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TOBACCO SMOKING AND CHEWING, ALCOHOL DRINKING AND LUNG CANCER RISK AMONG MEN IN SOUTHERN INDIA

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In India, lung cancer is one of the most common and lethal cancers, and tobacco smoking remains its most important etiologic factors. The objective of our study is to examine the effects of different tobacco consumption forms, including smoking and chewing, on lung cancer risk of men in southern India, especially to compare the effects of *bidi* smoking to cigarette smoking on lung carcinogenesis. We also evaluated the possible role of Indian alcohol beverages and non-Indian alcohol beverages on lung carcinogenesis. We conducted a case-control study in Chennai and Trivandrum. In total, 778 lung cancer cases and 3,430 controls, including 1,503 cancer controls and 1,927 healthy controls, were recruited. The effects of cigarette, *bidi* smoking, chewing and alcohol drinking on the risk of lung cancer were estimated from unconditional multivariate logistic regression. We also applied the generalized additive model (GAM) with locally-weighted running-line smoothers *(loess)* to find the most plausible curve for the dose-response relationship. The results from GAM suggest a plateau after 35 years of smoking or 10 cigarette-equivalent pack-years for both cigarette and *bidi*. The OR is 4.54 (95%CI=2.96–6.95) and 6.45 (95%CI=4.38–9.50) for more than 30 years of cigarette-only and *bidi*-only smoking, respectively, and 6.87 (95%CI=4.62–10.2) and 10.7 (95%CI=5.82–19.6) for more than 12 weighted cumulative cigarette-only and *bidi*-only consumption, respectively. The lung cancer risk of former cigarette smokers drops down more quickly after quitting smoking compared to former *bidi* smokers. There is no evidence for the effect of chewing and lung cancer risk nor clear evidence of an effect of overall alcohol drinking among never-smokers, although Indian alcohol drinking seemed to remain associated with lung cancer risk under limited power (OR=2.67, 95%CI=1.02–7.02). *Bidi* smoking seems to have a stronger carcinogenic effect than cigarette smoking: this difference holds no matter which aspect of smoking was considered.

Key words: *lung cancer; tobacco smoking; chewing; Southern India; Generalized Additive Model*

Lung cancer is one of the most common and lethal cancers in India, with an estimation of 34,000 incidence cases and 31,000 deaths in men per year.[1] Tobacco consumption remains the major risk factor of lung cancer worldwide, especially in men,[2,3] and several epidemiological studies have shown that tobacco smoking is the most important etiologic factors of lung cancer in India.[4–6] The smoking prevalence in Indian women is low, and only around 6% of the female lung cancer patients have ever smoked.[7]

Cigarette smoking is a relatively recent habit in India compared to the smoking of other traditional Indian products, and its prevalence has increased steadily in the past 40 years.[8] The traditional Indian smoking product is *bidi*, which is made with aged Indian tobacco, hand wrapped in a *tembhurni* leaf, nubbed on one end and bound with a thin string on the other.[9] It contains around 0.2–0.3g of locally grown tobacco.[9,10] It is estimated that 136 out of 400 million adults in India smoke *bidis*.[9] It has been suggested that *bidi* is equal to or more harmful than cigarette smoking for the development of lung cancer. However only a few epidemiological studies have examined the role of *bidi* smoking on lung carcinogenesis, and the results were inconsistent.[6,11–15] Another traditional, but less common, smoking product is *chutta*, which is a coarsely prepared cheroot often smoked in reverse (lit end in the mouth).[9]

Oral use of tobacco is another common form of tobacco consumption in India. Chewing tobacco in India is made from sun-dried, coarsely cure leaves, which are usually broken into little pieces and consumed raw.[10] It contains abundant tobacco-specific N-nitrosamines (TSNA), mainly NNK and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL).[9] A number of studies have shown an effect of chewing tobacco on the risk of oral, pharyngeal and esophageal cancers.[16,10] Despite the fact that one of the major targets of TSNA is the lung, and the effect of TSNA on lung cancer development was suggested to be independent from the route of administration in experimental models,[10,17] there is no sufficient evidence of the effect of chewing habit on lung cancer in humans so far.[6,10,14]

Alcohol drinking was proposed as a potential risk factor of lung cancer by Potter and McMichael,[18] and its carcinogenic potential has been reviewed.[19,20] However, the epidemiological evidence of its relationship with lung cancer has not been conclusive, mainly due to potential residual confounding by cigarette smoking.[21,20] No data is available on the possible effects of alcohol drinking on lung cancer risk in India, where mainly locally-produced liquors, including toddy, arrack and country liquor, are drunk. Toddy is a locally fermented palm sap, arrack is locally brewed liquor with approximately 40% ethanol content and country liquor is a synonym of arrack.

The objective of our study was to examine the effects of different tobacco consumption forms, including smoking and chewing, on lung cancer risk of men in southern India, especially to compare the effects of *bidi* smoking to cigarette smoking on lung carcinogenesis, and also to evaluate the possible role of Indian and non-Indian alcohol beverages on lung carcinogenesis.

MATERIAL AND METHODS

Study population and data collection

This case-control study was conducted at the Cancer Institute of Chennai, Tamic Nadu, and the Regional Cancer Center in Trivandrum, Kerala. Male patients of lung cancer who reported to these institutions between 1993 and 1999 were recruited as cases. Male patients with non-tobacco-related cancers who registered into the cancer centers during the same period of time were recruited as cancer controls. The eligible diseases for cancer control excluded tobacco-related cancers[22] and included cancers of the small intes-

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tine, colon, rectum, gallbladder, retroperitoneum, bone, connective tissue, male breast, prostate and eye, as well as Hodgkin's lymphoma and multiple myeloma [Ninth Revision of International Classification of Diseases (ICD-9) code 152, 153, 154, 156, 158, 170, 171, 173, 175, 185, 190, 200, 201, 202 and 203]. Male healthy visitors to non-tobacco related cancer patients in Cancer Institute of Chennai were also recruited as healthy controls. In total, 778 lung cancer cases and 3,430 controls including 1,503 cancer controls and 1,927 healthy controls were recruited. All cases and cancer controls were histologically confirmed. All subjects were interviewed by trained social investigators with standard questionnaires. Information on demographic variables, medical histories, smoking habits, chewing habits, alcohol habits and working histories was collected. The collected data of each center was compiled, cleaned and quality checked centrally.

Smokers were defined as people who smoked a tobacco product at least once a day for at least 6 months. Former smokers were defined as smokers who had stopped smoking for more than 1 year before the interview. Comparable definitions of categories were applied to the chewing habit. To combine different tobacco smoking products, we calculated cigarette-equivalents, by assigning a weight of 1 for cigarettes and 0.25 for *bidis*, based on grams of tobacco content. Smoking pack-year was calculated as the product of smoking duration (years) and average number of packs (*i.e.*, 20 cigarettes equivalents) smoked per day. The total smoking pack-year is the sum of all product-specific pack-years the subject consumed. Alcohol beverage was dichotomized into Indian authentic alcohol, which include toddy, arrack and country liquor, and non-Indian alcohol such as beer, whiskey, gin, rum and brandy. Alcohol drinkers were defined as people who drink alcoholic beverages at least once a day for at least 6 months. Former drinkers were defined as drinkers who have stopped drinking alcohol for more than 1 year before the interview. The quantity of alcohol drunk per day was the product of the amount consumed (ml) and the percentage of the alcohol in the product (assuming 3% for beer, 10% for toddy and 40% for the rest of the alcoholic drinks). The quantity of Indian and non-Indian alcohol consumed was the sum of the alcohol amount from the relevant beverages as specified above.

Statistical analysis

The frequency distribution of demographic variables and study variables, including age, education, smoking and alcohol drinking, were examined by center for cases, cancer controls and healthy controls. Based on the distribution of our data and the prior knowledge of lung cancer, we adjusted for age, education and center as potential confounders in our multivariate models.

The effects of cigarette and *bidi* smoking on the risk of lung cancer were estimated with odds ratio (OR) and its 95% confidence interval (CI), which were derived from unconditional multivariate logistic regression using STATA software. Continuous variables, such as smoking duration, pack-year and smoking cessation, were analyzed both as continuous variables and categorical variables. We tested the trend of dose-response relationship by assigning the score i to the ith exposure level of ordered variables (where $i = 0, 1, 2. . .$) and treated the assigned score as a continuous variable. The effects of chewing and drinking habits were estimated with a similar modeling.

We used 2 statistical models to assess the exposure effects and control for the potential confounders. In one, we adjusted for age (continuous variable), education (categorical variables as shown in Table I) and center. Smoking pack-year was adjusted for as a continuous variable for the effect estimation of chewing and drinking habits. In the other model, we adjusted for age, education, centers and the 2 habits (as dichotomous variables) other than the main exposure of interest. For example, chewing and alcohol drinking habits were adjusted for when investigating the effect of smoking. For smoking-related exposure, we reported the results from the latter model since the results from the 2 models were very similar.

To avoid modeling assumption of logistic regression, we also applied the generalized additive model (GAM) with locally-weighted running-line smoothers (*loess*)[23] in S-PLUS software[24] (as F-1) to find the most plausible curve for the dose-response

TABLE I – COMPARE FREQUENCY DISTRIBUTION OF DEMOGRAPHIC CHARACTERISTICS BY CENTER

	Cases			Controls				
				Chennai			Trivandrum	
	Chennai	Trivandrum	Total	Cancer	Visiting	Total	Cancer	Total
Total	277	501	778	661	1,927	2,588	842	3,430
Age								
≤34	7	9	16	117	429	546	128	674
35–44	31	40	71	135	479	614	193	807
45–54	77	149	226	124	511	635	198	833
55–64	98	249	347	162	356	518	271	789
65–74	57	54	111	99	130	229	52	281
≥75	7	0	7	24	22	46	0	46
Education								
None	43	71	114	125	215	340	58	398
<5th grade	48	163	211	88	159	247	200	447
5th grade-high school	173	135	308	348	1,240	1,588	209	1797
High school	13	96	109	100	313	413	255	668
≥College	0	36	36	0	0	0	120	120
Smoking								
Never	56	31	87	331	1,119	1,450	267	1717
Former	38	72	110	98	156	254	152	406
Current	183	398	581	232	652	884	423	1307
Duration mean (years)								
Current cigarette only	31.5	32.0	31.8	20.7	18.6	19.1	24.0	20.2
Current *bidi* only	33.9	36.9	35.8	25.8	25.2	25.4	31.0	26.9
Intensity mean (no./day)								
Current cigarette only	13.2	14.6	13.9	8.11	7.88	7.93	9.86	8.36
Current *bidi* only	19.5	19.0	19.2	12.9	11.8	12.1	15.3	12.9
Alcohol drinking								
Never	209	246	455	544	1,742	2,286	485	2,771
Former	20	55	75	32	35	67	112	179
Current	48	200	248	85	150	235	245	480

relationship between lung cancer risk and duration, pack-year and time since quitting of cigarette and *bidi* smoking.[25]

Loess smoothing is computed in a number of steps:(1) Specify the λ % of the nearest-neighbors, which is a window span used in the analysis, to the target point X_o.(2) Compute the distance of the furthest near-neighbor to X_o.(3) A weight is assigned to each point within the window span using a tri-cube kernel function, which is centered at X_o and becomes zero at the furthest neighbor. (4) The fitted value at X_o is computed from the least-squares fit confined to the window span using the weights computed in Step (3):[25]

$$\log it(P_i) = \beta_0 + f_1(smoking - variable)_i + \beta_2(age)_i + \beta_3(education)_i + \beta_4(center)_i \quad \text{(F-1)}$$

Age (continuous), education (categorical) and center were adjusted in the model as linear terms. Never-smokers attributed to zero exposure in the analysis of smoking duration and pack-years. We conducted sensitivity analysis on the span width to test the robustness of the model applied. The graphs with 50% of window span were presented.

Besides assessing the main effects of smoking, chewing and drinking habits, stratified analyses were used to assess the differences between the effects of different tobacco and alcohol consumption forms: cigarette and *bidi* smoking were considered separately, chewing with tobacco were considered separately from chewing without tobacco, and drinking of Indian alcohol were analyzed separated from non-Indian alcohol. To avoid the possible residual confounding effect of smoking, we also examined the effect of alcohol drinking and chewing habits after restricting the dataset to never-smokers.

In evaluating the possible interaction of tobacco smoking and chewing, we assessed departures from multiplicative effects by dichotomizing the potential risk factors and comparing the effect of the presence of both risk factors to only single risk factors, using subjects with no risk factor as a reference group.

RESULTS

The demographic characteristics of lung cancer cases and controls by center are shown in Table I. The distribution differed between cases and controls on age, education and center. The controls were more educated than the cases. Both cases and controls recruited in Trivandrum were more educated than the corresponding groups from Chennai. In Chennai, there were no major differences between cancer controls and healthy controls in demographic factors, leading to the possibility to combine them in the final analyses.

The ORs of lung cancer increased from never-smokers to former and to current smokers with p-value of the trend test < 0.01. The OR of lung cancer for former and current cigarette smokers were 1.49 (95%CI=0.89–2.50) and 3.77 (95%CI=2.70–5.28), respectively, while the OR of lung cancer for former and current *bidi* smokers were 3.36 (95%CI=2.08–5.43) and 5.28 (95%CI=3.81–7.32), respectively. ORs for mixed smoking of cigarette and *bidi* were 4.04 (95%CI= 2.46–6.61) and 9.10 (95%CI= 6.25–13.2) for former and current smokers, respectively. The OR for ever *chutta*-only smokers was 2.53 (95%CI= 1.24–5.18) compared to never-smokers; however, the number of *chutta*-only smokers was not enough for conducting further product-specific analyses. The attributable fractions in this population (AF) for total smoking was 0.69 (data not shown).

Taking subjects who only smoked cigarettes as the reference group, *bidi*-only smoking conferred OR of 4.47 (95%CI= 3.38–5.93) after adjusting for cumulative tobacco consumption and time since quitting (data not shown).

The results of the analysis according to smoking duration and cumulative tobacco consumption among current smokers are shown in Table II. For smokers of any tobacco product for more than 30 years, the risk of lung cancer increased up to 7 times (OR=7.31, 95%CI=5.43–9.84). For each category of duration of smoking, smoking of *bidis* seemed to entail a higher risk than smoking of cigarettes. The results of treating smoking duration as continuous variables in GAM were consistent with the results of categorical exposures, and it suggested a plateau in the increase of risk above 35 years of smoking of either product (Fig. 1). Note that the risk estimates above 45 years of smoking were imprecise.

Considering the effect of cumulative tobacco consumption, *bidi* smoking seemed to confer a higher risk of lung cancer than cigarette smoking. The results from analyses of continuous variables using GAM with *loess* smoother showed a stronger dose-relationship between lung cancer risk and *bidi* smoking with drastic increase of risk up to 10 pack-years, compared to cigarette smoking, which also conferred an upward but relatively slower increase of dose-response relationship (Fig. 2). The weight factor assigned to *bidi* pack-year did not seem to have a major influence on the results. For example, the ORs for *bidi* pack-year, weighted by 0.5, for the same cut-off of Table II, were 0.69 (95%CI=0.16–2.95), 1.56 (95%CI=0.70–3.47), 5.04 (95%CI= 3.33–7.61) and 10.8 (95%CI=7.15–16.3), respectively.

There was an independent effect of duration and intensity for both cigarette smoking and *bidi* smoking (Table III). Regardless of the duration and compared to the never-smokers, the ORs (95%CI) for intensity of cigarette-only smoking were 1.72 (1.04–2.84),

TABLE II – ODDS RATIO OF LUNG CANCER FOR SMOKING DURATION AND CUMULATIVE TOBACCO CONSUMPTION AMONG CURRENT SMOKERS[1]

	Any smoked tobacco products		Cigarettes only		*Bidi* only	
	Case/control	OR (95% CI)	Case/control	OR (95% CI)	Case/control	OR (95% CI)
DURATION						
Never smokers	87/1717	1 (Ref)	87/1717	1 (Ref)	87/1717	1 (Ref)
≤10	12/247	1.33 (0.70, 2.54)	6/160	1.53 (0.63, 3.71)	3/54	1.56 (0.46, 5.34)
10.1–20	46/316	2.65 (1.75, 4.01)	10/152	1.65 (0.80, 3.41)	16/95	3.44 (1.80, 6.57)
20.1–30	143/340	5.23 (3.82, 7.17)	41/139	4.56 (2.89, 7.21)	40/103	5.57 (3.47, 8.93)
>30	380/404	7.31 (5.43, 9.84)	56/113	4.54 (2.96, 6.95)	145/161	6.45 (4.38, 9.50)
Trend p		<0.01		<0.01		<0.01
Continuous[2]		1.05 (1.03, 1.07)		1.03 (1.00, 1.06)		1.05 (1.02, 1.08)
PACKYEAR						
Never smokers	87/1717	1 (Ref)	87/1717	1 (Ref)	87/1717	1 Ref
≤2	14/288	1.23 (0.68, 2.24)	6/131	1.58 (0.65, 3.83)	6/137	0.95 (0.39, 2.27)
2.1–5	61/335	2.63 (1.81, 2.83)	5/142	0.83 (0.32, 2.13)	47/139	4.09 (2.62, 6.40)
5.1–12	214/393	5.64 (4.17, 7.61)	26/153	2.69 (1.61, 4.51)	111/109	9.86 (6.56, 14.8)
>12	292/291	9.10 (6.76, 12.2)	76/138	6.87 (4.62, 10.2)	40/28	10.7 (5.82, 19.6)
Trend p		<0.01		<0.01		<0.01
Continuous[2]		1.04 (1.03, 1.05)		1.03 (1.02, 1.05)		1.12 (1.07, 1.18)

[1]OR, Odds ratio adjusted for age, educational level, chewing tobacco, alcohol consumption and center. CI, Confidence interval Trend p, p-value of the linear trend.–[2]OR and 95% CI for 1 year of smoking.

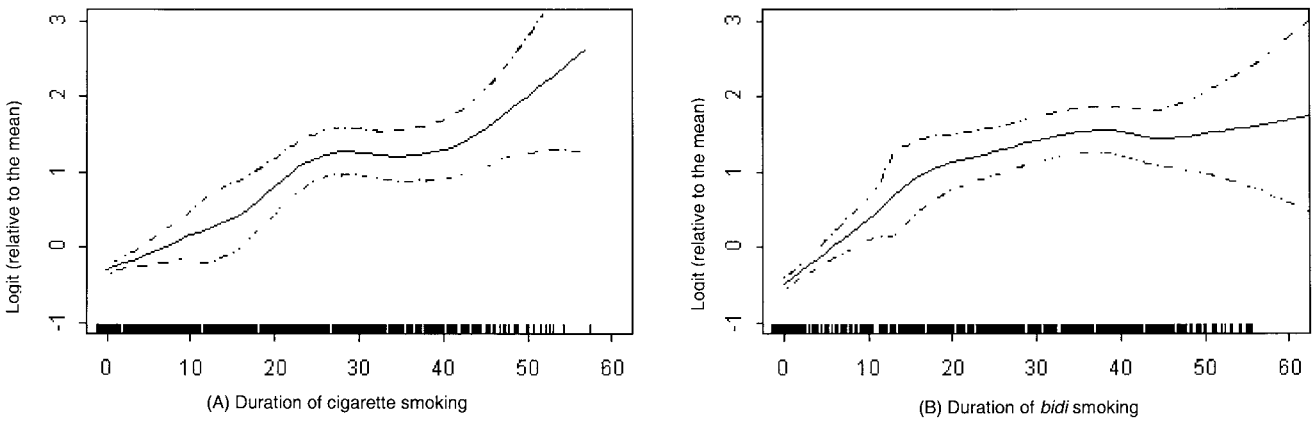

FIGURE 1 – (*a*) Log odds for smoking duration (years) of current cigarette smokers with 50% of weighted window span (relative to the mean). (*b*) Log odds for smoking duration (years) of current *bidi* smokers with 50% of weighted window span (relative to the mean).

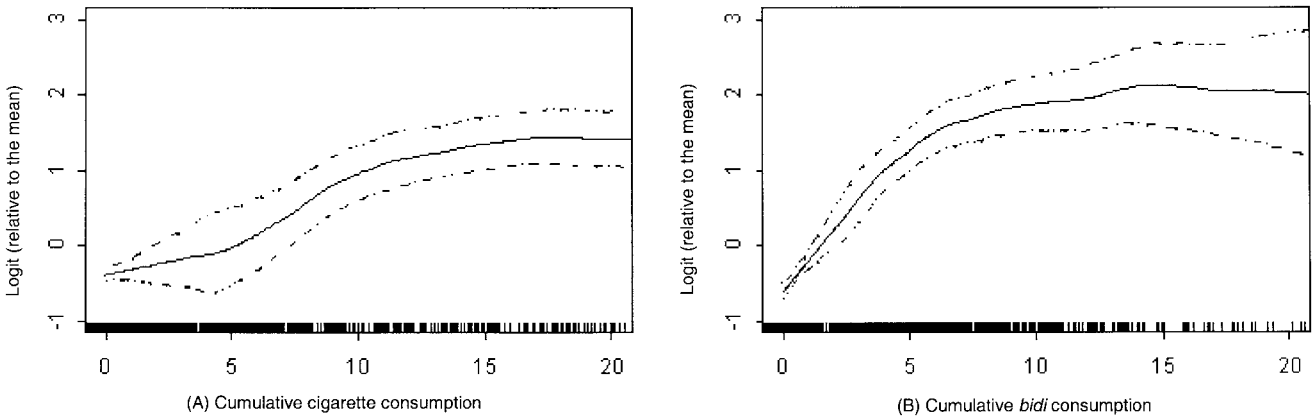

FIGURE 2 – (*a*) Log odds for cumulative tobacco consumption of current cigarette smokers with 50% of weighted window span (relative to the mean). (*b*) Log odds for cumulative tobacco consumption of current *bidi* smokers with 50% of weighted window span (relative to the mean).

TABLE III – ODDS RATIO OF LUNG CANCER FOR SMOKING INTENSITY AND DURATION AMONG CURRENT SMOKER COMPARING TO NONSMOKERS[1]

	Intensity (number/day)		Duration			
			<15 years	15.1–25 years	25.1–35 years	>35 years
Cigarette[2]	≤10	Case/control	22/253	38/164	90/147	104/102
		OR	2.45 (1.43, 4.20)	3.84 (2.42, 6.11)	6.27 (4.31, 9.13)	5.74 (3.85, 8.55)
	>10	Case/control	4/24	14/51	44/38	43/34
		OR	2.58 (0.80, 8.32)	4.57 (2.31, 9.04)	9.95 (5.86, 16.9)	8.83 (5.15, 15.1)
Bidi[2]	≤10	Case/control	6/97	17/85	17/75	39/75
		OR	1.60 (0.66, 3.87)	3.49 (1.91, 6.37)	2.63 (1.45, 4.77)	4.24 (2.60, 6.91)
	>10	Case/control	14/41	40/91	125/95	182/105
		OR	6.15 (3.02, 12.5)	6.29 (3.88, 10.2)	12.8 (8.68, 19.0)	11.5 (7.79, 17.0)

[1]OR, Odds ratio adjusted for age, educational level, center, chewing and alcohol habit. CI, Confidence interval.–[2]Not product-specific.

5.03(3.14–8.04), 5.27 (2.74–10.2) and 6.04(3.58–10.2) using the cut-off of 6, 10 and 15 (cigarettes/day). The ORs for *bidi*-only smoking were 0.69(0.27–1.79), 3.67 (2.16–6.21), 8.56(5.26–14.0) and 9.61(6.43–14.4).

Table IV and Figure 3 show the association of lung cancer risk and time since quitting smoking, and suggest a difference between the relationship of smoking cessation and lung cancer risk among former cigarette smokers and former *bidi* smokers. The lung cancer risk of former cigarette smokers dropped down more quickly after quitting smoking compared to former *bidi* smokers. Note that the dose-response relationship beyond 10 years of smoking cessation was uncertain because of the very small number of subjects in the product-specific analyses.

There was no significant association between chewing and lung cancer risk after adjusting for age, education, center and smoking, nor was there evidence for increasing trend of lung cancer risk along with prolonged chewing duration. Compared to never chewers, ever, former and current chewers of tobacco-containing products conferred the OR of 0.74 (95%CI=0.57–0.96), 0.75 (95%CI=0.46–1.21) and 0.76 (95%CI=0.57–1.02) after adjusting for age, center and smoking (pack-years). Similarly, there was no evidence among never-smokers: the ORs of lung cancer for never-smokers who were former or current chewers of tobacco-containing products were 0.30 (95%CI= 0.04–2.30) and 0.47 (95%CI=0.18–1.22), respectively. There was no clear evidence of interaction between chewing tobacco and smoking, nor evidence on the combined effect of the 2 potential factors.

TABLE IV – ODDS RATIO OF LUNG CANCER FOR TIME SINCE QUITTING[1]

Smoking cessation (years)	Case number	Control number	OR	95% CI	Trend *p*
All smoking					
Current smokers	581	1,307	1	Ref	<0.01
≤3	45	116	0.65	(0.44, 0.97)	
3.1–10	44	169	0.41	(0.28, 0.59)	
10.1–15	8	45	0.32	(0.14, 0.71)	
>15	13	76	0.29	(0.16, 0.54)	
Never smokers	87	1,717	0.19	(0.14, 0.24)	
Continuous[2]			0.93	(0.91, 0.96)	
Cigarette only					
Current smokers	113	564	1	Ref	<0.01
≤3	7	48	0.56	(0.24, 1.33)	
3.1–10	9	76	0.37	(0.17, 0.80)	
10.1–15	4	27	0.47	(0.15, 1.46)	
>15	4	39	0.25	(0.08, 0.74)	
Never smokers	87	1,717	0.26	(0.19, 0.37)	
Continuous[2]			0.92	(0.88, 0.97)	
Bidi only					
Current smokers	204	413	1	Ref	<0.01
≤3	19	36	0.81	(0.42, 1.56)	
3.1–10	17	39	0.64	(0.33, 1.20)	
10.1–15	1	6	0.19	(0.02, 1.77)	
>15	3	16	0.42	(0.12, 1.52)	
Never smokers	87	1,717	0.19	(0.14, 0.26)	
Continuous[2]			0.96	(0.91, 1.00)	

[1]OR, Odds ratio adjusted for age, educational level, chewing tobacco, alcohol consumption and center. CI, Confidence interval. Trend *p*, *p*-value of trend test.–[2]OR of one year of smoking cessation.

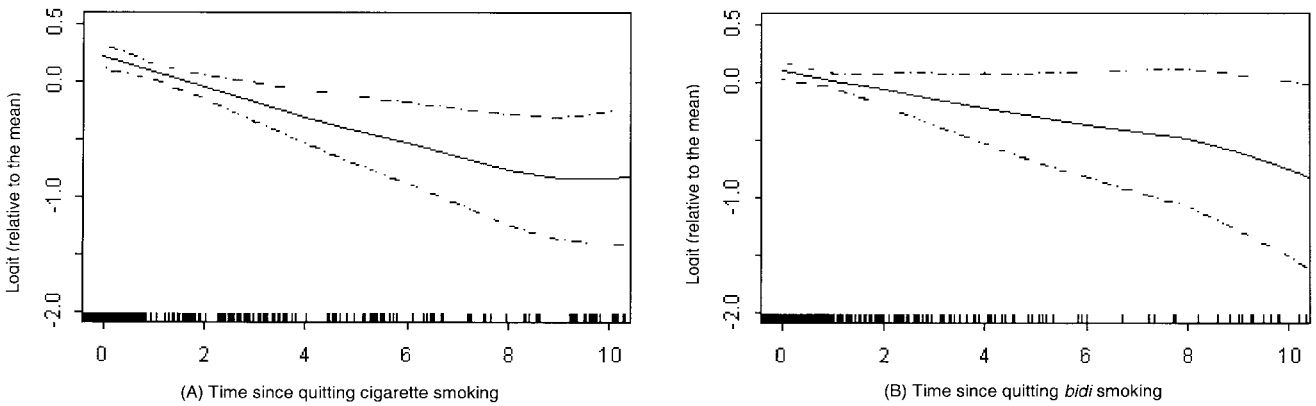

FIGURE 3 – (*a*) Log odds for time since quitting cigarette smoking with 50% of weighted window span (relative to the mean.) (*b*) Log odds for time since quitting *bidi* smoking with 50% of weighted window span (relative to the mean).

Table V displays the result on the association of alcohol drinking habits and lung cancer risk. After adjusting for tobacco smoking, the ORs of lung cancer for current drinker of all alcohol, foreign alcohol and Indian alcohol were 1.66 (95%CI=1.33–2.07), 1.30 (95%CI=0.98–1.73) and 1.83 (95%CI=1.41–2.36), respectively. There was no clear evidence of an effect among never-smokers, among whom ORs for former or current alcohol drinking were 2.49 (95%CI=0.67–9.25) and 1.15 (95%CI=0.44–3.02), respectively, suggesting a residual confounding effect of smoking in the analysis of all alcohol drinking including the whole study population. However, Indian alcohol drinking remained associated with lung cancer risk among never-smokers, with OR of 2.67 (95%CI=1.02–7.02) for ever drinker. We did not find an interaction between smoking and alcohol drinking, for neither foreign nor Indian local alcohol (data not shown).

TABLE V – OR OF LUNG CANCER FOR ALCOHOL DRINKING[1]

Alcohol consumption	Case number	Control number	OR	95% CI
All alcohol				
Never	455	2,771	1	Ref
Former	75	179	0.90	(0.65, 1.26)
Current	248	480	1.66	(1.33, 2.07)
Non-Indian alcohol				
Never	634	3,018	1	Ref
Former	33	105	0.78	(0.49, 1.24)
Current	111	307	1.30	(0.98, 1.73)
Indian alcohol				
Never	541	3,085	1	Ref
Former	59	110	0.90	(0.61, 1.31)
Current	178	235	1.83	(1.41, 2.36)

[1]OR, Odds ratio adjusted for age, educational level, center and smoking packyear. CI, Confidence interval.

DISCUSSION

A major role of tobacco smoking in causing lung cancer is well established.[22] However, tobacco use in India is different from other parts of the world, especially because of smoking of *bidis* and chewing of tobacco-containing products. Our results indicate that the risk of lung cancer varies according to the type of tobacco consumption. As expected, for all smoking products combined,

dose-response relationships were seen for both smoking duration and intensity of smoking, and a decrease in risk was seen along with the time since quitting. However, *bidi* smoking seems to have a stronger carcinogenic effect than cigarette smoking: this difference holds no matter which aspect of smoking was considered. Chewing tobacco-containing products does not seem to have an effect on lung cancer risk in our population.

There are some possible limitations that need to be considered in our study. First, the heterogeneity of the 2 centers might influence the validity of the study. One of the most important differences is the recruitment of the control group. In the final analysis, the control group is a combination of cancer controls and healthy controls including visitors to cancer patients. A major problem of clinic-based controls is that they may not be selected independently from the exposure. However, the exclusion of tobacco-related diseases from control eligibility should reduce this bias. In addition, the high homogeneity of the results for smoking, no matter which control group was used, as well as between 2 centers was remarkable and reassuring. For example, compared to cancer controls, the OR for former smokers was 1.61 (95% CI= 0.98–2.64) in Chennai and 2.56 (95%CI=1.56–4.20) in Trivandrum (p-value of heterogeneity = 0.2); and the OR for current smokers was 4.82 (95% CI=3.30—7.05) and 6.23 (95%CI=4.05–9.59) in Chennai and Trivandrum (p-value of heterogeneity = 0.4). Within Chennai, the OR of ever smoking compared to cancer control is 3.56 (95%CI=2.50–5.08) and 4.15 (95%CI=2.99–5.76) compared to healthy control (p-value of heterogeneity= 0.5).

The results of alcohol drinking stratified by center were also homogeneous. Comparing both to the cancer controls, the OR for former drinkers in Chennai and in Trivandrum was 1.09 (95%CI=0.57–2.10) and 0.71 (95%CI=0.48–1.04), respectively (p-value of heterogeneity=0.3); the OR for current drinkers in Chennai and in Trivandrum was 1.39 (95%CI=0.90–2.14) and 1.49 (95%CI=1.14–1.95), respectively (p-value of heterogeneity =0.8). However, there was suggestive evidence of heterogeneity between the control sources. Within Chennai, the estimates for alcohol were toward null when compared to the cancer controls. The difference might reflect the over-representativeness of alcohol drinking in cancer controls, which may lead to the underestimation of the alcohol effects. On the other hand, it might result from the different recall pattern among cancer and healthy controls, which lead to the differential misclassification.

Besides the recall bias, information bias may have occurred in our study due to exposure measurement error. The questionnaire that documented different tobacco consumption forms was one of the strengths of our study. The possibility of measurement errors might be increased because of the variety of tobacco products, the complexity of consumption habits and temporal changes of habits, therefore leading to nondifferential misclassification. This misclassification might bias the point estimates toward either direction due to multiple categories of exposures.[26,27] In particular, owing to the limited number of never-smokers, our analyses for the effects of alcohol drinking were confined to simplified categories, which may be also suffered from nondifferential misclassification. For example, occasional drinkers could be classified as nondrinkers in these categories.

Residual confounding of smoking is also one of the limitations in the estimates of the effects of chewing and alcohol drinking. We have adjusted smoking in all the statistical models in the analyses. However, the adjustment of cumulative tobacco consumption might not entail a complete elimination of confounding effect from smoking. In order to address this potential problem, we have estimated the effects after restricting the dataset to never-smokers, even though the statistical power was reduced. Other factors, which were shown to have possible effects on lung cancer risk but were not considered in the analyses, such as diet, can lead to potential confounding on the estimates of risks.

The stronger association found between lung cancer and *bidi* smoking as compared to cigarette smoking is one the most interesting findings in our study. The epidemiological evidence on *bidi* smoking in India is still limited.[28,12,6,5,15,14] Two previous case-control studies in India also reported a stronger association for *bidi* than cigarette smoking;[6,12] however, a study in Charndigarh and a study in Mumbai reported similar effects.[29,5] Our study has the advantage of a larger number of subjects that provides sufficient power in conducting product-specific analyses.

A significant decrease in risk was observed along with the time since quitting smoking cigarettes and *bidis*. However the decline seems to be more pronounced for pure cigarette smokers as compared to pure *bidi* smokers. This result is compatible with the hypothesis that *bidi* might hold a stronger potential of inducing carcinogenesis than cigarettes.

Bidis deliver more nicotine and contains more N′-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in comparison to Indian cigarettes.[9] Furthermore, compared to U.S. cigarettes, the mainstream smoke of *bidi* contains a higher concentration of several toxic and mutagenic substances, including hydrogen cyanide, carbon monoxide, volatile phenols and carcinogenic hydrocarbons such as benz[*a*]anthracene and benzo[*a*]pyrene.[9]

The carcinogenic potential of tobacco products for chewing is suggested by animal models. A previous study by Dikshit *et al*.[6] also reported a null estimate after adjusting for age and smoking, while another study from Pakistan reported an elevated OR of lung cancer for heavy chewers.[14] We did not observe an association between chewing tobacco and lung cancer risk after adjusting for age, education, center and smoking. The possible explanations include the high-dose of carcinogen applied in the animal studies, which is not likely to be observed in humans, and also the competing risk from oral cancer, which is likely to develop earlier than cancer of the lung among susceptible individuals. We observed a significantly elevated risk estimate for former chewers of tobacco products; however, this finding may be due to chance because of the small number of subjects. The lack of any association between chewing habits and lung cancer risk among never-smokers confirmed the results of the main analyses.

Drinking of alcoholic beverages, and in particular local beverages, seems to be a possible risk factor of lung cancer in our study after adjusting for smoking, age, education and center. The residual confounding of smoking was controlled for after we restricted the dataset to never-smokers. However, the analysis on never-smokers was based on a small number of subjects and provided neither evidence of an independent effect of total alcohol drinking nor strong evidence of lack of an effect. Since a recent meta-analyses suggested that the association between alcohol drinking and lung cancer risk is limited to very high consumption groups,[20] the possible association between local beverage and lung cancer risk might reflect the importance of drinking intensity, since local alcohol was usually consumed in higher amounts than foreign alcohol (the median quantity of foreign alcohol beverage is 11.7 ml/day and 20.6 ml/day among cases and controls, respectively; *vs.* 22.1 ml/day and 34.3 ml/day for local alcohol drinking). However, the power of our study to further evaluate the possible association of lung cancer and heavy drinker in the never-smoker group was limited.

Our study has the strengths of a relatively large sample size and the heterogeneity of exposure levels, which allowed us to conduct detailed analyses for the effect of different tobacco products. The strength of the GAM modeling with a *loess* smoothing term is that it does not have any assumption on the shape of the dose-response relationship and it makes more efficient use of the data as compared to the categorical approach. However, there is a trade-off between the variance and bias when choosing the width of the weighted span: the bigger is the span, then the lower is the variance; however, the potential for bias increases. We chose the hypothesis-driven approach and present graphs that are biologically plausible but with the smallest width of span in order to minimize the potential bias, although there are other methods for choosing the window width, such as cross-validation.[25]

In conclusion, *bidi* smoking seems to have a stronger carcinogenic effect than cigarette smoking: this difference holds no matter which aspect of smoking was considered. The effect of alcohol on lung cancer needs to be investigated in a larger study. We did not find evidence of a role of chewing tobacco on lung cancer risk.

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