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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 preparation 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 (Bhansli 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, 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 = $\exp(\beta)$) 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 betel nut 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

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