk					
≤2.5	1	22	0.3	(0.04–2.5)	0.04
>2.5	6	22	3.5	(1.1–10.6)	
No. of years used					
≤20	1	10	1.1	(0.1–11.0)	0.42
>20	6	33	1.5	(0.6–4.0)	

[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

DOI:10.1158/1055-9965.EPI-03-0033

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.

Acknowledgments

We thank Dr. Robert Hoover (Division of Cancer Epidemiology and Genetics, National Cancer Institute) for his astute scientific contribution to all aspects of the study since its inception and the following principal investigators at each collaborating center: Dr. G. Marie Swanson [formerly with the Barbara Ann Karmanos Cancer Center (Detroit, MI) and currently with the College of Public Health, University of Arizona (Tucson, AZ)]; Dr. Raymond S. Greenberg [formerly with the Division of Epidemiology, Emory University School of Public Health (Atlanta, GA) and currently with the Medical University of South Carolina Charleston, SC)]; Janet B. Schoenberg [formerly with the Special Epidemiology Program, New Jersey State Department of Health (Trenton, NJ)]; Dr. Ann G. Schwartz [Barbara Ann Karmanos Cancer Center (Detroit, MI)]; and Dr. Jonathan Liff [Division of Epidemiology, Emory University School of Public Health (Atlanta, GA)]. We also thank Drs. Keith Lillemoe (The John Hopkins School of Medicine) and Mark Shiffman (Division of Cancer Epidemiology, National Cancer Institute) for their careful medical chart review of the pancreatic cancer cases; Ruth Thomson (Westat, Inc.) for her assistance in study management and coordination; Stella Semiti, Andrew Sabaka, Emily Harvey, and Dave Castenson (Information Management Systems) for computer support; Judy Lichaa and Amie Seisay for clerical assistance; study coordinators, interviewers, and support staff in each study area for their diligent work; and the many physicians, hospitals, and study participants who cooperated in this study.

References

1. Baker, F., Ainsworth, S. R., Dye, J. T., Crammer, C., Thun, M. J., Hoffmann, D., Repace, J. L., Henningfield, J. E., Slade, J., Pinney, J., Shanks, T., Burns, D. M., Connolly, G. N., and Shopland, D. R. Health risks associated with cigar smoking. J. Am. Med. Assoc., *284:* 735–740, 2000.

2. Burns, D. M., Cummings, K. M., and Hoffman, D. Cigars: health effects and trends. Smoking and tobacco control, p. 9. Bethesda, MD: U. S. Department of Health and Human Services, NIH, 1998.

3. Shapiro, J. A., Jacobs, E. J., and Thun, M. J. Cigar smoking in men and risk of death from tobacco-related cancers. J. Natl. Cancer Inst. (Bethesda), *92:* 333–337, 2000.

4. Porta, M., Malats, N., Pinol, J. L., Rifa, J., Andreu, M., and Real, F. X. Diagnostic certainty and potential for misclassification in exocrine pancreatic cancer. PANKRAS I project investigations. J. Clin. Epidemiol., *47:* 1069–1079, 1994.

5. Silverman, D. T., Dunn, J. A., Hoover, R. N., Schiffman, M., Lillemoe, K. D., Schoenberg, J. B., Brown, L. M., Greenberg, R. S., Hayes, R. B., Swanson, G. M., *et al.* Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. J. Natl. Cancer Inst. (Bethesda), *86:* 1510–1516, 1994.

6. Silverman, D. T., Schiffman, M., and Devesa, S. Diagnostic certainty in pancreatic cancer. J. Clin. Epidemiol., *49:* 601–603, 1996.

7. Breslow, N., and Day, N. Statistical Methods in Cancer Research: The Analysis of Cohort Studies, Vol. II, p. 82. Lyon, France: IARC, 1987.

8. Iribarren, C., Tekawa, I. S., Sidney, S., and Friedman, G. D. Effect of cigar smoking on the risk of cardiovascular disease, chronic obstructive pulmonary disease, and cancer in men. N. Engl. J. Med., *340:* 1773–1780, 1999.

9. Kahn, J. A. The Dorn study of smoking and mortality among U. S. veterans: report on eight and one-half years of observation. *In:* W. Haenszel (ed.), Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases, pp. 1–125. Bethesda, MD: NIH, 1966.

10. Muscat, J. E., Stellman, S. D., Hoffmann, D., and Wynder, E. L. Smoking and pancreatic cancer in men and women. Cancer Epidemiol. Biomark. Prev., *6:* 15–19, 1997.

11. Partanen, T. J., Vainio, H. U., Ojajarvi, I. A., and Kauppinen, T. P. Pancreas cancer, tobacco smoking and consumption of alcoholic beverages: a case-control study. Cancer Lett., *116:* 27–32, 1997.

12. Wynder, E. L., Mabuchi, K., Maruchi, N., and Fortner, J. G. Epidemiology of cancer of the pancreas. J. Natl. Cancer Inst. (Bethesda), *50:* 645–667, 1973.

13. Boyle, P., Maisonneuve, P., Bueno, D. M., Ghadirian, P., Howe, G. R., Zatonski, W., Baghurst, P., Moerman, C. J., Simard, A., Miller, A. B., Przewoniak, K., McMichael, A. J., Hsieh, C. C., and Walker, A. M. Cigarette smoking and pancreas cancer: a case control study of the search programme of the IARC. Int. J. Cancer, *67:* 63–71, 1996.

14. Engeland, A., Andersen, A., Haldorsen, T., and Tretli, S. Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. Cancer Causes Control, *7:* 497–506, 1996.

15. Zheng, W., McLaughlin, J. K., Gridley, G., Bjelke, E., Schuman, L. M., Silverman, D. T., Wacholder, S., Co-Chien, H. T., Blot, W. J., and Fraumeni, J. F., Jr. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). Cancer Causes Control, *4:* 477–482, 1993.

16. Heuch, I., Kvale, G., Jacobsen, B. K., and Bjelke, E. Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. Br. J. Cancer, *48:* 637–643, 1983.

17. Farrow, D. C., and Davis, S. Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. Int. J. Cancer, *45:* 816–820, 1990.

18. MacMahon, B., Yen, S., Trichopoulos, D., Warren, K., and Nardi, G. Coffee and cancer of the pancreas. N. Engl. J. Med., *304:* 630–633, 1981.

19. Mack, T. M., Yu, M. C., Hanisch, R., and Henderson, B. E. Pancreas cancer and smoking, beverage consumption, and past medical history. J. Natl. Cancer Inst. (Bethesda), *76:* 49–60, 1986.

20. Carstensen, J. M., Pershagen, G., and Eklund, G. Mortality in relation to cigarette and pipe smoking: 16 years' observation of 25,000 Swedish men. J. Epidemiol. Community Health, *41:* 166–172, 1987.

21. Prokopczyk, B., Hoffmann, D., Bologna, M., Cunningham, A. J., Trushin, N., Akerkar, S., Boyiri, T., Amin, S., Desai, D., Colosimo, S., Pittman, B., Leder, G., Ramadani, M., Henne-Bruns, D., Beger, H. G., and El Bayoumy, K. Identification of tobacco-derived compounds in human pancreatic juice. Chem. Res. Toxicol., *15:* 677–685, 2002.

22. Anderson, K. E., Hammons, G. J., Kadlubar, F. F., Potter, J. D., Kaderlik, K. R., Ilett, K. F., Minchin, R. F., Teitel, C. H., Chou, H. C., Martin, M. V., Guengerich, F. P., Barone, G. W., Lang, N. P., and Peterson, L. A. Metabolic activation of aromatic amines by human pancreas. Carcinogenesis (Lond.), *18:* 1085–1092, 1997.

23. Foster, J. R., Idle, J. R., Hardwick, J. P., Bars, R., Scott, P., and Braganza, J. M. Induction of drug-metabolizing enzymes in human pancreatic cancer and chronic pancreatitis. J. Pathol., *169:* 457–463, 1993.

24. Crespi, C. L., Penman, B. W., Gelboin, H. V., and Gonzalez, F. J. A tobacco smoke-derived nitrosamine, 4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone, is activated by multiple human cytochrome P450s including the polymorphic human cytochrome P4502D6. Carcinogenesis (Lond.), *12:* 1197–1201, 1991.

25. Schulze, J., Richter, E., Binder, U., and Zwickenpflug, W. Biliary excretion of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in the rat. Carcinogenesis (Lond.), *13:* 1961–1965, 1992.

26. Rivenson, A., Hoffmann, D., Prokopczyk, B., Amin, S., and Hecht, S. S. Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and Areca-derived *N*-nitrosamines. Cancer Res., *48:* 6912–6917, 1988.

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

Juhua Luo, Weimin Ye, Kazem Zendehdel, Johanna Adami, Hans-Olov Adami, Paolo Boffetta, Olof Nyrén

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.

Lancet 2007; 369: 2015–20

Published Online May 10, 2007
DOI:10.1016/S0140-6736(07)60678-3

See Comment page 1976

See Articles page 2010

Department of Medical Epidemiology and Biostatistics (J Luo MSc, W Ye MD, K Zendehdel MD, J Adami MD, Prof H-O Adami MD, Prof P Boffetta MD, Prof O Nyrén MD), and Department of Medicine, Clinical Epidemiology Unit (J Adami), Karolinska Institutet, Box 281, SE 171 77, Stockholm, Sweden; Cancer Institute Research Center, Medical Sciences/University of Tehran, Tehran, Iran (K Zendehdel); Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA (Prof H-O Adami); and International Agency for Research on Cancer, Lyon, France (P Boffetta)

Correspondence to: Prof Olof Nyrén olof.nyren@ki.se

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.

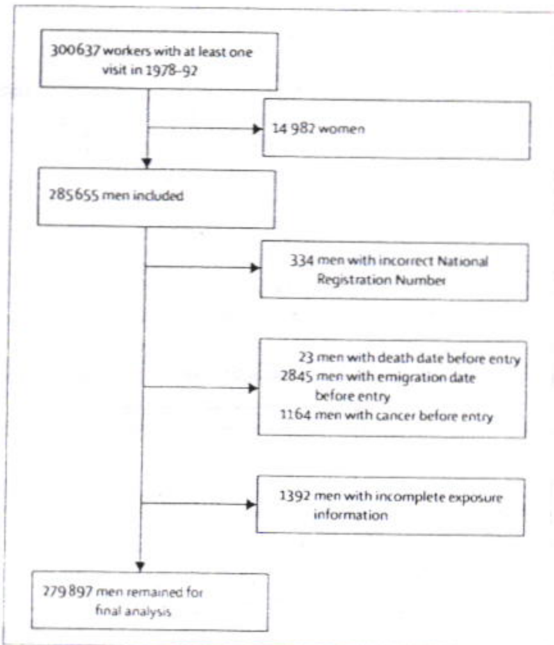

Figure: Summary of inclusion and exclusion criteria and final cohort used for analysis

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 279 897 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%)	5505 (8%)	4648 (7%)	46 538 (67%)	30 719 (44%)
40–49 years	45 065 (16%)	927 998	10 530 (23%)	7700 (17%)	2021 (4%)	1711 (4%)	30 879 (69%)	18 990 (42%)
50–59 years	32 455 (12%)	612 408	6262 (19%)	4569 (14%)	1043 (3%)	911 (3%)	22 593 (70%)	12 913 (40%)
≥60 years	10 341 (4%)	167 405	2177 (21%)	1601 (15%)	497 (5%)	426 (4%)	7102 (69%)	3621 (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	10·2 (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.[7] 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

749

	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	87 821	1 751 072	50	3·1	1 (ref)	136	8·6	1 (ref)	63	3·9	1 (ref)
Ever-users of snus	37 755	698 542	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	50 469	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	34 818	648 074	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	134 390	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	30 683	564 152	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[30] 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.[8,10,33,34] 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.[33] 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.

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.[37] 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,[38] 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[39] 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.

Acknowledgments

This study was partly funded by a grant from the Swedish Cancer Society (4409-B00-01XAC).

References

1 Rodu B, Nasic S, Cole P. Tobacco use among Swedish schoolchildren. *Tob Control* 2005; **14:** 405–08.
2 Stegmayr B, Eliasson M, Rodu B. The decline of smoking in northern Sweden. *Scand J Public Health* 2005; **33:** 321–24.
3 Hoffmann D, Djordjevic MV, Fan J, Zang E, Glynn T, Connolly GN. Five leading U.S. commercial brands of moist snuff in 1994: assessment of carcinogenic N–nitrosamines. *J Natl Cancer Inst* 1995; **87:** 1862–69.
4 Hecht SS. DNA adduct formation from tobacco-specific N-nitrosamines. *Mutat Res* 1999; **424:** 127–42.
5 Hoffmann D, Djordjevic MV. Chemical composition and carcinogenicity of smokeless tobacco. *Adv Dent Res* 1997; **11:** 322–29.
6 Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. *Chem Res Toxicol* 1998; **11:** 559–603.
7 Rodu B, Jansson C. Smokeless tobacco and oral cancer: a review of the risks and determinants. *Crit Rev Oral Biol Med* 2004; **15:** 252–63.
8 Lewin F, Norell SE, Johansson H, et al. Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck: a population-based case-referent study in Sweden. *Cancer* 1998; **82:** 1367–75.
9 Bjelke E SL. Chew tobacco and use of snuff: relationship to cancer of the pancreas and other sites in two prospective studies. Proceedings of the 13th International Cancer Congress, 1982; 207 (abstr).

751

10 Boffetta P, Aagnes B, Weiderpass E, Andersen A. Smokeless tobacco use and risk of cancer of the pancreas and other organs. *Int J Cancer* 2005; 114: 992–95.

11 Gupta PC, Ray CS. Smokeless tobacco and health in India and South Asia. *Respirology* 2003; 8: 419–31.

12 IARC Working Group. Tobacco habits other than smoking: betel-quid and areca-nut chewing; and some related nitrosamines. *IARC Monogr Eval Carcinog Risk Chem Hum* 1985; 37: 1–268.

13 Cogliano V, Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F. Smokeless tobacco and tobacco-related nitrosamines. *Lancet Oncol* 2004; 5: 708.

14 Rivenson A, Hoffmann D, Prokopczyk B, Amin S, Hecht SS. Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and Areca-derived N-nitrosamines. *Cancer Res* 1988; 48: 6912–17.

15 Prokopczyk B, Rivenson A, Hoffmann D. A study of betel quid carcinogenesis. IX. Comparative carcinogenicity of 3-(methylnitrosamino)propionitrile and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone upon local application to mouse skin and rat oral mucosa. *Cancer Lett* 1991; 60: 153–57.

16 Alguacil J, Silverman DT. Smokeless and other noncigarette tobacco use and pancreatic cancer: a case-control study based on direct interviews. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 55–58.

17 Zheng W, McLaughlin JK, Gridley G, et al. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control* 1993; 4: 477–82.

18 Muscat JE, Stellman SD, Hoffmann D, Wynder EL. Smoking and pancreatic cancer in men and women. *Cancer Epidemiol Biomarkers Prev* 1997; 6: 15–19.

19 Rodu B, Stegmayr B, Nasic S, Asplund K. Impact of smokeless tobacco use on smoking in northern Sweden. *J Intern Med* 2002; 252: 398–404.

20 Ramström L. Reduction of smoking and smoking-related health hazards by promoting alternative nicotine delivery systems. UN Focal Point on Tobacco and Health. Geneva: ICAA and EMASH, 1997.

21 Nyren O, Bergstrom R, Nystrom L, et al. Smoking and colorectal cancer: a 20-year follow-up study of Swedish construction workers. *J Natl Cancer Inst* 1996; 88: 1302–07.

22 Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* 1984; 23: 305–13.

23 Ekstrom AM, Signorello LB, Hansson LE, Bergstrom R, Lindgren A, Nyren O. Evaluating gastric cancer misclassification: a potential explanation for the rise in cardia cancer incidence. *J Natl Cancer Inst* 1999; 91: 786–90.

24 Lin D, Wei L, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* 1993; 80: 557–72.

25 Boffetta P, Aagnes B, Weiderpass E, Andersen A. Response to comments by Drs. Rutqvist, Lewin, Nilsson, Ramstrom, Rodu and Cole further to the publication of the manuscript "smokeless tobacco use and risk of cancer of the pancreas and other organs". *Int J Cancer* 2006; 118: 1586–87.

26 Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *J Natl Cancer Inst* 1977; 58: 525–47.

27 Farrow DC, Davis S. Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. *Int J Cancer* 1990; 45: 816–20.

28 Gilljam H, Galanti MR. Role of snus (oral moist snuff) in smoking cessation and smoking reduction in Sweden. *Addiction* 2003; 98: 1183–89.

29 Prokopczyk B, Hoffmann D, Bologna M, et al. Identification of tobacco-derived compounds in human pancreatic juice. *Chem Res Toxicol* 2002; 15: 677–85.

30 Schuller HM. Mechanisms of smoking-related lung and pancreatic adenocarcinoma development. *Nat Rev Cancer* 2002; 2: 455–63.

31 Persson PG, Carlsson S, Svanstrom L, Ostenson CG, Efendic S, Grill V. Cigarette smoking, oral moist snuff use and glucose intolerance. *J Intern Med* 2000; 248: 103–10.

32 Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. *Jama* 2000; 283: 2552–58.

33 Rosenquist K, Wennerberg J, Schildt EB, Bladstrom A, Hansson BG, Andersson G. Use of Swedish moist snuff, smoking and alcohol consumption in the aetiology of oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. *Acta Otolaryngol* 2005; 125: 991–98.

34 Schildt EB, Eriksson M, Hardell L, Magnuson A. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. *Int J Cancer* 1998; 77: 341–46.

35 Henley SJ, Thun MJ, Connell C, Calle EE. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control* 2005; 16: 347–58.

36 Accortt NA, Waterbor JW, Beall C, Howard G. Cancer incidence among a cohort of smokeless tobacco users (United States). *Cancer Causes Control* 2005; 16: 1107–15.

37 Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006; 15: 291–303.

38 Furberg H, Lichtenstein P, Pedersen NL, Bulik C, Sullivan PF. Cigarettes and oral snuff use in Sweden: prevalence and transitions. *Addiction* 2006; 101: 1509–15.

39 Ekbom A, Hunter D. Pancreatic cancer. In: Adami HO, Hunter D, Trichopoulos D, eds. Textbook of cancer epidemiology. New York: Oxford University Press, 2002: 233–47.

752

ORAL SURGERY
ORAL MEDICINE
ORAL PATHOLOGY

REVIEW ARTICLE

Smokeless tobacco use and cancer of the upper respiratory tract

Brad Rodu, DDS,[a] and Philip Cole, MD, DrPH,[b] Birmingham, Ala
UNIVERSITY OF ALABAMA AT BIRMINGHAM

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

Supported in part by an unrestricted gift from the United States Tobacco Company to the Tobacco Research Fund of the University of Alabama at Birmingham.
[a]Department of Pathology, School of Medicine, University of Alabama at Birmingham.
[b]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham.
Neither author has any other financial involvement with the manufacturer of any product mentioned in this paper.
Received for publication Nov 14, 2001; returned for revision Jan 4, 2002; accepted for publication Jan 10, 2002.

1079-2104/2002/$35.00 + 0 7/14/123497
doi:10.1067/moe.2002.123497

753

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.

REFERENCES

1. Baron JA, Rohan TE. Tobacco. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. 2nd ed. New York: Oxford University Press; 1996; p. 269-89
2. Cullen JW, Blot W, Henningfield J, Boyd G, Mecklenburg R, Masey MM. Health consequences of using smokeless tobacco: summary of the Advisory Committee's report to the Surgeon General. Public Health Rep 1986;101:355-73.
3. Wynder EL, Hultberg S, Jacobsson F, et al. Environmental factors in cancer of the upper alimentary tract: a Swedish study with special reference to Plummer-Vinson (Patterson-Kelly) syndrome. Cancer 1957;10:470-87.
4. Wynder EL, Bross IJ, Feldman RM. A study of the etiological factors in cancer of the mouth. Cancer 1957;10:1300-23.
5. Peacock EE, Greenberg BG, Brawley BW. The effect of snuff and tobacco on the production of oral carcinoma: an experimental and epidemiological study. Ann Surg 1960;151:542-50.
6. Vogler WR, Lloyd JW, Milmore BK. A retrospective study of etiological factors in cancer of the mouth, pharynx, and larynx. Cancer 1962;15:246-58.
7. Vincent RG, Marchetta F. The relationship of the use of tobacco and alcohol to cancer of the oral cavity, pharynx, or larynx. Am J Surg 1963;106:501-5.
8. Martinez I. Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. J Natl Cancer Inst 1969;42:1069-94.
9. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. J Natl Cancer Inst 1977;58:525-47.
10. Wynder EL, Stellman SD. Comparative epidemiology of tobacco-related cancers. Cancer Res 1977;37:4608-22.
11. Browne RM, Camsey MC, Waterhouse JAH, Manning GL. Etiological factors in oral squamous cell carcinoma. Community Dent Oral Epidemiol 1977;5:301-6.
12. Winn DM, Blot WJ, Shy CM, Pickle LW, Toledo A, Fraumeni JF Jr. Snuff dipping and oral cancer among women in the Southern United States. N Engl J Med 1981;304:745-9.
13. Stockwell HG, Lyman GH. Impact of smoking and smokeless tobacco on the risk of cancer of the head and neck. Head Neck Surg 1986;9:104-110.
14. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988;48:3282-7.
15. Spitz MR, Fueger JJ, Goepfert H, Hong WK, Newell GR. Squamous cell carcinoma of the upper aerodigestive tract. Cancer 1988;61:203-8.

758