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Oral cavity cancer risk in relation to tobacco chewing and bidi smoking among men in Karunagappally, Kerala, India: Karunagappally cohort study

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The Karunagapally cohort in Kerala, India was established in the 1990s. The present study examined oral cancer risk among 66 277 men aged 30–84 years in the cohort, using Poisson regression analysis of grouped data, stratified on attained age, calendar time, education, and family income. By the end of 2005, 160 oral cancer cases were identified by the Karunagapally Cancer Registry. Tobacco chewing increased oral cancer risk ($P < 0.001$). Particularly increased was the risk of cancers of the gum and mouth (relative risk [RR] = 4.7; 95% confidence interval [CI] = 2.8–7.9), which increased with higher daily frequencies ($P < 0.001$) and longer duration ($P < 0.001$) of tobacco chewing. Alcohol drinking was not significantly related to oral cancer risk regardless of tobacco chewing. Bidi smoking significantly increased oral cancer risk (RR = 2.6; 95%CI = 1.4–4.9) only among men without tobacco chewing habits. The risk increased with higher daily consumption ($P < 0.001$), longer duration ($P = 0.001$), and younger age at start of bidi smoking ($P = 0.007$). In location-specific analysis, bidi smoking was significantly associated with cancer of the gum and mouth (RR = 3.6; 95%CI = 1.1–12.1), and its risk significantly increased with larger daily consumption of bidis ($P = 0.013$) and younger age at the start of smoking ($P = 0.044$). Tongue cancer risk was significantly increased among men who smoked bidis for 30 years or longer, and men started bidi smoking at 18 years old or younger. The present study is the first cohort study showing that tobacco chewing increases cancers of the gum and mouth among men keeping chewing tobacco in the cheek, and that bidi smoking strongly increased oral cancer risk among men without a tobacco chewing habit. (*Cancer Sci* 2011; 102: 460–467)

Oral cancer is the 11th most common cancer in the world in terms of number of cases, and cancer of the pharynx ranks as 20th. Worldwide, approximately 389 000 new cases occurred in 2000, two-thirds of which were in economically developing countries, and these cancers are responsible for some 200 000 deaths each year.[1] In South Asia, including the Indian subcontinent, oral cancer is a major cancer problem[2] and its most important risk factor is tobacco use.[3,4] A review by Boyle *et al.* pointed out that oral cancer in Western countries can largely be ascribed to the joint effect of cigarette smoking and alcohol drinking, whereas, in Asian countries, smoking cigarettes and chewing betel leaves and betel nuts with tobacco are major risk factors.[5] Indeed, Asian societies where tobacco is used in a smokeless form have generally a high oral cancer incidence.[6–11]

In southern India, the most popularly smoked tobacco is bidi, which is made of 0.15–0.25 g sun-dried flaked tobacco rolled into a conical shape in a dried rectangular piece of Temburni leaf (*Diospyros melanoxylon*) and a thread securing the roll.[12] Bidi smoking is also an important risk factor for oral cancer. In 2003, Rahman *et al.* reported the results of a meta-analysis of case–control study data and showed that bidi smoking increased risk of oral cancer by 3.1-fold.[13] Studies reported afterward confirmed their conclusion.[11] Oral cancer risk analysis specific for its location is quite limited in number. Sankaranarayanan *et al.* reported a significantly increased risk of cancers of the tongue and the floor of the mouth in association with pan-tobacco chewing, bidi smoking and bidi plus cigarette smoking but not with cigarette smoking alone in males in Kerala, India.[6] They also found an association with alcohol drinking. In a later report, Sankaranarayanan *et al.* reported that cancers of the buccal and labial mucosa in Kerala were related to pan chewing.[2] Rao and Desai reported that tobacco chewing and bidi smoking increased the risks of the anterior portion and the base of the tongue, respectively.[14] To date, however, the risk factors of oral cancer have been evaluated mainly by case–control studies, particularly in Asian countries.[15] In the early 1990s, we established a cohort comprised of virtually all the residents in Karunagappally.[16] In the present study, we analyzed the oral cancer risk in relation to tobacco use, alcohol drinking, and socioeconomic status (SES) on the basis of a cohort study in a rural population in Kerala.

Subjects and Methods

The present study was approved by the Institutional Review Board of Regional Cancer Center, Trivandrum in Kerala, India.

Baseline survey. Karunagappally taluk consisted of 12 panchayats. Taluk is an administrative unit, corresponding to a county, and panchayat is a subunit of taluk. According to the 1991 census, this taluk had a population of 385 103 (191 149 males and 193 954 females) residing in an area of 192 square km. In the late 1980s, we planned to establish a cohort of the entire residents in Karanagappally taluk in order to examine the risk of cancer in relation to natural radiation exposure, lifestyles, and other factors.[17] All households ($n = 71\,674$) in Karunagappally taluk were visited by 12–14 interviewers, starting from January 1, 1990 and ending on December 31, 1997. Using a six-page standardized questionnaire, they collected information on sociodemographic factors, lifestyles, and other factors. Sociodemographic factors included religion, family income in Rupees, education, and occupation. Regarding tobacco chewing, we asked whether residents never had the habit of chewing tobacco, habitually chewed tobacco in the past, or habitually chewed currently. For those who answered to have chewed tobacco in the past or to chew tobacco currently, further questions on the daily frequency of tobacco chewing, age at the start of chewing tobacco, and the duration of tobacco chewing were asked. For

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ex-chewers, age stopped chewing tobacco was also asked. Similar types of questions were asked for bidi and cigarette smokers and alcohol drinkers.

Study population. In total, this household survey collected personal information on 359 614 subjects in 71 674 households, which correspond to 93% of the population and 94% of households in Karunagappally by the 1991 census. There were 69 943 men who were 30–84 years old at the time of interview. Those younger than 30 years of age were excluded from analysis as cancer risk was low in this range. Those aged 85 years or older were also excluded from the analysis as the elderly are less likely to seek medical care for malignancy, possibly resulting in lower completeness of cancer case ascertainment and lower accuracy of diagnosis. Also excluded were workers from Indian Rare Earth Limited, who might have been exposed to various occupational exposures (n = 1428). Indian Rare Earth Limited is a private company, jointly owned by the Government of India and the Government of Kerala. This company has a factory in the study area to process coastal sands to isolate various minerals, including radioactive thorium. In addition, 136 subjects, who had died or had been diagnosed with cancer before the baseline interview survey, were excluded from analysis. Furthermore, 2102 men who died within 3 years of interview were also excluded from analysis as their lifestyles might have been affected by their health conditions. Thus, there were 66 277 subjects for statistical analysis.

Cancer case ascertainment. In the present study, we analyzed cancer incidence during the period between January 1, 1990 and December 31, 2005. Cancer cases among the cohort were ascertained by the cancer registry in Karunagappally, which was officially initiated as of January 1, 1990. The registry reports have been presented in *Cancer Incidence in Five Continents* volumes VII,[18] VIII,[19] and IX.[20] To identify cancer cases, we undertook: (i) monthly routine visits to the Regional Cancer Centre (RCC) in Trivandrum, which is the comprehensive cancer centre in the state of Kerala, and more than half of cancer cases registered in Karunagappally cancer registry were those who sought medical treatment in RCC (unpublished data); (ii) annual visits to Trivandrum Medical College Hospital in Trivandrum; (iii) annual visits to major pathological laboratories in Karunagappally taluk and its neighboring areas, and in Trivandrum; (iv) annual visits to all the hospitals and medical practitioners in Karunagappally taluk; (v) three or four visits each year to three primary health centers in the taluk, which have cancer screening facilities; (vi) our clinics to provide monthly follow-up care for local cancer patients, which became popular because it provides cancer patients with palliative care and a palliative care home service as well; and (vii) our cancer screening camps carried out twice a year on average in all panchayats in the taluk. Our registry workers retrieved medical records and other relevant documents of cancer cases of Karunagappally residents diagnosed in the RCC and other medical facilities, and abstracted information on cancer cases diagnosed.

Death reports were obtained from the death registers kept in the vital statistics division of each panchayat. House visits of the deceased, to supplement information on cause of death, were started in 1997. The proportion of death certificate only cases in Karunagappally cancer registry was 14% during 1990–1994,[18] and 10% during 1993–1997.[19] In 1997, when the active tracing back of all deaths was started, the death certificate only percentage decreased substantially, and was 4% during 1998–2002.[20] The ratio between incidence and mortality for all cancer among men was 53% during the period 1993–2001[21] and was similar to those in other major cancer registries in this country.[22] Data linkage of the cohort database with death register or cancer registry data was carried out, using record matching keys, including names, dates of birth, past and current address of residence, and other relevant information.

The extent of migration among cohort members was assessed by a door-to-door survey of all households in six panchayats (Chavara, Neendakara, Panmana, Alappad, Oachira, and Thevalakkara) in 2001, and in the remaining six panchayats in 2003. The survey findings were linked to incident cases through name, address, age, house number etc. This survey showed that migration was negligible. Movement within a panchayat was approximately 10%, while temporal migration to outside the taluk was approximately 6% in the 13-year study period. Only 0.7% was lost to follow-up due to permanent migration. The majority of migration took place for job opportunities in Middle Eastern countries.

Statistical analysis. Statistical analysis was based on the data in cross-classifications by attained age (5-year category), and other covariates. Relative risk (RR) and 95% confidence intervals (95%CI) were obtained from Poisson regression analysis of grouped survival data[23] using the DATAB and AMFIT procedures of the Epicure program.[24]

In the analysis examining the association of cancer risk with tobacco chewing, which has the three categories (never, former, and current), the following model was used to estimate the RRs of former tobacco chewers (represented by S_2) and current-chewers (represented by S_3):

$$H_0 \text{ (attained age, calendar time, income, education) exp } (\beta_2 S_2 + \beta_3 S_3),$$

where H_0 represents the baseline, or background, oral cancer incidence (e.g., incidence rate for never smokers) for cross-classified strata by 5-year attained age categories, calendar time (1990–1997, 1998–2001, and 2002–2005), and sociodemographic variables. Attained age at the time of the midpoint of the 1-year interval during the observation period (1990–2005) was calculated for each cohort member by the DATAB procedure of the Epicure program.[24] The maximum likelihood estimates of β_2 and β_3, for example, are log RRs for the indicator variables S_2 and S_3, respectively, when compared to the reference category of S_1, adjusting for attained age, calendar time, family income, and education attained. Heterogeneity test was based on a global P-value for a set of indicator variables. Trend test was carried out by assigning the mean duration of, for example, duration of tobacco chewing, in each category of duration. In the analysis comparing the magnitude of the association between oral cancer risk and daily frequency of tobacco chewing, the following model was used:

$$H_0 \text{ (attained age, SES variables) exp } (\beta_2 C_2 + \beta_3 C)$$

where C is the mean of daily frequency of tobacco chewing, assigned to each category. Tobacco use, including bidi smoking, cigarette smoking, and tobacco chewing, is related to SES in this cohort as shown in our previous study.[25] For example, our previous study showed that those smoking bidis had lower family income and lower levels of education when compared to those smoking only cigarettes. Therefore, the analysis of the present study was stratified by SES factors significantly related to oral cancer risk.

The entry into the cohort was January 1, 1990 or the date of interview; interviews started on January 1, 1990 and ended on December 31, 1997. A member of the cohort was considered to be censored when he was diagnosed with cancer other than oral cancer or died of causes other than oral cancer. Thus, the end of follow-up was the date of diagnosis for cancer cases, the date of death for those deceased, the end of follow-up (December 31, 2005), or the date attaining age of 85.

Results

The present study examined 66 277 men aged 30–84 years. By the end of 2005, we identified 160 cases of oral cavity

Table 1. Sociodemographic features of male study subjects living in Karunagappally (Kerala, India), and their associations with oral cancer risk

	n	Person-years	All oral cancers			Tongue			Gum and mouth		
			n	RR	95%CI	*n*	RR	95%CI	*n*	RR	95%CI
Total	66 277	769 202	160			70			82		
Religion				$P = 0.172$			$P = 0.423$			$P = 0.224$	
Hindu	48 227	563 080	127	1.0	RP	55	1.0	RP	66	1.0	RP
Moslem	11 982	138 145	22	0.7	0.4–1.1	9	0.7	0.3–14	12	0.7	0.4–1.4
Christian	6068	67 977	11	0.7	0.4–1.3	6	0.9	0.4–2.0	4	0.5	0.2–1.4
Family income (Rs)†				$P = 0.004$			$P > 0.5$			$P = 0.005$	
<500	4371	53 321	19	1.8	1.0–3.0	6	1.3	0.5–3.2	12	2.2	1.1–4.4
501–1200	19 542	230 502	49	1.0	RP	21	1.0	RP	25	1.0	RP
1201–2500	25 141	288 177	65	1.0	0.7–1.4	28	1.0	0.6–1.8	34	1.0	0.6–1.7
2501–3500	11 006	124 515	15	0.5	0.3–0.9	7	0.5	0.2–1.3	8	0.5	0.2–1.2
3500+	6217	72 687	12	0.7	0.4–1.3	8	1.1	0.5–2.4	3	0.3	0.1–1.1
Education				$P = 0.023$			$P = 0.097$			$P = 0.180$	
Illiterate	4228	46 652	12	0.8	0.4–1.5	2	0.3	0.1–1.3	10	1.3	0.6–2.6
Primary school	17 199	193 785	58	1.0	RP	25	1.0	RP	30	1.0	RP
Middle school	17 514	203 700	53	1.0	0.7–1.4	25	1.1	0.6–1.9	23	0.8	0.5–1.4
High school	20 888	249 295	27	0.5	0.3–0.8	13	0.6	0.3–1.1	14	0.5	0.2–0.9
College	5732	67 512	9	0.6	0.3–1.3	5	0.8	0.3–2.1	4	0.5	0.2–1.5
Unknown	716	8257	1	0.4	0.1–3.1	0	0.0	0.0	1	0.8	0.1–6.0
Occupation				$P = 0.302$			$P = 0.384$			$P = 0.221$	
Farmers/fishermen	12 509	143 423	36	1.0	RP	13	1.0	RP	22	1.0	RP
Unemployed	15 311	174 398	35	0.8	0.5–1.3	20	1.3	0.6–2.6	13	0.5	0.2–1.0
Students	872	9909	1	0.4	0.1–2.9	0	0.0	0.0	1	0.6	0.1–4.8
Skilled workers	33 668	395 559	83	0.9	0.6–1.4	35	1.1	0.6–2.1	43	0.8	0.5–1.3
Others	3917	45 912	5	0.5	0.2–1.2	2	0.5	0.1–2.3	3	0.4	0.1–1.5

International Classification of Diseases-9 classifications: oral cancer, 140–145; cancer of the tongue, 141; cancer of the gum and mouth, 143–145. Relative risk was obtained from the following model: $H = H_s \exp(B_i X_i)$, where background hazard (Hs) was stratified by 5-year categories of attained age and calendar time (1990–1997, 1998–2001, 2002–2005), and X_i are categorical variables of sociodemographic factors. †Monthly family income expressed in Indian rupees (1Rs = 2–3 US cents). CI, confidence interval; RP, reference point; RR, relative risk.

Table 2. Oral cancer incidence in relation to tobacco use and alcohol drinking among men in Karunagappally (Kerala, India)

	n	Person-years	All oral cancers			Tongue			Gum and mouth		
			n	RR	95%CI	*n*	RR	95%CI	*n*	RR	95%CI
Total	66 277	769 202	160			70			82		
Tobacco chewing				$P < 0.001$			$P = 0.422$			$P < 0.001$	
Never	42 652	496 606	64	1.0	RP	39	1.0	RP	21	1.0	RP
Former	4518	49 079	19	2.1	1.3–3.6	9	1.7	0.8–3.5	10	3.4	1.6–7.3
Current	18 692	218 673	75	2.4	1.7–3.3	21	1.1	0.7–1.9	50	4.7	2.8–7.9
Unknown	415	4844	2	3.3	0.8–13.6	1	2.5	0.3–18.4	1	5.4	0.7–40.0
Bidi smoking				$P > 0.5$			$P > 0.5$			$P > 0.5$	
Never	31 473	371 650	59	1.0	RP	26	1.0	RP	31	1	RP
Former	6032	64 193	18	1.0	0.6–1.8	10	1.4	0.7–3.1	7	0.7	0.3–1.6
Current	25 692	297 564	74	1.1	0.7–1.5	30	1.1	0.6–2.0	39	1.0	0.6–1.6
Unknown	3080	35 794	9	1.3	0.6–2.6	4	1.5	0.5–4.3	5	1.2	0.5–3.2
Alcohol drinking				$P = 0.165$			$P = 0.283$			$P = 0.319$	
Never	33 657	388 540	67	1.0	RP	32	1.0	RP	33	1	RP
Former	8075	88 218	30	1.5	0.9–2.2	15	1.6	0.9–3.0	12	1.2	0.6–2.4
Current	24 514	292 096	63	1.2	0.8–1.7	23	1.0	0.6–1.7	37	1.4	0.9–2.3
Unknown	31	348	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0

International Classification of Diseases-9 classifications: oral cancer, 140–145; cancer of the tongue, 141; cancer of the gum and mouth, 143–145. Relative risk was obtained from the following model: H = Hs exp (BiXi), where background hazard (Hs) was stratified by attained age, calendar time, income, and education; and Xi are categorical variables of tobacco use or alcohol drinking. *P*-values were obtained from analysis excluding the unknown category. CI, confidence interval; RP, reference point; RR, relative risk.

(International Classification of Diseases [ICD]-9: 140–145). Table 1 presents the sociodemographic features of study subjects and RR for those factors. The RRs were obtained by the analysis stratified on attained age and calendar time period. Among factors related to SES, lower income and lower education levels were significantly related to increased oral cavity cancer risk. In subsite-specific analysis, cancer of the tongue (ICD-9: 141) was not significantly related to any of those factors. However, the risk of cancer of the gum and mouth (ICD-9: 143–145) was significantly related to lower family income.

Table 2 summarizes the analysis examining the effects of tobacco chewing, bidi smoking and alcohol drinking. All of the

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following analyses were stratified on attained age, calendar time period, family income, and educational levels. Tobacco chewing was strongly related to the risk of oral cavity cancer ($P < 0.001$), particularly cancers of the gum and mouth ($P < 0.001$). Current tobacco chewing increased oral cavity cancer risk 2.4-fold. In subsite-specific analysis, tobacco chewing increased cancers of the gum and mouth 4.7-fold but cancer of the tongue only slightly (RR = 1.1). Neither bidi smoking nor alcohol drinking was significantly associated with oral cancer risk in this analysis.

The results of further analysis on tobacco chewing are summarized in Table 3. Oral cancer risk increased with high daily frequency ($P < 0.001$) and longer duration ($P < 0.001$). In subsite-specific analysis, the incidence of cancer of the gum and mouth was significantly related to daily frequency ($P < 0.001$) and duration ($P < 0.001$) of tobacco chewing. The risk of tongue cancer increased among those who used chewing tobacco 15 or more times a day.

When analysis was restricted to men who had never smoked bidis (Table 4), the association between oral cancer and tobacco chewing became even stronger. The risk of oral cavity cancer among current tobacco chewers was 5.4-fold higher than men who had never had tobacco chewing habit. However, tobacco chewing was not significantly related to oral cancer risk among current bidi smokers.

Table 5 summarizes the results of further risk analysis on alcohol drinking. Alcohol drinking did not evidently increase oral cavity cancer risk among men with or without tobacco chewing habits. Neither was an association found between alcohol drinking and oral cancer risk regardless of bidi smoking.

In the analysis shown in Table 2, bidi smoking was not significantly related to oral cavity cancer risk. However, this analysis included both tobacco chewers and non-chewers. A possibility is that the strong effects of tobacco chewing masked the possible association between bidi smoking and oral cancer risk. Table 6 shows the frequencies of bidi smokers according to tobacco chewing. Current and former tobacco chewers tended to be bidi smokers and bidi heavier smokers when compared to life-time non-tobacco chewers.

In order to eliminate the effects of tobacco chewing, analysis restricted to men who never had tobacco chewing habit was carried out. The results are summarized in Table 7. Bidi smoking increased the risk of oral cavity cancer ($P = 0.015$). Oral

Table 3. Oral cancer risk in relation to tobacco chewing among men living in Karunagappally (Kerala, India)

	Person-years	All oral cancers			Tongue			Gum and mouth		
		n	RR	95%CI	*n*	RR	95%CI	*n*	RR	95%CI
Total	769 202	160	—	—	70	—	—	82	—	—
Daily frequency		*P* for trend <0.001			*P* for trend = 0.468			*P* for trend < 0.001		
Never	496 606	64	1.0	RP	39	1.0	RP	21	1.0	RP
Former	49 079	19	2.1	1.3–3.6	9	1.7	0.8–3.6	10	3.4	1.6–7.4
1–4	139 624	36	1.9	1.2–2.8	9	0.8	0.4–1.6	25	3.9	2.2–6.9
5–14	61 970	30	3.1	2.0–4.8	7	1.2	0.5–2.7	22	6.7	3.7–12.3
≥15	8905	7	4.6	2.1–10.1	3	3.5	1.1–11.4	3	5.7	1.7–19.4
Unknown	13 017	4	2.5	0.9–6.8	3	3.0	0.9–9.7	1	1.9	0.3–13.8
Duration (years)		*P* for trend <0.001			*P* for trend = 0.252			*P* for trend <0.001		
Never	496 606	64	1.0	RP	39	1.0	RP	21	1.0	RP
1–14	120 199	30	2.0	1.3–3.2	9	1.0	0.5–2.1	20	4.2	2.3–7.8
15–29	83 246	33	2.5	1.6–3.8	9	1.1	0.5–2.3	23	5.2	2.9–9.5
30–44	39 689	20	2.4	1.4–4.1	5	1.1	0.4–2.9	13	4.4	2.2–9.0
≥45	10 701	4	1.7	0.6–4.8	4	2.9	0.9–8.8	0	0.0	0.0
Unknown	18 761	9	3.7	1.8–7.5	4	2.7	1.0–7.7	5	6.1	2.3–16.5
Starting age (years) – former tobacco chewers were excluded from analysis		*P* for trend = 0.365†			*P* for trend = 0.046†			*P* for trend > 0.5†		
<25	70 475	23	2.3	1.4–3.7	7	1.2	0.5–2.6	15	4.5	2.3–8.8
25–34	75 126	28	3.1	2.0–4.9	11	2.1	1.1–4.1	15	5.0	2.6–9.8
35–44	34 061	10	1.8	0.9–3.5	1	0.3	0.04–2.1	9	5.0	2.2–11.0
≥45	25 021	9	1.6	0.8–3.4	0	0.0		8	4.6	2.0–10.5
Never	496 606	64	1.0	RP	39	1.0	RP	21	1.0	RP
Unknown	18 834	7	2.9	1.3–6.3	3	2.1	0.6–6.8	4	4.8	1.6–14.1
Time since cessation (years)		*P* for trend = 0.101†			*P* for trend > 0.5†			*P* for trend = 0.115†		
Current chewers	218 673	75	1.0	RP	21	1.0	RP	50	1.0	RP
0–9	27 466	12	1.1	0.6–2.0	5	1.6	0.6–4.3	7	0.9	0.4–2.1
≥10	14 944	2	0.3	0.1–1.2	1	0.5	0.1–4.0	1	0.2	0.03–1.5
Never	496 606	64	0.4	0.3–0.6	39	0.9	0.5–1.5	21	0.2	0.1–0.4
Unknown	11 513	7	1.6	0.7–3.4	4	2.8	0.9–8.3	3	1.1	0.4–3.7

International Classification of Diseases-9 classifications: oral cancer, 140–145; cancer of the tongue, 141; cancer of the gum and mouth, 143–145. Relative risk was obtained from the following model: H = Hs exp(BiXi), where background hazard (Hs) was stratified by attained age, calendar time, income, and education. Xi are categorical variables for bidi smoking. Those in the ''unknown'' category were excluded when calculating *P*-values for trend. †''Never'' category was also excluded when calculating *P*-values for trend; —, not applicable. CI, confidence interval; RP, reference point; RR, relative risk.

Table 4. Oral cancer risk in relation to tobacco chewing among men living in Karunagappally (Kerala, India): Comparison between current and never bidi smokers

	Never smoked bidis				Current bidi smokers			
	Person-years	*n*	RR	95%CI	Person-years	*n*	RR	95%CI
Total	371 650	59	—	—	297 564	74	—	—
Tobacco chewing			$P < 0.001$				$P > 0.5$	
Never	270 450	18	1.0	RP	171 222	38	1.0	RP
Former	12 983	4	3.2	1.1–9.6	20 758	7	1.3	0.6–2.9
Current	86 184	37	5.4	3.0–9.0	103 371	27	1.3	0.8–2.1
Unknown	2033	0	0.0	0.0	2213	2	4.2	1.0–18.1
Daily frequency			P for trend < 0.001				P for trend = 0.263	
Never	270 450	18	1.0	RP	171 222	38	1.0	RP
Former	12 983	4	3.3	1.1–9.9	20 758	7	1.3	0.6–2.9
1–4	52 108	14	3.7	1.8–7.4	74 145	18	1.2	0.7–2.2
5–14	27 128	18	7.6	3.9–14.8	25 482	7	1.2	0.5–2.8
≥15	4317	5	12.8	4.6–35.4	3114	2	2.9	0.7–12.1
Unknown	4664	0			2842	2	3.2	0.8–13.6
Duration (years)			P for trend < 0.001				P for trend = 0.200	
Never	270 450	18	1.0	RP	171 222	38	1.0	RP
1–14	48 451	16	5.2	2.6–10.3	55 661	9	0.9	0.4–1.9
15–29	29 318	15	5.6	2.8–11.3	43 627	14	1.5	0.8–2.9
30–44	12 845	8	5.2	2.1–12.6	19 259	9	1.5	0.7–3.1
≥45	3671	1	2.1	0.2–18.1	4732	2	1.2	0.3–5.3
Unknown	6917	1	2.2	0.3–16.5	3063	2	3.1	0.7–13.0
Starting age (years) – former tobacco chewers were excluded from analysis			P for trend > 0.5†				P for trend = 0.295†	
<25	27 896	12	5.3	2.5–11.2	37 558	38	1.6	0.8–3.1
25–34	33 018	16	7.3	3.7–14.4	37 271	11	1.4	0.7–3.0
35–44	13 100	4	3.1	1.0–9.4	16 427	9	1.4	0.6–3.7
≥45	7073	5	6.5	2.3–18.5	11 012	5	0.5	0.1–2.2
Never	270 450	18	1.0	RP	171 222	2	1.0	RP
Unknown	7129	0	0.0	0.0	3316	2	2.8	0.7–11.9

Relative risk was obtained from the following model: $H = H_s \exp(B_i X_i)$, where background hazard (Hs) was stratified by attained age, calendar time, income, and education. X_i are categorical variables for bidi smoking. Those in the ''unknown'' category were excluded when calculating P-values for trend. † ''Never'' category also excluded when calculating *P*-values for trend; —, not applicable. CI, confidence interval; RP, reference point; RR, relative risk.

Table 5. Oral cancer risks in relation to alcohol drinking among men living in Karunagappally (Kerala, India), according to tobacco chewing habit

	Never chewed tobacco				Current tobacco chewers			
	Person-years	*n*	RR	95%CI	Person-years	*n*	RR	95%CI
Weekly alcohol consumption			P for trend > 0.5				P for trend > 0.5	
Never	290 919	38	1.0	RP	78 886	24	1.0	RP
Former	44 464	12	1.5	0.8–3.0	26 440	12	1.3	0.6–2.6
<70 mg/day	61 194	1	0.1	0.02–1.0	40 423	12	1.2	0.6–2.4
≥70 mg/day	83 500	12	1.0	0.5–2.0	63 125	23	1.2	0.7–2.2
Unknown	16 529	1	0.5	0.1–3.6	9799	4	1.6	0.6–4.7

Relative risk was obtained from the following model: H = Hs exp (BiXi), where background hazard (Hs) was stratified by attained age, calendar time, income, and education. Xi are categorical variables for alcohol drinking. Those in ''unknown'' category were excluded when calculating *P*-values for trend. CI, confidence interval; RP, reference point; RR, relative risk.

cavity cancer risk increased with larger numbers of bidis smoked per day ($P < 0.001$), longer duration of bidi smoking ($P = 0.001$), and younger age at starting bidi smoking ($P = 0.007$). In subsite-specific analysis, the risk of cancers of the gum and mouth among those who never used chewing tobacco was significantly related to bidi smoking ($P = 0.012$). The risk of cancer in this subsite was significantly related to larger numbers of bidis smoked a day ($P = 0.013$) and younger age at starting bidi smoking ($P = 0.044$). The risk was also related to longer duration of bidi smoking with a marginal statistical significance ($P = 0.053$). In contrast, tongue cancer risk increased with longer duration of bidi smoking ($P = 0.034$). Its risk was significantly increased among men who smoked bidis for 30 years or longer, and its RR and 95%CI were 3.4 and

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Table 6. Bidi smoking frequency among men living in Karunagappally (Kerala, India), according to tobacco chewing

Age at interview (years)	Bidi smoking frequency (per day)	Tobacco chewing							
		Never		Former		Current		Unknown	
		n	%	*n*	%	*n*	%	*n*	%
<40	Never	10 302	68	198	43	2770	46	103	55
	Former	231	2	67	15	192	3	7	4
	1–4	616	4	30	7	422	7	11	6
	5–14	1679	11	69	15	1151	19	33	18
	15–24	1111	7	52	11	709	12	21	11
	25+	518	3	35	8	411	7	8	4
	Unknown	786	5	5	1	308	5	4	2
	Total	15 243	100	456	100	5963	100	187	100
50–59	Never	6275	54	272	30	2198	38	48	39
	Former	540	5	210	23	385	7	10	8
	1–4	449	4	39	4		356	6	8
	5–14	1459	13	131	14	1075	19	17	14
	15–24	1294	11	143	16	872	15	19	15
	25+	882	8	96	11	593	10	17	14
	Unknown	692	6	20	2	315	5	4	3
	Total	11 591	100	911	100	5794	100	123	100
≥60	Never	6249	40	698	22	2338	34	22	21
	Former	2081	13	1106	35	1177	17	26	25
	1–4	555	4	128	4	385	6	3	3
	5–14	2527	16	447	14	1263	18	11	10
	15–24	2241	14	376	12	915	13	16	15
	25+	1407	9	330	10	573	8	25	24
	Unknown	758	5	66	2	284	4	2	2
	Total	15 818	100	3151	100	6935	100	105	100

1.3–8.9, respectively (data not shown). Starting bidi smoking at 18 years or younger was also related to the cancer risk of this subsite.

Discussion

The present cohort study carried out in Kerala, where many people chew tobacco in the cheek, showed that tobacco chewing increases the risk of cancers of the gum and mouth nearly 5.0-fold. Our findings support the notion that most cancers of the cheek and gum are considered to be caused by tobacco chewing.[12,26] However, the present study found no statistically significant association between cancer of the tongue with tobacco chewing, although its risk was increased among frequent tobacco chewers. In South Asia, including India, smokeless tobacco use encompasses nass (naswar), khaini, mawa, mishri, and gudakhu, which are mixtures of tobacco leaves and areca nuts, as well as betel leaves and betel nuts.[15] In Kerala, South India, chewing tobacco alone is not common; the most common form of smokeless tobacco use is chewing betel leaves and betel nuts with tobacco in the raw state rather than after processing.[4] It was reported that chewing pan with or without tobacco increased oral cavity cancer risk in men and women, based on analysis of data obtained from a case–control study nested in a cohort in the Trivandrum area in Kerala, India.[11,27] In the present study, however, it was difficult to examine whether the use of betel leaves and betel nuts or pan together with tobacco was more harmful or not, as the tobacco chewing was almost always associated with pan use.

This is the first cohort study to show the association between bidi smoking and the risk of diseases of the oral cavity, particularly cancers of the gum and mouth. Among men without a tobacco chewing habit, the risk of cancers of the gum and mouth was associated with larger amounts of bidi smoked a day ($P = 0.013$) and younger age at starting smoking ($P = 0.044$). The risk was also related to longer duration of bidi smoking with marginal statistical significance ($P = 0.053$). The risk was not limited to cancer of the gum and mouth. The risk of tongue cancer among those without a tobacco chewing habit was related to a longer duration of bidi smoking ($P = 0.034$), and those who smoked bidis for 30 years or longer had significantly higher cancer of the tongue (RR = 3.4; 95%CI = 1.3–8.9). Its risk was also related to starting bidi smoking at 18 years or younger. In contrast, among men with a tobacco chewing habit, bidi smoking did not evidently increase the risk of oral cancer. Our findings are similar to those reported by Sankranarayanan *et al.*[2], who showed that bidi smoking increased buccal and labial cancer risk by 4.21-fold, but only 1.5-fold among pan-tobacco chewers. Sankaranarayanan *et al.* made a similar finding in cancers of the tongue and floor of the mouth. They reported that the risk of cancer of the tongue and floor the of mouth was increased 4.98-fold among men without the habit of pan-tobacco chewing, but only 1.1-fold among pan-tobacco chewers.[7] Although it is suspected that the combined habits of bidi smoking and tobacco chewing is associated with larger oral cancer risk than the sum of the risk associated with bidi smoking alone and tobacco chewing alone, no study has clearly shown such synergistic effects. As was already described in ''Results'', the present study also did not find such a synergism.

Alcohol drinking was not evidently related to oral cancer risk regardless of tobacco chewing habit in the present study, confirming the notion made in the review by Boyle *et al.*,[5] which pointed out that alcohol drinking was an important risk factor in Western countries but not in Asian societies.

In the present study, cigarette smoking was not significantly related to oral cancer risk (data not shown). In this rural community, the number of long-term cigarette smokers was limited, and it was difficult to examine its risk with oral cancer.

Socioeconomic status is also suspected to be related to oral cancer risk. In the present study, oral cancer risk among men

Table 7. Oral cancer risk in relation to bidi smoking among men living in Karunagappally (Kerala, India), without tobacco chewing habit

	Person-years	All oral cancers			Tongue			Gum and mouth		
		n	RR	95%CI	*n*	RR	95%CI	*n*	RR	95%CI
Bidi smoking		*P* = 0.015			*P* for trend = 0.281			*P* for trend = 0.012		
Never	270 450	18	1.0	RP	14	1.0	RP	4	1.0	RP
Former	30 205	5	1.6	0.6– 4.6	5	2.3	0.8–6.8	0	0.0	0.0
Current	171 222	38	2.6	1.4–4.9	18	1.8	0.8–4.0	16	3.6	1.1–12.1
Unknown	24 729	3	1.6	0.5–5.8	2	1.7	0.4–7.5	1	1.7	0.2–17.0
No. smoked per day		*P* for trend < 0.001			*P* for trend = 0.121			*P* for trend = 0.013		
Never	270 450	18	1.0	RP	14	1	RP	4	1.0	RP
Former	30 205	5	1.7	0.6–4.7	5	2.3	0.8–6.9	0	0.0	0.0
1–4	19 042	1	0.8	0.1–5.7	1	1.1	0.1–8.3	0	0.0	0.0
5–14	65 144	12	2.3	1.0–5.1	5	1.4	0.5–4.0	6	4.1	1.1–16.1
15–24	53 349	14	3.0	1.4–6.5	9	2.8	1.1–7.1	3	2.1	0.4–10.2
≥25	32 356	11	3.5	1.5–8.1	3	1.4	0.4–5.4	7	6.7	1.7–26.1
Unknown	26 059	3	1.6	0.4–5.7	2	1.6	0.3–7.3	1	1.6	
Duration of smoking (years)		*P* for trend = 0.001			*P* for trend = 0.034			*P* for trend = 0.053		
Never	270 450	18	1.0	RP	14	1	RP	4	1.0	RP
1–29	119 085	13	1.6	0.7–3.4	6	1.0	0.3–2.8	5	2.4	0.6–9.8
30–44	59 204	19	3.1	1.4–6.8	11	3.1	1.1–8.5	7	3.0	0.7–12.3
≥45	22 971	11	6.3	2.2–18.1	6	5.2	1.3–20.6	4	6.6	1.1–39.6
Unknown	24 896	3	1.6	0.4–5.6	2	1.6	0.4–7.5	1	1.5	0.2–15.7
Age started smoking (years) – former smokers were excluded from analysis		*P* for trend = 0.007†			*P* for trend = 0.066†			*P* for trend = 0.044†		
<18	32 648	17	5.4	2.7–12.4	8	4.2	1.5–11.6	9	9.1	2.5–33.8
18–22	87 720	13	1.9	0.9–4.2	6	1.3	0.4–3.7	3	1.5	0.3–7.4
≥23	50 726	8	1.9	0.8–4.6	4	1.4	0.4–4.6	4	3.1	0.7–13.2
Never	270 450	18	1.0	RP	14	1	RP	4	1.0	RP
Unknown	24 858	3	1.7	0.5–6.0	2	1.7	0.4–8.0	1	1.7	0.2–17.2
Time since quitting (years)		*P* for trend = 0.267†			*P* for trend > 0.5†			*P* for trend > 0.5†		
Current smokers	171 222	38	1.0	RP	18	1.0	RP	16	1.0	RP
0–9	20 214	4	0.8	0.3–2.3	4	1.6	0.5–5.0	0	0.0	0.0
≥10	9578	1	0.4	0.05–2.6	1	0.7	0.1–5.3	0	0.0	0.0
Never	270 450	18	0.4	0.2–0.7	14	0.6	0.2–1.2	4	0.3	0.1–0.9
Unknown	25 142	3	0.6	0.2–2.1	2	0.9	0.2–3.9	1	0.5	0.1–3.8

International Classification of Diseases-9 classifications: oral cancer, 140–145; cancer of the tongue, 141; cancer of the gum and mouth, 143–145. Relative risk was obtained from the following model: H = Hs exp (BiXi), where background hazard (Hs) was stratified by attained age, calendar time, income and education. Xi are categorical variables for Bidi smoking. Those in the ''unknown'' category were excluded when calculating *P*-values. †''Never'' was also excluded when calculating *P*-values for trend. CI, confidence interval; RP, reference point; RR, relative risk.

was related to monthly income and to education levels. However, when tobacco chewing and bidi smoking were included in the statistical model, oral cancer risk was not significantly related to income or education (data not shown). Case–control studies carried out in India also showed that lower education levels were related to increased oral cancer risk.[9,10] However, the results obtained from studies on the association with SES, awareness and lifestyle are mixed. A review by Faggiano *et al.* concluded that most incidence studies did not show a clear association, whereas oral cancer mortality was elevated in lower SES sections of various populations.[28] Recently, Hashibe *et al.* reported a case–control study in Kerala, India, that showed that lower levels of education and income were related to relatively high prevalence of oral premalignant lesions.[29] Note here, however, inconsistent results on SES are not unexpected, as SES is most likely a surrogate marker of risk factors related to oral cancer risk, and the associations of those risk factors with SES are different from society to society.

The best and only way to avoid cancer risk associated with smokeless tobacco is cessation of its use. Unfortunately, however, tobacco chewing is not rare even among highly educated people in Kerala State,[17] where the literacy rate is more than 90% and public health is relatively good, as indicated by the infant mortality rate being <20 per 1000 births.[30] It should also be noted that smokeless tobacco, including chewing tobacco, is getting popular in North America and Western Europe because of the antismoking movement.[31] It is necessary to step up our efforts in public education regarding the harm of tobacco use.

A disadvantage of a cohort study is the fact that the lifestyle of cohort members, examined at the start of its following-up, may change during follow-up. In the present study, no attempt was made to re-interview the cohort members. We cannot deny the possibility that those who answered to be lifetime non-tobacco chewers at the baseline survey started tobacco chewing during our follow-up period, and those who answered as having a tobacco chewing habit at the time of interview stopped the habit during the follow-up. Because of such problems, the RRs for tobacco chewing shown in the present study might have been underestimated. In addition, the duration of tobacco chewing and years after cessation of tobacco chewing is probably underestimated as the information used in the present study is the period until the time of interview. The same arguments are also true for bidi smoking.

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In summary, the present study is the first cohort study showing that tobacco chewing increases cancers of the gum and mouth among men who chew tobacco in the cheek, and that bidi smoking strongly increases the risk of oral cancer among men without a tobacco chewing habit.

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