Dose-response relationships of oral habits associated with the risk of oral pre-malignant lesions among men who chew betel quid

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Summary Betel quid, cigarettes and alcohol are well-recognized risk factors for oral cancer. However, the combined effect of the frequency and duration of these oral habits on the risk for developing oral pre-malignancies among betel quid users has not been fully addressed. In this study, an oral screening programme for men chewing betel quid was carried out by well-trained dentists for early detection of oral pre-malignancy lesions. Using generalized logit model and proportional odds model, we found that, compared with the occasional user, the adjusted odds ratios of developing leukoplakia for men chewing one to 10 pieces of betel quid, 11–20 pieces, and more than 20 pieces per day were estimated as 2.14 (95% confidence interval [CI] 1.62–2.81), 2.99 (95% CI 2.06–4.27), and 5.37 (95% CI 3.76–7.47), respectively. The corresponding figures for erythroleukoplakia were 3.69 (95% CI 1.55–8.79), 13.78 (95% CI 5.76–32.98), and 36.64 (95% CI 15.94–84.16), respectively. Similar results were found while the duration was considered. The dose-response relationships were not as noteworthy for cigarette and alcohol drinking.

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Introduction

There is a body of evidence showing the potential for malignant transformation of oral pre-malignancy.^{1–4} Oral pre-malignancy can lead to oral cancer via three routes: oral leukoplakia (erythroplakia)-cancer, oral submucous fibrosis-cancer sequence, and oral lichen planus-cancer. The first

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pathway is related to oral leukoplakia, the most common oral pre-cancerous lesion. The potential rate of malignant transformation with or without treatment varies greatly, and ranges from 0.0003 to 0.113 per year.⁵ However, such rates of malignant transformation may not be representative of the natural course of progression for oral leukoplakia. Using a three-stage model, Shiu and Chen⁶ reported the natural history of oral leukoplakia expressed by the annual rate of incidence of oral leukoplakia and annual transition rate from asymptomatic leukoplakia to invasive oral cancer. However, this model did not consider the refined classification of oral leukoplakia characterized by the progression from homogeneous leukoplakia to non-homogeneous leukoplakia following Bouquot classification.⁷

Although many studies have demonstrated the association of oral habits (betel quid chewing, smoking and drinking) with oral cancer, the quantified relationship between these habits and oral pre-malignancy with Bouquot classification has rarely been addressed. More importantly, few data have been published on dose-response relationships associated with the quantity and duration of these oral habits and oral pre-malignancy. Establishing dose-response relationships has important implications for betel quid chewers because such information provides evidence of the effect of educating users to reduce the quantity of chewing betel quid and to stop chewing completely. Doing so may reduce the occurrence of malignant transformation of oral pre-malignancy related to betel quid chewing, and further reduce the incidence of, and mortality from, oral cancer.

In this study, we used data from an oral screening programme among betel quid chewers to estimate the prevalence of various types of oral pre-malignancy, and to establish the dose-response effect of the duration and quantity of betel quid, cigarette and alcohol on the various types of oral pre-malignancy.

Materials and methods

Target population

The screening programme was conducted between 1998 and 1999. The target population consisted of men with the habit of chewing betel quid, living in Taipei at least 6 months before the study. Samples from catchment areas of 12 health post units scattered around Taipei city were selected, and included drivers, technicians, cleaners, and other labour groups. A total of 8360 participants aged between 15 and 85 years were enrolled into this study.

The screening programme

The screening programme for oral pre-malignancy and oral cancer comprised a team of 14 dentists, administrators and volunteer social workers. All dentists involved in this study received formal training on the diagnosis and classification of oral pre-malignancy, including leukoplakia, erythroplakia, erythroplakia, oral submucosa fibrosis, lichen planus, fibroma, ulceration and other clinical diagnosis, such as the opening degree of the mouth, colour and resilience of mucosa and lingual lesion. A series of on-site screening programmes were conducted to detect the above

oral lesions, particularly leukoplakia, erythroplakia, erythroplakia and oral submucosa fibrosis. For simplification, erythroplakia and erythroplakia are combined into one group.

Questionnaire

In addition to oral examination, every participant was asked to complete a questionnaire to provide information on socio-demographic variables, quantity, duration and frequency of betel quid, cigarette and alcohol consumption. The content and wording of the questionnaire was first reviewed by a panel committee and revised after a series of discussions. The operational definitions for the exposure of betel quid, cigarette and alcohol are described as follows. To establish the dose-response relationship between betel quid, cigarette smoking, alcohol consumption and oral pre-malignancy, the levels of betel quid chewing and smoking in quantity (per day) are defined as occasional use, one to 10 pieces, 10–20 pieces, and more than 20 pieces per day. These categories are based on commercial packs that contain 10 pieces in each pack. Ten sticks for smoking were also considered to be an easy number to remember. Alcohol consumption is divided into three categories: occasional use, drinking every week, and drinking everyday.

Statistical analysis

Multiple outcomes of oral pre-malignancy were encountered in this study; therefore, the effect of risk factors such as betel quid, cigarette and alcohol on a series of multiple outcomes was assessed using the generalized logit model, expressed as follows:

Logit $\pi_k = \alpha_k + X^T \beta_k$, where π_k ($k = 1, 2, 3$) represents three probabilities of becoming erythroplakia, leukoplakia and free of oral pre-malignancy; X^T represents covariates of quantity or duration of consuming betel quid, cigarette and alcohol, and socio-demographic characteristics; β s are the corresponding regression coefficients for covariates. Statistical significance was set at $\alpha = 0.05$ level for all analyses. All analyses were carried out using SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Results

Description

Of 8360 participants, 491 had leukoplakia, 124 had erythroplakia, 441 had oral submucous fibrosis, and 104 participants had lichen planus or other abnormal lesions. The frequency and prevalence of oral pre-malignancy and other abnormal lesions by age groups are listed in Table 1. The overall prevalence rates of leukoplakia, erythroplakia and oral submucous fibrosis were 5.9%, 1.5% and 5.3%, respectively. The prevalence rate of erythroplakia increased with age from 0.6% among individuals aged below 25 years to 2.3% among individuals aged over 55 years, whereas no remarkable difference in leukoplakia and oral submucous fibrosis was observed across age groups. The overall rate of other abnormal lesions was 1.2%.

Table 1 Frequency and prevalence of oral pre-malignancy and other abnormal oral lesions by 10-year age group

Age group (years)	Leukoplakia		Erythroleukoplakia		Oral submucous fibrosis		Oral lichen planus	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
<25	58	4.5	8	0.6	48	3.7	14	1.1
25–34	118	6.5	21	1.2	97	5.4	21	1.2
35–44	149	5.6	44	1.7	140	5.3	35	1.3
45–54	132	6.5	38	1.9	119	5.9	26	1.3
≥55	34	5.9	13	2.3	37	6.5	8	1.4
Total	491	5.9	124	1.5	441	5.3	104	1.2

The association between risk factors and oral pre-malignancy

The univariate analysis for the relationships between demographic characteristics and oral pre-malignancy is shown in Table 2. Significant factors accounting for oral pre-malignancy included age ($p < 0.0001$), educational level ($p < 0.0001$) and occupation ($p = 0.0022$). The effect of betel quid, cigarettes and alcohol on oral pre-malignancy by quantity and duration are shown in Figure 1, after adjusting for age, educational level and occupation. After adjusting for age, education, occupational level and quantity of the three risk factors (betel quid, cigarette, and alcohol), betel quid still remained statistically significant. The adjusted odds ratios for individuals chewing more than 20 pieces a day compared with occasional use were estimated as 5.37 (95% CI 3.81–7.56), 36.64 (95% CI 15.94–84.16), and 6.89 (95% CI 4.96–9.58) for leukoplakia, erythroplakia and oral submucous fibrosis, respectively. The corresponding figures for individuals chewing 11–20 pieces a day compared with occasional use and one to 10 pieces per day compared with occasional use were 2.99 (95% CI 2.08–4.30), and 2.14 (95% CI 1.62–2.81) for leukoplakia, 13.78 (95% CI 5.76–32.98) and 3.69 (95% CI 1.55–8.79) for erythroplakia, and 3.88 (95% CI 2.75–5.60) and 1.26 (95% CI 0.91–1.74) for oral submucous fibrosis.

Similarly, the significant effect of smoking on oral pre-malignancy still persists but is smaller than that of betel quid after adjusting for age, education, occupational level, and quantity of the two other risk factors. Similar results were found for the duration of drinking.

Discussion

To the best of our knowledge, this is the first study to establish the dose-response effect of duration and quantity of betel quid chewing on various types of oral pre-malignancy (including leukoplakia, erythroplakia and oral submucous fibrosis) rather than oral pre-malignancy in aggregate among betel quid chewers in blue-collar occupations. The duration and quantity of betel quid, to a larger extent, and of smoking, to a lesser extent, significantly contribute to the development of oral pre-malignancy even after adjusting for demographic characteristics and the three risk factors. However, the effect of alcohol on the risk for oral pre-malignancy disappears after controlling for significant confounders such as betel quid and smoking among betel quid chewers.

The above findings shed light on the magnitude of the effect of oral habits on the severity and types of various oral pre-malignancy. In modelling the effect of quantity of the

Table 2 Univariate analysis for the relationships of demographic characteristics to oral pre-malignancy

Variable	Leukoplakia OR (95% CI)	Erythroleukoplakia OR (95% CI)	Oral submucous fibrosis OR (95% CI)	<i>p</i> -Value
Age (years)				0.0001
≤25	1.00	1.00	1.00	
25–45	1.39 (1.04–1.86)	2.46 (1.17–5.13)	1.49 (1.09–2.05)	
45+	1.51 (1.11–2.06)	3.37 (1.59–7.13)	1.72 (1.23–2.39)	
Educational level (year)				<0.0001
0–6	1.00	1.00	1.00	
7–9	0.87 (0.66–1.16)	0.66 (0.41–1.08)	0.76 (0.59–0.98)	
10–12	0.92 (0.71–1.18)	0.52 (0.33–0.81)	0.47 (0.37–0.60)	
12+	0.59 (0.40–0.85)	0.15 (0.05–0.42)	0.14 (0.08–0.24)	
Occupation				0.0022
Service	1.00	1.00	1.00	
Technician	1.34 (0.98–1.82)	0.42 (0.20–0.89)	0.75 (0.54–1.05)	
Driver	1.06 (0.81–1.40)	0.73 (0.44–1.22)	0.74 (0.56–0.98)	
Others	0.79 (0.60–1.05)	0.81 (0.50–1.31)	0.77 (0.59–1.00)

Figure 1 Adjusted odds ratios and 95% confidence intervals of (a) consumption quantity and (b) duration of betel quid, smoking, and alcohol quantity for three oral malignancies. **, Adjusted for age, educational level, occupation, and three risk factors. The vertical line in the box represents the point estimate of odds ratio with ends at lower- and upper-limits of 95% confidence interval. The reference groups for betel quids, cigarette and alcohol in (a) are occasional use, no smoking and no drinking, respectively. In (b), the corresponding reference groups are less than 1 year, no smoking and no drinking, respectively. A, alcohol; B, betel quid; C, cigarette.

three oral habits on leukoplakia and erythroplakia, it can be easily seen that betel quid chewers who chewed more than 10 pieces a day were five times at risk for leukoplakia, and 40 times at risk for erythroplakia.

On the basis of the progressive and multiple properties of oral leukoplakia, we also found that the effect of betel quid chewing on the development of leukoplakia and erythroplakia is cumulative. Longer duration and higher consumption of betel quid is more likely to progress towards malignant transformation for leukoplakia. The threshold value of such a cumulative effect can also be recommended from such dose-response relationships. As seen in Figure 1, the adjusted odds ratio among those who had consumed one to 10 pieces of betel quid was 2.1 for leukoplakia and increased to 3.7 for the development of erythroplakia compared with those who were infrequent chewers. However, for those who had consumed between 11 and 20 pieces of betel quid, the adjusted odds ratio increased from 2.99 for leukoplakia to 13.78 for erythroplakia compared with infrequent chewers. A similar finding was observed for those who consumed more than 20 pieces a day.

The above findings show that educating users about betel quid chewing prompts them to reduce their consumption in areas of high prevalence of betel quid chewing. Quitting betel quid chewing is the best way to reduce incidence of, and mortality from, oral cancer. However, among people of certain occupations in Taiwan (i.e. technicians or taxi drivers), the habit of betel quid chewing is difficult to stop immedi-

ately. Therefore, prevention programmes may be feasible if a stepped approach is used. This would involve reducing the quantity of chewing betel quid to less than 10 pieces a day initially, with the final aim of stopping chewing betel quid completely.

To assess the absolute effect of reducing consumption of these three oral habits, we further divided participants with oral habits of areca nuts, chewing and smoking into high-exposure (duration $\times$ quantity)- and low-exposure users by using medians of consumption amounts as cut-off points for betel quid and smoking separately. The results show that 60%, 83%, and 71% of leukoplakia, erythroplakia and oral submucous fibrosis would be prevented if the use of betel quid is changed from high exposure to low exposure. When taking the exposure distribution of betel quid into account, three estimates of population attributable proportion were given as 43%, 71%, and 55%, respectively. Attributable proportion for smokers with high exposure was estimated as 35%, 51% and 53%. Population attributable proportion was given as 22%, 35%, and 37% for smoking. After adjusting for smoking, about 21%, 42%, and 39% of leukoplakia, erythroplakia and oral submucous fibrosis would be averted if high exposure to betel quid can be changed to low exposure.

This study has two possible limitations. First, the diagnosis of leukoplakia and erythroplakia in most cases was based on clinical diagnosis rather than on a biopsy-proven process. Thus, information on false-positive cases or pathological findings was not available. However, using a biopsy process

to detect asymptomatic cases was not feasible for on-site screening. As all dentists were well trained by senior dentists in pathology before starting the screening programme, we believed the quality and standard of clinical diagnosis was acceptable. Second, the population of betel quid chewers selected for study was blue-collar. The prevalence rate of leukoplakia among this group is 5.9%, which is higher than 2% of those at risk in the average population reported in earlier studies. This suggests that our results may not be generalizable to average-risk populations. However, as betel quid chewers are predominantly from lower socio-economic backgrounds, targeting high-risk groups may be efficient.

Conclusion

By assessing the quantity and duration of betel quid chewing, smoking and alcohol consumption in association with various types of oral pre-malignancy among betel quid chewers, we found that the dose-response relationships associated with quantity and duration of use between betel quid and oral pre-malignancy were significant but not so noteworthy for cigarette and alcohol consumption.

Conflict of Interest Statement

None to declare.

Role of the Funding Source

None to declare.

References

1. Silverman S, Bhargava R, Mani NJ, Smith LW, Malaowalla AM. Malignant transformation and natural history of oral leukoplakia in 57,518 industrial workers of Gujarat, India. *Cancer* 1976;**38**: 1790–5.
2. Silverman S, Gorsky M, Lozada F. Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. *Cancer* 1984;**53**:563–8.
3. Einhorn J, Wersall J. Incidence of oral carcinoma in patients with leukoplakia of the oral mucosa. *Cancer* 1967;**20**:2189–93.
4. Pindborg JJ, Jolst O, Renstrup G, Roed Petersen B. Studies in oral leukoplakia: a preliminary report on the period prevalence of malignant transformation in leukoplakia based on a follow-up study of 248 patients. *J Am Dent Assoc* 1968;**76**:767–71.
5. Shiu MN, Chen THH. Intervention efficacy and malignant transformation to oral cancer among patients with leukoplakia. *Oncol Rep* 2003;**10**:1683–92.
6. Shiu MN, Chen THH. Impact of betel quid, tobacco and alcohol on three-stage disease natural history of oral leukoplakia and cancer: implication for prevention of oral cancer. *Eur J Cancer Prev* 2004;**13**:39–45.
7. Bouquot JE, Whitaker SB. Oral leukoplakia—rationale for diagnosis and prognosis of its clinical subtypes or 'phases'. *Quintessence Int* 1994;**25**:133–40.