Chewing Tobacco, Alcohol, and the Risk of Erythroplakia[1]

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Abstract

Although chewing tobacco, smoking, and alcohol drinking have been suggested as risk factors for oral cancer, no study has examined the relationship between those factors and the risk of erythroplakia, an uncommon but severe oral premalignant lesion. In this study, we have analyzed the effects of chewing tobacco, smoking, alcohol drinking, body mass index, and vegetable, fruit, and vitamin/iron intake on the risk of erythroplakia and explored potential interactions between those factors in an Indian population. A case-control study including 100 erythroplakia cases and 47,773 controls was conducted, as part of an on-going randomized oral cancer screening trial in Kerala, India. The analysis was based on the data from the baseline screening for the intervention group, where the diagnostic information was available. The information on epidemiological risk factors was collected with interviews conducted by trained health workers. The erythroplakia cases were identified by health workers with oral visual inspections, and then confirmed by dentists and oncologists who made the final diagnosis. The odds ratios (OR) and their 95% confidence intervals (CIs) were calculated by the logistic regression model using SAS software. The adjusted OR for erythroplakia was 19.8 (95% CI, 9.8–40.0) for individuals who had ever chewed tobacco, after controlling for age, sex, education, body mass index, smoking, and drinking. The adjusted OR for ever-alcohol-drinkers was 3.0 (95% CI, 1.6–5.7) after controlling for age, sex, education, body mass index, chewing tobacco, and smoking. For ever-smokers, the adjusted OR was 1.6 (95% CI, 0.9–2.9). A more than additive interaction on the risk of erythroplakia was suggested between tobacco chewing and low vegetable intake, whereas a more than multiplicative interaction was indicated between alcohol drinking and low vegetable intake, and between drinking and low fruit intake. We concluded that tobacco chewing and alcohol drinking are strong risk factors for erythroplakia in the Indian population. Because the CIs of interaction terms were wide and overlapping with those of the main effects, only potential interactions are suggested.

Introduction

Oral cancer is the most common site of cancer for men and the third most common site of cancer for women in Trivandrum, which is located in the state of Kerala, India. The high incidence of oral cancer in Kerala has been attributed to tobacco chewing, tobacco smoking, and alcohol drinking (1–3). Tobacco is chewed predominantly as an ingredient of betel quid or pan, which is a combination of betel leaf, areca nut, and lime. It is smoked mostly in the form of bidi (a native cigarette of coarse tobacco hand-rolled in a dry tembhurni leaf) and cigarettes.

The study of oral premalignant lesions is of importance for the prevention of oral cancer because premalignant lesions may be treated to prevent their progression to oral cancer or used as surrogate (intermediate) markers for oral cancer intervention. Cessation of chewing tobacco and smoking has been associated with the regression of oral leukoplakia, a common oral premalignant lesion (4). Dietary supplements of vitamin A and β-carotene have also been implicated in the regression as well as in the prevention of oral leukoplakia (5−7). Although several studies have been conducted on risk factors for oral leukoplakia, very few have focused on erythroplakia, the most advanced type among oral premalignant lesions.

Erythroplakia is an uncommon but severe disease, defined by WHO as "any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterized clinically or pathologically as any other recognizable condition" (8). An updated definition for erythroplakia was proposed by Bouquot (9) as "a chronic red mucosal macule which cannot be given another specific diagnostic name and cannot be attributed to traumatic, vascular, or inflammatory causes". Erythroplakia patches may be located near, or associated with, oral leukoplakias. Bouquot and Whitaker (10) suggested that erythroplakia may occur with leukoplakia in the stage called erythroleukoplakia. Erythroplakia has been considered the most severe form among all of the oral premalignant lesions because of its high malignant potential (11). When erythroplakia biopsies were studied, 91% were dysplasia, carcinoma *in situ*, or cancer (12).

There are very few studies on the prevalence of erythroplakia. When 65,354 cases from two oral pathology departments were reviewed, 58 erythroplakia cases were identified

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(0.09%; Ref. 12). In a house-to-house survey in Burma among 6000 villagers over the age of 15 years, five cases were diagnosed, with a prevalence of 0.83% (13). In an oral lesion survey in Malaysia among 11,707 adults over the age of 35 years, one case of erythroplakia was identified (14).

In the study of 58 cases of erythroplakia, the disease was found to be more common among people in their 50s and 60s (12). The risk factors for oral cancer such as chewing tobacco, smoking, and alcohol drinking are assumed to be associated with erythroplakia. In a recent case-series study, erythroplakia was associated with a high prevalence of *TP53* mutations (15). *TP53* mutations may be associated with tobacco exposure for oral cancer(16–17), which would possibly indicate that tobacco exposure may play an important role in the development of erythroplakia.

To our knowledge, there have not been any case-control studies focusing on chewing tobacco, smoking, drinking, and the risk of erythroplakia in the literature, although the risk factors for erythroplakia have been assumed to be similar to those of oral cancer. The purpose of this study is to examine the independent effects of major potential risk factors, such as chewing tobacco, cigarette smoking, and alcohol drinking, and to explore possible interactions between them.

Subjects and Methods

Study Population and Data Collection. A randomized oral cancer screening trial is currently being conducted in Kerala, India, with the objective of evaluating the efficacy of oral visual inspection by trained health workers in preventing death from this cancer (18). The state of Kerala is located on the west coast of southern India with an area of approximately 38,900 km^2. Kerala is an ideal place for the screening trial because of the high prevalence of chewing tobacco and smoking habits, with 59.1% of the population practicing at least one of the tobacco habits, and because of the high risk of oral cancer. Keeping the chewing tobacco in the lower groove of the mouth is a habit especially common in Kerala.

This case-control study was conducted within the framework of the intervention trial, using data from the intervention arm. A total of 59,894 subjects, ages ≥35, resident in seven panchayaths or rural administrative structures (total resident population 172,567) were randomized to the intervention group to receive three rounds of screening at 3-year intervals. In the first round of intervention, 49,174 eligible subjects participated and were interviewed and screened in their homes by trained health workers. The 100 cases of erythroplakia and 47,773 controls in this study were identified from this group.

The health workers were required to be college graduates who were residents of the area. They were trained specifically in epidemiology, diagnosis, investigation, and management of oral precancers and cancers as described previously (18). The health workers conducted face-to-face interviews with a structured questionnaire. The subjects were asked about demographic information and their tobacco chewing, smoking, and alcohol drinking habits in terms of duration, frequency, and type of tobacco or alcohol used. For chewing tobacco, the subjects were also asked whether they kept the chewing tobacco in their mouth overnight and whether they swallowed the chewing tobacco fluid. Health workers asked whether fruits were taken frequently, vegetables were taken daily, and vitamins/iron supplements were taken currently or in the past. Their blood pressure, body weight, and height were measured. After this, the health workers conducted systematic visual inspections of the buccal and labial mucosa, gingivae, bucco alveolar sulci, tongue, and palate and floor of the mouth, under adequate light to identify lesions suggestive of oral leukoplakia, erythroplakia, submucous fibrosis, and/or oral cancer, and then referred subjects with positive findings. Subjects with tobacco and alcohol habits were advised to stop these practices. Two dentists and three oncologists who used uniform criteria were involved in the final diagnosis of these oral premalignant lesions. Of the 3585 subjects referred, a little more than one-half were examined by dentists, and various lesions were confirmed. Erythroplakia cases were defined as subjects diagnosed with erythroplakia by the dentists ($n = 100$). Controls were defined as subjects who were inspected by the health workers and diagnosed to be free of any oral condition or disease ($n = 47{,}773$).

Statistical Analysis. The effects of chewing tobacco, smoking, and alcohol drinking on the risk of erythroplakia were estimated with ORs[3] and their 95% CIs, derived from logistic regression analysis. Continuous variables such as years of chewing, smoking, or drinking, and frequency of use were first analyzed as continuous variables and then were categorized into groups according to categories often used in previous studies. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Dummy variables were created to estimate OR for each category of exposure in logistic regression analysis. Trend tests for ordered variables were performed by assigning the score j to the jth exposure level of a categorical variable (where $j = 1, 2, \ldots$) and treating it as a continuous predictor in unconditional logistic regression.

The distributions for age, sex, religion, occupation, and education were examined for cases and controls. The distributions differed greatly between cases and controls for age, sex, and education. BMI has been indicated as a potential risk factor for oral cancer (19). On the basis of these distributions and of prior knowledge of potential risk factors for oral premalignant lesions and oral cancer, we adjusted for age, sex, education, and BMI in our data analysis.

Three models were used to assess exposure effects: (*a*) no covariates (crude analysis); (*b*) statistical adjustment for age (continuous), sex (F/M), education (categorical, as shown in Table 1), and BMI (continuous, kg/m^2); and (*c*) statistical adjustment for additional covariates, including chewing tobacco (continuous, duration in years), smoking (continuous, pack-years), and drinking (continuous, duration in years) in the logistic regression model where appropriate.

Stratified analysis was used to assess departures from additive and multiplicative effects among major potential risk factors, including tobacco chewing, cigarette smoking, alcohol drinking, low vegetable intake, and low fruit intake. The null hypotheses of additivity and multiplicativity were tested. A more than additive interaction is indicated when: $OR_{11} > OR_{10} + OR_{01} - 1$, where $OR_{11} = OR$ when both factors are present, $OR_{10} = OR$ when only factor 1 is present, $OR_{01} = OR$ when only factor 2 is present. A more than multiplicative interaction is suggested when: $OR_{11} > OR_{10} \times OR_{01}$ (20). Departures from multiplicative effects were assessed and tested by including main effects and a product term of the main effects in the logistic regression model.

Results

The general characteristics of the erythroplakia cases and controls are shown in Table 1. The erythroplakia cases were con-

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table 1 General characteristics of the erythroplakia cases and controls

	Cases		Controls	
	n	%	*n*	%
Age groups				
<45 yr	20	20.0	18,748	39.2
45–54 yr	38	38.0	12,777	26.7
55–64 yr	35	35.0	9,804	20.5
≥65 yr	7	7.0	6,444	13.5
Sex				
Female	49	49.0	29,876	62.5
Male	51	51.0	17,897	37.5
Religion				
Hindu	52	52.0	32,968	69.0
Muslim	21	21.0	9,555	20.0
Christian	27	27.0	5,250	11.0
Occupation				
Manual	90	90.0	39,918	83.6
Teacher/Office worker	2	2.0	2,577	5.4
Business	2	2.0	1,227	2.6
Retired	4	4.0	2,801	5.9
Others	2	2.0	1,250	2.6
Education				
None and illiterate	39	39.0	8,351	17.5
None and literate	11	11.0	3,078	6.4
Primary	30	30.0	10,758	22.5
Middle	11	11.0	8,399	17.6
High School	8	8.0	12,788	26.8
Technical/College or Professional	1	1.0	4,390	9.2
Unknown	0	0.0	9	0.0

centrated in the older age groups, compared with the controls. The highest percentage of cases were in the 45–54-year age group, whereas the highest percentage of controls were in the <45-year age group. The percentage of females was 62.5% among controls but only 49.0% among the cases. For religion, there were a higher percentage of Hindus and lower percentage of Christians in the controls, compared with the cases. The distribution for occupation was similar in cases and controls; most had a manual occupation. For education, a higher percentage of cases were in the lower education groups than the controls, with 39.0% of cases and 17.5% of controls in the "none/illiterate" group.

The distribution of the chewing, smoking, and drinking habits were examined for cases and controls by sex (not presented). Current chewing habits were very high among both male cases (74.5%) and female cases (83.7%). The percentage of current chewers among female and male controls was approximately 20%. The prevalence of current smoking among women was low but was higher in the cases (8.2%) than the controls (1.8%). Smoking habits among men were slightly higher among cases (54.9%) than among controls (50.7%). The overall current smoking habit prevalence was 32.0% among cases and 20.1% among controls. Alcohol drinking was rare among women: 2.0% in cases and 0.2% in controls. For men, the prevalence of current drinking was 15.3% among controls and 39.2% among cases. The percentage of occasional drinkers was high among male controls (15.2%), whereas the percentage of past drinkers was high among male cases (27.5%). The overall drinking habit prevalence was 21.0% among cases and 5.8% among controls. Because drinking is not well accepted socially in India, underreporting may have occurred.

The ORs for chewing tobacco are shown in Table 2. The adjusted OR for ever-chewers was 19.8 (95% CI, 9.8–40.0) after controlling for age, sex, education, BMI, pack-years of smoking, and years of alcohol drinking. The adjusted OR was highest for current chewers, followed by the OR for past chewers, and the OR for occasional chewers. A strong dose-response relationship was shown for the frequency (times per day; *P* for trend, 0.0001) and duration of tobacco chewing (years; *P* for trend, 0.0001) with the risk of erythroplakia. Chewers who swallowed chewing tobacco fluid had a higher adjusted OR than for chewers who did not swallow. Chewers who kept the chewing tobacco in the mouth overnight also had a higher adjusted OR than chewers who did not.

Table 3 shows the relationship between alcohol drinking and the risk of erythroplakia. The adjusted OR for ever-drinkers was 3.0 (95% CI, 1.6–5.7) when adjusted for age, sex, education, BMI, years of chewing, and pack-years of smoking. The adjusted ORs were highest for current drinkers, followed by those of past drinkers. No association was observed for occasional drinkers, but this category had only three erythroplakia cases. Dose-response relationships were suggested for both the frequency (times per day; *P* for trend, 0.0001) and duration of drinking (years; *P* for trend, 0.0001) on the risk of erythroplakia.

For cigarette smoking, the adjusted OR for ever-smokers was 1.6 (95% CI, 0.9–2.9) when adjusted for age, sex, education, BMI, years of chewing, and years of drinking (not presented). The adjusted OR for erythroplakia among occasional smokers (OR, 3.7; 95% CI, 1.5–9.6) was higher than for past smokers (OR, 1.6; 95% CI, 0.8–2.9), and for current smokers (OR, 1.1; 95% CI, 0.4–3.0), possibly because of misclassification of the exposure by the subjects or the small number of erythroplakia cases in the past and occasional categories. The adjusted OR for frequency of smoking (times per day) as a continuous variable was 1.02 (95% CI, 0.98–1.07). A dose-response relationship was shown in the crude analysis for the frequency of smoking and the risk of erythroplakia (*P* for trend, 0.0003), but when adjusted for various factors, the trend was no longer seen. The adjusted OR was 1.2 (95% CI, 0.6–2.4) for those who smoked 1–20 times per day and 2.3 (95% CI, 1.1–5.1) for those who smoked 21–40 times per day. For duration of smoking (years) as a continuous variable, the adjusted OR was 1.00 (95% CI, 0.99–1.02). Although a dose-response relationship was seen for years of smoking and the risk of erythroplakia in the crude analysis (*P* for trend, 0.0004), it was no longer apparent after adjusting for potential confounding factors.

Both vegetables and fruits showed potential protective effects against erythroplakia for the crude ORs (not presented). The adjusted ORs were 0.4 (95% CI, 0.3–0.7) for vegetable intake and 0.5 (95% CI, 0.3–0.9) for fruit intake after controlling for age, sex, education, and BMI. However, when further adjusted for chewing tobacco, smoking, and drinking, the CIs include the null value. Vitamins and iron supplements appeared to be risk factors for erythroplakia in the crude analysis and after controlling for age, sex, education, BMI (OR for current use, 1.9; 95% CI, 1.3–2.9) but no association was observed after further adjusting for chewing tobacco, smoking, and drinking (OR for current use, 1.4; 95% CI, 0.9–2.1). No obvious association was observed for BMI and risk of erythroplakia (*P* for trend, 0.7557) in the crude or adjusted logistic regression models (data not shown).

Table 4 shows the ORs for possible interactions between chewing, smoking, and drinking. For chewing and smoking, a slightly more than additive interaction was seen ($OR_{11} > OR_{10} + OR_{01} - 1$; $50.1 > 5.8 + 43.3 - 1$). However, when we estimated the adjusted ORs for tobacco chewing among smok-

Table 2 Chewing tobacco habits and risk of erythroplakia (ORs and 95% CIs)

	Cases	Controls	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Further adjusted OR[b] (95% CI)
Chewing tobacco					
No chewing	9	34,373	1.0	1.0	1.0
Ever chewing	91	13,400	25.9 (13.1–51.5)	20.6 (10.2–41.5)	19.8 (9.8–40.0)
Chewing tobacco					
No chewing	9	34,373	1.0	1.0	1.0
Past	10	1,276	29.9 (12.1–13.5)	26.8 (13.1–54.7)	25.8 (12.6–52.8)
Occasional	2	2,625	2.9 (0.6–13.5)	2.4 (0.5–11.1)	2.3 (0.5–10.9)
Current	79	9,499	31.7 (15.9–63.3)	29.4 (11.6–74.6)	27.6 (10.8–70.4)
Frequency of chewing (times per day)					
Continuous			1.05 (1.03–1.07)	1.04 (1.02–1.06)	1.04 (1.02–1.06)
No chewing	9	34,373	1.0	1.0	1.0
1–10	60	8,991	25.5 (12.6–51.4)	23.8 (11.5–49.3)	28.6 (14.0–58.7)
11–20	18	1,443	47.6 (21.4–106.2)	39.1 (17.0–90.1)	49.8 (22.0–113.1)
≥20	11	271	155.0 (63.7–377.1)	100.4 (39.3–256.8)	130.8 (52.5–326.3)
Missing	2	2,695			
P for trend			0.0001	0.0001	0.0001
Duration of chewing (yr)					
Continuous			1.01 (0.99–1.02)	1.02 (1.00–1.04)	1.01 (0.99–1.03)
No chewing	9	34,373	1.0	1.0	1.0
1–20	42	5,971	26.9 (13.1–55.2)	23.7 (11.3–49.6)	29.3 (14.2–60.8)
21–40	38	3,470	41.8 (20.2–86.6)	41.4 (19.0–90.1)	53.3 (24.7–114.8)
≥40	9	1,217	28.2 (11.2–71.3)	40.6 (14.0–117.4)	52.8 (18.3–152.6)
Missing	2	2,742			
P for trend			0.0001	0.0001	0.0001
Swallow chewing tobacco fluid					
No chewing	9	34,373	1.0	1.0	1.0[c]
Chewing/no swallowing	77	10,117	29.1 (15.6–58.0)	26.6 (13.0–54.4)	20.8 (9.8–44.4)
Chewing/Swallowing	9	291	118.1 (46.6–299.7)	83.0 (31.5–218.6)	50.6 (17.9–143.4)
Occasionally swallow	3	303	37.8 (10.2–140.4)	23.2 (6.0–89.2)	14.5 (3.6–58.9)
Missing	2	2,689			
Keep chewing tobacco in mouth overnight					
No chewing	9	34,373	1.0	1.0	1.0[c]
Chewing/Don't keep	82	10,351	30.3 (15.2–60.2)	27.3 (13.4–55.8)	21.2 (10.0–45.2)
Chewing/Keep	7	310	86.2 (31.9–233.0)	64.6 (23.0–181.4)	36.3 (11.9–111.6)
Missing	2	2,687			

[a] OR adjusted for age (continuous), sex (M/F), education (categories from Table 2), and BMI (continuous, kg/m^2).
[b] OR adjusted for age, sex, education, BMI, smoking (continuous, pack-years), and drinking (continuous, duration in years).
[c] OR adjusted for age, sex, education, BMI, smoking, drinking, and tobacco chewing (years and times per day).

ers and nonsmokers (not presented), the ORs were higher for nonsmokers (OR, 41.5; 95% CI, 12.5–137.6) than for smokers (OR, 8.0; 95% CI, 3.3, 19.4). Thus, there did not appear to be a positive effect modification for smoking and tobacco chewing. A more than additive interaction was seen for chewing and drinking ($43.1 > 3.7 + 22.7 - 1$), but when we estimated the adjusted ORs of tobacco chewing among drinkers and nondrinkers, the OR for nondrinkers was higher (OR, 24.9; 95% CI, 10.4–59.7) than for drinkers (OR, 9.8; 95% CI, 3.0–32.7). No obvious interaction was seen between drinking and smoking. The interactions for all of the three habits together could not be calculated because of the low number of total erythroplakia cases.

Several interactions were suggested for low fruit intake and low vegetable intake with tobacco and alcohol habits (not presented). A more than additive interaction between tobacco chewing and low vegetable intake was seen in regard to the risk of erythroplakia. The adjusted OR was 26.7 (95% CI, 11.4–62.5) for the main effect of tobacco chewing, 5.7 (95% CI, 1.4–23.2) for the main effect of low vegetable intake, and 33.5 (95% CI, 12.9–87.1) for the interaction. The risk of erythroplakia for subjects with low vegetable intake appeared to be much higher among tobacco chewers (adjusted OR, 25.5; 95% CI, 10.8–60.0) than among nonchewers (OR, 4.3; 95% CI, 1.3–16.2). There appeared to be a more than multiplicative interaction between drinking and low fruit intake and between drinking and low vegetable intake. The adjusted OR was 2.3 (95% CI, 1.1–4.6) for the main effect of drinking, 0.8 (95% CI, 0.4–1.9) for the main effect of low fruit intake, and 4.4 (95% CI, 2.1–9.2) for the interaction. Low fruit intake was associated with a lower risk of erythroplakia among nondrinkers (OR, 0.9; 95% CI, 0.4–2.0) than among drinkers (OR, 1.5; 95% CI, 0.7–3.2), although the CIs overlapped between the two ORs. The adjusted OR was 2.2 (95% CI, 1.1–4.5) for the main effect of drinking, 1.0 (95% CI, 0.4–2.4) for the main effect of low vegetable intake, and 4.8 (95% CI, 2.3–9.9) for the interaction. The difference in the adjusted ORs between drinkers (OR, 1.0; 95% CI, 0.4–2.4) and nondrinkers (OR, 1.6; 95% CI, 0.8–3.7) was also small for low vegetable intake. Only potential interactions were suggested because the CIs of the main effects overlapped with the CIs of the interaction terms.

Discussion

Our results indicate that tobacco chewing is a strong risk factor for erythroplakia. Dose-response relationships were seen for the frequency of chewing tobacco with the risk of erythroplakia. Chewers who swallowed the tobacco fluid and chewers who kept the chewing tobacco in their mouths overnight both had higher risks for erythroplakia than chewers who did not swal-

Table 3 Alcohol drinking habits and risk of erythroplakia (ORs and 95% CIs)

	Cases	Controls	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Further adjusted OR[b] (95% CI)
Alcohol drinking					
No drinking	62	40,801	1.0	1.0	1.0
Ever drinking	38	6,972	3.6 (2.4–5.4)	3.8 (2.1–7.1)	3.0 (1.6–5.7)
Alcohol drinking					
No drinking	62	40,801	1.0	1.0	1.0
Past	14	1,475	6.2 (3.5–11.2)	4.6 (2.3–9.2)	4.8 (2.4–9.7)
Occasional	3	2,743	0.7 (0.2–2.3)	1.0 (0.3–3.5)	0.9 (0.3–3.1)
Current	21	2,754	5.0 (3.1–8.2)	5.9 (2.8–12.4)	5.8 (2.7–12.5)
Frequency of drinking (days per week)					
Continuous			1.13 (0.96–1.34)	1.13 (0.96–1.34)	1.12 (0.95–1.33)
No drinking	62	40,801	1.0	1.0	1.0
1–2	4	659	4.0 (1.4–11.0)	4.2 (1.4–12.8)	3.9 (1.2–12.0)
3–5	10	1,474	4.5 (2.3–8.7)	4.1 (1.8–9.3)	4.3 (1.9–9.8)
6–7	21	1,986	7.0 (4.2–11.4)	6.4 (3.2–12.8)	6.7 (3.3–13.7)
Missing	3	2,853			
P for trend			0.0001	0.0001	0.0001
Duration of drinking (yr)					
Continuous			1.02 (1.00–1.05)	1.02 (0.99–1.06)	1.01 (0.97–1.04)
No drinking	62	40,801	1.0	1.0	1.0
1–10	4	988	2.7 (1.0–7.3)	2.8 (0.9–8.5)	2.7 (0.9–8.4)
11–20	7	1,330	3.5 (1.6–7.6)	3.4 (1.3–8.6)	3.7 (1.5–9.5)
21–30	14	1,016	9.1 (5.1–16.2)	8.3 (3.9–17.8)	8.9 (4.1–19.4)
>30	10	795	8.3 (4.2–16.2)	6.9 (3.0–16.0)	6.5 (2.7–15.7)
Missing	3	2,843			
P for trend			0.0001	0.0001	0.0001

[a] OR adjusted for age (continuous), sex (M/F), education (categories from Table 2), and BMI (continuous, kg/m^2).
[b] OR adjusted for age, sex, education, BMI, smoking (continuous, pack-years), and chewing tobacco (continuous, duration in years).

Table 4 Risk of erythroplakia and interactions between chewing, smoking, and drinking

	Cases	Controls	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Further adjusted OR[b] (95% CI)
Chewing/Smoking					
No/No	3	26,731	1.0	1.0	1.0
No/Yes	6	7,642	7.0 (1.7–28.0)	5.6 (1.3–24.0)	5.8 (1.3–25.3)
Yes/No	54	8,836	54.5 (17.0–174.2)	43.0 (13.2–140.0)	43.3 (13.3–141.1)
Yes/Yes	37	4,564	72.2 (22.3–234.4)	53.6 (15.2–188.5)	50.1 (14.1–178.4)
Chewing/Drinking					
No/No	6	30,566	1.0	1.0	1.0
No/Yes	3	3,807	4.0 (1.0–16.1)	3.8 (0.9–16.3)	3.7 (0.9–16.1)
Yes/No	56	10,235	27.9 (12.0–64.7)	22.6 (9.6–53.5)	22.7 (9.6–53.7)
Yes/Yes	35	3,165	56.3 (23.7–134.0)	43.6 (16.4–116.1)	43.1 (16.1–115.3)
Drinking/Smoking					
No/No	48	34,472	1.0	1.0	1.0
No/Yes	14	6,329	1.6 (0.9–2.9)	2.2 (1.0–4.8)	2.1 (1.0–4.4)
Yes/No	9	1,095	5.9 (2.9–12.1)	8.1 (3.0–21.9)	4.8 (1.8–13.1)
Yes/Yes	29	5,877	3.5 (2.2–5.6)	5.9 (2.5–13.7)	4.7 (2.0–10.6)

[a] OR adjusted for age (continuous), sex (M/F), education (categories from Table 2), and BMI (continuous, kg/m^2).
[b] In addition to the adjustment of age, sex, education, and BMI, for the model to assess the interactions between chewing and smoking, drinking was further adjusted; for the model to assess the interactions between chewing and drinking, smoking was further adjusted; for the model to assess the interactions between drinking and smoking, chewing was further adjusted.

low or keep the chewing tobacco fluid. Tobacco chewing has been reported as a risk factor for both oral leukoplakia and oral cancer. According to a previous study, the relative risk of oral cancer (tongue and floor of mouth) for tobacco chewers (≥10 pan tobacco chewing/day) in Kerala, India was approximately 5.52 for males and 9.27 in females (2). In another study on oral cancers of the buccal and labial mucosa in Kerala, India, the relative risk for pan tobacco chewing was 16.36 for male subjects who had chewed more than 10 per day and was 14.24 for female subjects (3). The IARC concluded that there is sufficient evidence for the carcinogenicity of chewing betel quid containing tobacco for humans (21). For oral leukoplakia, the risk for ever-tobacco-chewing was 3.80 in a study in Uzbekistan (22). Our results indicate that tobacco chewing is a stronger risk factor for erythroplakia in comparison with the effects for oral cancer and oral leukoplakia. This is the first time that a strong association between chewing tobacco and the risk of erythroplakia was found in a case-control study.

Alcohol drinking was also indicated as a strong risk factor for erythroplakia in our study. Dose-response relationships were shown for the frequency and duration of alcohol use with the risk of erythroplakia. Alcohol drinking has been associated with oral cancer as a risk factor and may be involved in a multiplicative interaction with smoking (23). Alcohol may pos-

sibly act as a solvent, allowing the carcinogens from tobacco to penetrate into the tissues or it may act as a catalyst in metabolically activating tobacco carcinogens (23). Another possible mechanism is that alcohol lessens the protective effect of vegetables and fruits by decreasing the nutrient intake or absorption (23). Our study did not show any obvious interactions between alcohol and tobacco habits, but an interaction between alcohol and nutrition was suggested for the risk of erythroplakia.

Smoking appears to be a weak risk factor for erythroplakia according to our results. Chewing tobacco may possibly be a stronger risk factor for erythroplakia than smoking in the Indian population, as is suggested for oral leukoplakia (24). Chewing tobacco may have a stronger effect than smoking because of the direct contact of the tobacco carcinogens with the oral epithelium as the chewing tobacco is chewed or kept in the mouth.

Fruit and vegetable intake showed potential protective effects, whereas vitamins and iron supplement intake seemed to show an increased risk for erythroplakia in the crude analysis and adjusted analysis controlling for age, sex, education, and BMI. BMI had no effect on the risk of erythroplakia. In our study, misclassification of fruit and vegetable intake may possibly have occurred because we did not define daily or frequent intake with specific amounts of intake. Fruit and vegetable intake may possibly help prevent erythroplakia or cause erythroplakia regression, similar to leukoplakia.

There are several possible limitations to this study. One limitation is the use of prevalent cases instead of incident cases. The OR may be overestimated if the prevalent cases may have had high levels of chewing, smoking, or drinking habits and less exposure to protective factors, which would lead to fewer patients regressing to a less severe lesion. On the other hand, the erythroplakia cases who did not progress to oral cancer and survived with the disease may be those subjects who had relatively healthier life-styles and weaker exposures to potential risk factors. In this case, the observed OR may have been underestimated. Another possibility is that the most severe cases may have been missed as they progressed to oral cancer.

Our study has potential for information bias. Perhaps some exposures were misclassified by the subjects during the interview because "occasional" and "past" use were not defined with specific frequency of use or with specific time periods. The possibility of recall bias may be small because the oral visual inspection was conducted and the final diagnosis was made after the interview. Moreover, the possibility of prior diagnosis of erythroplakia among cases is rather small. Another information bias was reporting bias. Drinking is not socially accepted in India, especially for women; thus, there may be an underestimation and misclassification of drinking habits. Because drinking may be associated with other potential risk factors, such as smoking and tobacco chewing, the misclassification may not necessarily be nondifferential between cases and controls. We have attempted to adjust for confounding by smoking and tobacco chewing by including these variables in the logistic regression models. However, there is still a possibility for residual confounding effects by other variables.

Detection bias is possible because the health workers knew the exposure status of the subjects and may have looked harder for oral lesions in subjects with high exposures to chewing tobacco, smoking, or alcohol drinking. In this situation, subjects who are actually controls may be misclassified as cases. The health workers may also have missed cases in the low- or no-exposure groups, leading to cases being diagnosed as controls. Detection bias may have led to an overestimation of the risk. However, the subjects with oral lesions were also examined by dentists or oncologists who did not know the exposure status; thus, the misclassification of controls as cases may be minimized. The cases who may have been misdiagnosed as controls would not be examined by the dentists or oncologists, making it difficult to control such misclassification in this study.

Another limitation is the small sample size of cases, which may lead to few cases in certain categories, resulting in imprecision of estimates. In our analysis, some of the exposure categories had only a few cases. For the interactions of drinking with low fruit intake and with low vegetable intake, at least one of the cells had a small number of cases ($n \leq 6$). The small number of cases in some of the cells may have limited our ability to estimate the OR precisely. However, the power of the study may have been compensated for by a very large sample of controls. To our knowledge, this study has one of the largest samples of erythroplakia cases ever studied in the literature. Moreover, the cases included in this study were derived from a well-defined population, which permits a generalization of results, provided that bias is minimized.

In conclusion, this is the first epidemiological study investigating the relationships between chewing tobacco, smoking, alcohol drinking, and the risk of erythroplakia. Our results indicate that chewing tobacco and drinking alcohol are strong risk factors for erythroplakia, whereas vegetable and fruit intake are possibly protective against erythroplakia. There was a suggestion of a more than additive interaction between tobacco chewing and low vegetable intake, and more than multiplicative interactions between low vegetable intake and drinking, and between low fruit intake and drinking.

References

1. Sankaranarayanan, R., Duffy, S. W., Padmakumary, G., Day, N. E., and Padmanabhan, T. K. Tobacco chewing, alcohol and nasal snuff in cancer of the gingiva in Kerala, India. Br. J. Cancer, *60:* 638–643, 1989.

2. Sankaranarayanan, R., Duffy, S. W., Day, N. E., Nair, M. K., and Padmakumary, G. A case-control investigation of cancer of the oral tongue and the floor of the mouth in southern India. Int. J. Cancer, *44:* 617–621, 1989.

3. Sankaranarayanan, R., Duffy, S. W., Padmakumary, G., Day, N. E., and Krishan, N. M. Risk factors for cancer of the buccal and labial mucosa in Kerala, southern India. J. Epidemiol. Community Health, *44:* 286–292, 1990.

4. Roed-Petersen, B. Effect on oral leukoplakia of reducing or ceasing tobacco smoking. Acta Dermato-Venereol., *62:* 164–167, 1982.

5. Stich, H. F., Hornby, A. P., Mathew, B., Sankaranarayanan, R., and Nair, M. K. Response of oral leukoplakias to the administration of vitamin A. Cancer Lett., *40:* 93–101, 1988.

6. Stich, H. F., Rosin, M. P., Hornby, A. P., Mathew, B., Sankaranarayanan, R., and Nair, M. K. Remission of oral leukoplakias and micronuclei in tobacco/betel quid chewers treated with β-carotene and with β-carotene plus vitamin A. Int. J. Cancer, *42:* 195–199, 1988.

7. Sankaranarayanan, R., Mathew, B., Varghese, C., Sudhakaran, P. R., Menon, V., Jayadeep, A., Nair, M. K., Mathews, C., Manalingam, T. R., Balaram, P., and Nair, P. P. Chemoprevention of oral leukoplakia with vitamin A and β-carotene: an assessment. Oral Oncol., *33:* 231–236, 1997.

8. Kramer, I. R., Lucas, R. B., Pindborg, J. J., and Sobin, L. H. Definition of leukoplakia and related lesions: an aid to studies on oral precancer. Oral Surg. Oral Med. Oral Pathol., *46:* 518–539, 1978.

9. Bouquot, J. E. Oral leukoplakia and erythroplakia: a review and update. Pract. Periodontics Aesthet. Dent., *6:* 9–17, 1994.

10. Bouquot, J. E., and Whitaker, S. B. Oral leukoplakia—rationale for diagnosis and prognosis of its clinical subtypes or "phases". Quintessence Int., *25:* 133–140, 1994.

11. Bouquot, J. E., and Ephros, H. Erythroplakia: the dangerous red mucosa. Pract. Periodontics Aesthet. Dent., *7:* 59–67, 1995.

12. Shafer, W. G., and Waldron, C. A. Erythroplakia of the oral cavity. Cancer (Phila.), *36:* 1021–1028, 1975.

13. Lay, K. M., Sein, K., Myint, A., Ko, S. K., Pindborg, J. J. Epidemiologic study of 600 villagers of oral precancerous lesions in Bilugyun: preliminary report. Commun. Dent. Oral Epidemiol., *10:* 152–155, 1982.

14. Zain, R. B., Ikeda, N., Razak, I. A., Axell, T., Majid, Z. A., Gupta, P. C., and Yaacob, M. A national epidemiological survey of oral mucosal lesions in Malaysia. Commun. Dent. Oral Epidemiol., *25:* 377–383, 1997.

15. Qin, G. Z., Park, J. Y., Chen, S. Y., and Lazarus, P. A high prevalence of p53 mutations in pre-malignant oral erythroplakia. Int. J. Cancer, *80:* 345–348, 1999.

16. Chiang, C. P., Huang, J. S., Wang, J. T., Chiang, C. P., Huang, J. S., Wang, J. T., Liu, B. Y., Kuo, Y. S., Haln, L. J., and Kuo, M. Y. Expression of p53 protein correlates with decreased survival in patients with areca quid chewing and smoking-associated oral squamous cell carcinomas in Taiwan. J. Oral Pathol. Med., *28:* 72–76, 1999.

17. Koch, W. M., Lango, M., Sewell, D., Zahurak, M., and Sidransky, D. Head and neck cancer in nonsmokers: a distinct clinical and molecular entity. Laryngoscope, *109:* 1544–1551, 1999.

18. Sankaranarayan, R., Mathew, B., Jacob, B. J., Thomas, G., Somanathan, T., Pisani, P., Pandey, M., Ramadas, K., Najeeb, K., and Abraham, E. Early findings from a community-based, cluster-randomized, controlled oral cancer screening trial in Kerala, India. The Trivandrum Oral Cancer Screening Study Group. Cancer (Phila.), *88:* 664–673, 2000.

19. Kabat, G. C., Chang, C. J., Wynder, E. L. The role of tobacco, alcohol use, and body mass index in oral and pharyngeal cancer. Int. J. Epidemiol., *23:* 1137–1144, 1994.

20. Kleinbaum, D. G., Kupper, L. L., Morgenstern, H. Epidemiologic Research: Principles and Quantitative Methods. London: Lifetime Learning Publications, 1982.

21. Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some related nitrosamines. IARC Working Group, Lyon, 23–30 October 1984. IARC Monogr. Eval. Carcinog. Risk Chem. Hum., *37:* 1–268, 1985.

22. Evstifeeva, T. V., and Zaridze, D. G. Nass use, cigarette smoking, alcohol consumption and risk of oral and oesophageal precancer. Eur. J. Cancer B Oral Oncol., *28B:* 29–35, 1992.

23. Blot, W. J. Alcohol and cancer. Cancer Res., *52* (Suppl.)*:* 2119s–2123s, 1992.

24. Mehta, F. S., Gupta, P. C., and Pindborg, J. J. Chewing and smoking habits in relation to precancer and oral cancer. J. Cancer Res. Clin. Oncol., *99:* 35–39, 1981.