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ANNEXURES

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

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

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

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

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

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

METHODS

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

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

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

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

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

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

RESULTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Chewing practices	Male					Female				
	Ca/Co	OR (95% CI)	P value	Adj OR (95% CI)	P value	Ca/Co	OR (95% CI)	P value	Adj OR (95% CI)	P value
Non-chewer	30/249	1				34/153	1			
Chadha	68/84	6.7 (2.7–16.9)	< 0.001	4.9 2.8–11.6	< 0.001	15/8	8.4 (2.4–18.8)	<0.001	3.4 1.3–5.6	<0.001
BL + R/G BN	50/120	3.5 (1.3–9.8)	< 0.001	1.9 0.08–6.3	0.089	20/56	1.6 (0.9–8.5)	0.073	0.5 0.03–3.7	0.422
BL + UG BN	65/132	4.1 (2.2–10.5)	< 0.001	2.3 0.7–8.4	< 0.05	15/32	2.1 (1.6–10.2)	0.062	0.8 0.06–4.6	0.351
BL + R/G BN + D	40/62	5.4 (2.4–15.2)	< 0.001	3.1 1.3–6.7	< 0.01	25/14	8 (2.2–13.8)	<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					Female				
	Ca/Co	OR (95% CI)	P value	Adj OR (95% CI)	P value	Ca/Co	OR (95% CI)	P value	Adj OR (95% CI)	P value
NCh & NAD	22/218	1				28/149	1			
Chadha	16/35	4.5 (1.6–10.3)	0.003	3.8 (1.9–8.5)	0.003	7//6	6.2 (2.4–15.9)	<0.001	5.8 (2.1–12.4)	< 0.001
Chadha+NCAD	19/28	6.7 (2.8–14.4)	< 0.001	6.1 (2.6–12.8)	0.004	4//3	7.1 (2.8–19.7)	< 0.001	6.3 (2.4–14.3)	< 0.001
Chadha+PA	15/23	6.5 (2.4–15.2)	< 0.001	5.3 (2.2–13.1)	0.002	3//3	5.3 (1.5–16.3)	< 0.001	4.4 (1.7–9.5)	< 0.001
BL+R/GBN	21/53	3.9 (1.4–12.6)	0.008	2.8 (1.3–7.5)	0.06	10//27	2 (0.7–8.5)	0.04	1.4 (0.3–6.5)	0.24
BL+R/GBN+NCAD	26/41	6.3 (2.5–11.4)	0.002	5.6 (2.2–9.6)	0.004	7//20	2 (0.3–10.6)	0.08	1.6 (0.2–9.3)	0.41
BL +R/GBN+PA	14/25	5.5 (1.9–10.8)	< 0.001	4.2 (1.8–10.5)	< 0.001	6//12	2.7 (1.1–9.5)	< 0.01	1.7 (0.6–8.5)	0.15
BL+UGBN	22/58	3.8 (1.2–9.6)	0.004	3.1 (1.6–8.5)	0.002	9//15	3.2 (1.8–11.5)	< 0.001	2.4 (0.9–7.2)	< 0.01
BL+UGBN+NCAD	39/46	8.4 (3.4–14.5)	< 0.001	6.2 (2.4–11.3)	< 0.001	7//10	3.7 (1.3–10.7)	< 0.001	2.1 (1.3–5.4)	0.04
BL+UGBN+PA	20/41	4.8 (1.6–11.2)	0.001	3.6 (1.7–9.5)	< 0.001	5//9	3 (1.5–8.6)	< 0.001	1.9 (0.4–7.5)	0.09
BL+R/GBN+D	21/38	5.5 (2.3–11.8)	< 0.001	5 (1.7–10.6)	< 0.001	8//8	5.3 (1.7–10.8)	< 0.001	4.2 (1.6–10.5)	< 0.001
BL+R/GBN+D+ NCAD	20/26	7.6 (2.8–12.3)	< 0.001	7.3 (2.5–12.8)	< 0.001	7//6	6.2 (2.3–14.2)	< 0.001	5.6 (2.3–12.4)	< 0.001
BL+R/GBN+D+PA	12/22	5.4 (1.8–10.6)	< 0.001	4.8 (1.7–9.3)	< 0.001	5//3	8.9 (2.4–19.8)	< 0.001	7.3 (2.6–10.3)	< 0.001
BL+UGBN+D	26/20	12.9 (3.2–18.5)	< 0.001	10.3 (3.6–20.8)	< 0.001	12//5	12.8 (4.2–20.8)	< 0.001	10.4 (2.6–18.5)	< 0.001
BL+UGBN+D+ NCAD	31/14	21.9 (7.5–32.4)	< 0.001	18.5 (5.6–27.3)	< 0.001	9//3	16 (8.3–26.4)	< 0.001	13.5 (3.1–20.6)	< 0.001
BL+UGBN+D+PA	12//15	7.9 (1.9–14.5)	< 0.001	6.3 (2.5–14.7)	< 0.001	5//2	13.3 (5.4–21.6)	< 0.001	10.6 (3.2–18.2)	< 0.001
BL+SBN+Z	9//6	14.9 (4.6–22.8)	< 0.001	8.4 (2.6–17.5)	< 0.001	7//4	9.3 (3.6–18.5)	< 0.001	8.4 (3.1–16.3)	< 0.001
BL+SBN+Z+NCAD	6//3	19.8 (5.3–28.6)	< 0.001	12.1 (4.3–21.4)	< 0.001	3//2	8 (2.4–17.3)	< 0.001	6.5 (2.7–14.6)	< 0.001
BL+SBN+Z+PA	7//4	17.3 (4.2–24.5)	< 0.001	13.6 (4.6–22.5)	< 0.001	2//1	10.6 (3.5–20.4)	< 0.001	7.3 (1.8–15.3)	< 0.001

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

DISCUSSION

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

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

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

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

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

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

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Annexure 61

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RISK FACTORS FOR CANCER OF THE OESOPHAGUS IN KERALA, INDIA

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

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

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

MATERIAL AND METHODS

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

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

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

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

RESULTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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Annexure 62

Original Article

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

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Abstract

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

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

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

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

Introduction

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

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

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Material and Methods

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

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

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

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

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

1. Socio-economic profile

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

Table 1 : Socio-demographic pattern

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

2. Nutritional or Dietary History

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

3. Intoxicant Consumption History

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

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

Results

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

Table 2 : Dietary status (relative risk factors)

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

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

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

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

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

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

Dietary Habits

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

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

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

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

Discussion

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

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

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Table 4 : Relative risk factors in relation to intoxicants consumed

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

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

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

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

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

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

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

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

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