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Oral precancerous disorders associated with areca quid chewing, smoking, and alcohol drinking in southern Taiwan

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OBJECTIVE: To investigate the prevalence and the associated risk factors of oral precancerous disorders in southern Taiwan.

METHODS: We conducted a cross-sectional community survey interviewing 1075 adult subjects, 15 years of age and over, gathered from randomly selected 591 households, and spanning five villages in southern Taiwan. The study protocol included a visual oral soft tissue examination and a questionnaire-based interview. The chi-square test was used to test the differences in prevalence of oral precancerous lesions and conditions by different 'life styles' relating to current risk habits of current areca quid chewing, smoking, and alcohol drinking. To control for possible confounding, a logistic regression model was used to estimate the Odds Ratios (OR) for leukoplakia and oral submucous fibrosis (OSF).

RESULTS: 136 precancerous lesions and conditions were detected among 1075 subjects (12.7%). The analysis of the spectrum of oral precancerous disorders detected, leukoplakia ($n = 80$), OSF ($n = 17$) and verrucous lesions ($n = 9$), demonstrated an association with gender ($P < 0.001$). There were statistically significant associations among leukoplakia ($P < 0.01$), OSF ($P < 0.0001$), and verrucous lesions ($P < 0.0001$) and the life style of current areca quid chewing, smoking, and alcohol drinking. The synergistic effect of smoking and areca quid chewing habit on leukoplakia and OSF was demonstrated.

CONCLUSION: This study reinforces the association of current areca quid chewing without tobacco, cigarette smoking, and alcohol drinking to leukoplakia, OSF, and verrucous lesions in Taiwan.

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Introduction

According to the Taiwan Cancer Registry, oral cancer in the population has increased in both incidence and mortality over the past decade, and is now the fifth leading cause of male cancer-related deaths. The mortality rate for Taiwanese males has increased from 2.28 per 100 000 people in 1982 to 10.52 per 100 000 in 1999, making oral cancer a major public health problem in Taiwan. A case-control study (1) in Taiwan showed that the odds radio was 123 times for patients with oral cancer who smoked, drank alcohol, or chewed areca quid than for non-users.

The malignant transformation of oral mucosal lesions including leukoplakia (2, 3), erythroplakia (4), and submucous fibrosis (5) are well documented but the controversies on oral lichen planus remain a subject for discussion (6, 7). A wide range of rates for the malignant transformation of leukoplakia has been reported from 0.13 to 19.8% but it is estimated that the annual transformation rate should not exceed 1% (8, 9). Precancerous disorders are known to be associated with cigarette smoking, excess alcohol consumption, and areca quid chewing among Asians. As of 1992, it was estimated that two million individuals in Taiwan chew areca quid (10), but until recently very little research into the association between these precancerous lesions and life style habits has been done in this country. There are three types of areca quids consumed in Taiwan (11) and none contain tobacco. Therefore its pattern of use is different from other South Asian countries. This allows an investigation of carcinogenic risks of areca nut quid

chewing without tobacco among Taiwanese people. The purpose of this study was to investigate the independent and synergistic effects of areca quid chewing, cigarette smoking, and alcohol consumption on oral precancerous lesions and conditions detected in a population survey in Taiwan.

Materials and methods

Study subjects

We used a cross-sectional community survey, employing a house-to-house method to screen for oral precancerous lesions and conditions in a suburban population. A total of 1000 households were randomly selected from five villages (two out of four counties) in southern Taiwan. It was assumed that each household had at least two members over the age of 15 years.

Oral examinations and diagnostic criteria for oral mucosal screening

Between September 1998 and April 1999, the oral cavities of 1075 subjects 15 years of age or older from 591 households were examined by one trained specialist dentist (CHC) in southern Taiwan. The diagnostic criteria for the detection of oral precancerous lesions and conditions such as leukoplakia, erythoplakia, oral lichen planus, and oral submucous fibrosis (OSF), were based on the recommendations of the WHO (12, 13) and the first international seminar on 'oral leukoplakia' (14). In the hospital clinics in Taiwan a 'verrucous lesion' had been noted in areca chewers, hitherto not reported in the scientific literature. In this paper, 'verrucous lesions' were grouped in a separate category because this is a novel oral mucosal lesion (Fig. 1) in Taiwan, despite lack of research into its prevalence or etiopathogenesis.

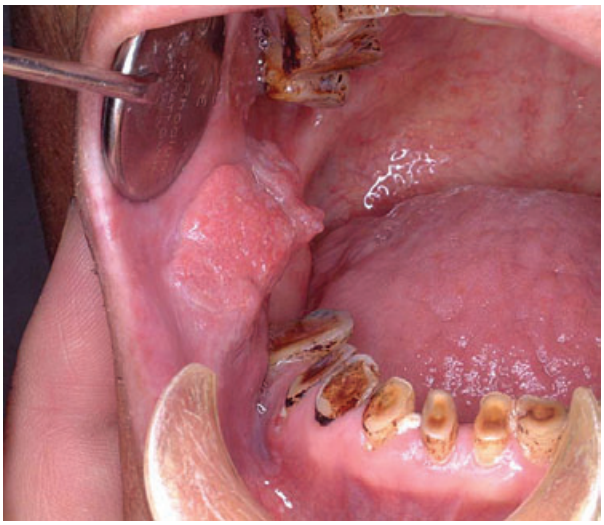

Figure 1 Verrucous lesion – an oral exophytic lesion on right buccal mucosa extending from the oral commissure to the retromolar region. The surface mucosa is pink with no obvious white plaques (hyper keratinization) and in part has a granular appearance. The surface is neither erythematous nor ulcerated. Some lobulations with no deep cefts are noted. Verrucous projections appear posteriorly.

Questionnaire interview

Trained research assistants or public health nurses interviewed study subjects in their own homes using a three-part questionnaire. The demographic section asked questions regarding age, gender, and education. The oral habits section included questions about regular use of alcohol, cigarette smoking, and areca quid consumption. The current life style of habits were defined as those subjects who chewed areca quid, smoked cigarettes, and drank alcohol regularly during the preceding 6 months. The Medical history section also recorded whether or not the interviewed subjects had previously been diagnosed with diabetes mellitus (DM) and/or hypertension.

Statistical analysis

Findings from the oral soft tissue examinations and information from the completed questionnaires were entered into Excel data files and analysed with Statistical Analysis System (SAS) software. The association between oral precancerous lesions and oral habits was tested by chi-square test with Yate-correction, Fisher's exact test, and logistic regression analysis. The relationships between two categorical variables were tested by the chi-square tests. However, for data with more than 20% of expected cell sizes being less than five, the Fisher's exact test was used instead. The chi-square test for trend-multiple strata was also used to control any confounding effect of risk habits. *P*-values lower than 0.05 were considered statistically significant. Odds ratios (OR) and 95% confidence intervals (95% CI) were computed to determine any association between the subjects with risk habits and oral precancerous lesions.

Results

In this study, 59.1% of the households volunteered to take part in the study (591 out of 1000 randomly selected households). Of these households, 1075 individuals were 15 years of age or older and were eligible for participation in this study. There were 526 males and 549 females. The number of subjects examined in each village ranged from 165 to 284 (mean 215). The mean age of the sample was 49.8 ± 17.3 (SD) years. The demographic variables of the participating subjects are presented in Table 1. The proportions of current users of areca quid, cigarette smokers, and alcohol users were found to be 7.16% (77/1075), 20.84% (224/1075), and 18.14% (195/1075), respectively. The prevalence of these risk habits in the population was strongly dependent on gender (Table 1).

The prevalence of leukoplakia, erythroplakia, oral lichen planus, OSF, and verrucous lesions were 7.44, 1.95, 2.98, 1.58 and 0.84%. Oral leukoplakia was divided into two groups, according to its etiological risk habit (idiopathic or tobacco/areca associated leukoplakia) and clinical presentation (homogenous or non-homogeneous leukoplakia) (Axell et al. 1984). By cross tabulation against the etiologic factors, the prevalence of idiopathic leukoplakia was 3.07% (33/1075) and tobacco/areca-associated leukoplakia was

Table 1 Demographic characteristic of 1075 subjects

	Male N (%)	*Female N (%)*	*Total N (%)*	*Sig tests and P-value*
Number	526 (48.9)	549 (51.0)	1075 (100)	
Age				
15–24	52 (9.89)	63 (11.48)	115 (10.70)	
25–34	47 (8.94)	69 (12.57)	116 (10.79)	
35–44	87 (16.54)	102 (18.85)	189 (17.58)	
45–54	87 (16.54)	96 (17.49)	183 (17.02)	
55–64	126 (23.95)	106 (19.31)	232 (21.58)	
>65	127 (24.14)	113 (20.58)	240 (22.33)	
Education[a]				
9 years	384 (73.14)	421 (77.00)	805 (75.09)	
≥9 years	141 (26.86)	126 (23.03)	267 (24.91)	
Habits				
Cigarette smoking	218 (41.44)	6 (1.09)	224 (20.84)	$P < 0.05$*
Alcohol drinking	180 (34.22)	15 (2.73)	195 (18.14)	$P < 0.05$*
Areca quid chewing	76 (14.45)	1 (0.18)	77 (7.16)	$P < 0.05$**
DM	41 (7.79)	23 (4.19)	64 (5.95)	
Hypertension	88 (16.73)	72 (13.11)	160 (14.88)	
Leukoplakia	65	15	80 (7.44)	$P < 0.05$*
oral lichen planus	19	13	32 (2.98)	
Erythroplakia	14	7	21 (1.95)	
OSF	17	0	17 (1.58)	$P < 0.05$**
Verrucous lesions	8	1	9 (0.84)	$P < 0.05$**

[a]Only 1072 disclosed their educational status.
*Yate-corrected chi-square test.
**Fisher's exact test.

4.37% (47/1075). According to the clinical factors, the prevalence of homogenous leukoplakia was 6.05% and non-homogenous leukoplakia (excluding verrucous lesions) was 1.4%. Homogeneous leukoplakia displayed significant differences ($P < 0.0005$) between men and women (Table 2).

Table 3 shows the relationship between oral precancerous lesions and current habits of the subjects. There were a total of 136 precancerous lesions among 1075 subjects examined (12.7%). The risk of oral precancerous lesions among subjects reporting cigarette smoking, alcohol drinking, and areca quid chewing were,

Table 2 Distribution of oral precancerous lesions and conditions by sex

	Men		*Women*		*Yate-corrected chi-square test value*	*P-value*
	N	*%*	*N*	*%*		
Leukoplakia	65	12.36	15	2.73	34.75	<0.0001
Homogenous	55	10.46	10	1.82	33.75	<0.0001
Non-homogenous	10	1.90	5	0.91	1.26	0.2611
Lichen planus	19	3.61	13	2.36	1.04	0.3075
Reticular	13	2.47	8	1.46	0.96	0.3270
Erythematousn	7	1.33	6	1.09	0.06	0.9380
Erosive/ulcerative	0	0.00	0	0.00		
Erythroplakia	14	2.66	7	1.27	2.02	0.1551
Submucous fibrosis	17	3.23	0	0.00	[a]	<0.0001
Verrucous lesion	8	1.52	1	0.16	[a]	<0.0001

[a]Fisher's exact test.

Table 3 Prevalence of oral precancerous lesions and conditions and life style habits

	Precancerous lesion, yes	*Precancerous lesion, no*	*Yate-corrected chi-square test*	*P-value*	*ORs*	*95% CI*
Areca quid chewing						
Yes	37 (48.05%)	10 (51.95%)	90.64	0.001	8.40	(5.13, 13.75)
No	99 (9.92%)	899 (90.08%)				
Cigarette smoking						
Yes	66 (29.46%)	158 (70.54%)	70.47	0.001	4.66	(3.20, 6.80)
No	70 (8.23%)	781 (91.77%)				
Alcohol drinking						
Yes	53 (27.18%)	142 (72.82%)	43.91	0.001	3.58	(2.43, 5.28)
No	83 (9.43%)	797 (90.57%)				

Table 4 The association between each oral precancerous lesions and conditions and life style of habits

	Total number	*Leukoplakia*		*Erythroplakia*		*Oral lichen planus*		*OSF*		*Verrucous lesion*	
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
BSA	44	17	38.64	3	6.82	2	4.55	7	15.91	4	9.09
BS	19	5	26.32	1	5.26	2	10.53	3	15.79	1	5.26
BA	10	2	20.00	1	10.00	2	20.00	1	10.00	0	0.00
B	4	1	25.00	0	0.00	0	0.00	0	0.00	0	0.00
SA	62	11	17.74	1	1.61	1	1.61	2	3.23	1	1.61
S	99	14	14.14	3	3.03	3	3.03	3	3.03	0	0.00
A	79	7	8.86	1	1.27	5	6.33	0	0.00	1	1.27
None	758	23	3.03	11	1.45	17	2.24	1	0.13	2	0.26
P-value		<0.0001		0.1072		0.01		<0.0001		<0.0001	

B, areca quid chewer; S, cigarette smoker; A, alcohol user; Betel quid in Taiwan does not contain tobacco.

respectively, 4.66-fold (95% CI = 3.20–6.80), 3.58-fold (95% CI = 2.43–5.28), and 8.4-fold (95% CI = 5.13–13.75) significantly higher than in abstainers.

Table 4 displays the prevalence of each oral precancerous lesion stratified by risk habits under study. By chi-square test for trend-multiple strata analysis there was a statistically significant trend relating to the development of leukoplakia ($\chi^2 = 113.57$, $P < 0.0001$), OSF ($\chi^2 = 101.12$, $P < 0.0001$), and verrucous lesions ($\chi^2 = 45.13$, $P < 0.0001$) with chewing areca quid, smoking cigarettes, and drinking alcohol. Combined risk factors of chewing areca quid and smoking increased the risks in all three categories of clinical lesions. Seventeen out of 32 subjects with lichen planus had no reported risk habits.

The synergistic effects of cigarette smoking, alcohol drinking, and areca quid chewing for leukoplakia and OSF by logistical regression analysis are shown in Tables 5 and 6. The occurrence of leukoplakia among subjects with cigarette smoking, alcohol drinking, and areca quid chewing was 15-fold (OR = 15.12, 95% CI = 6.34–36.05) higher than among abstainers. Male subjects whose habits were limited to alcohol drinking and all women were not entered to the model on risk analysis for OSF. Therefore, alcohol drinking and female sex were not considered independent variables in the analysis of synergistic effects for OSF. The subjects who chewed areca quid and smoked cigarettes were found to exhibit a 152-fold (OR = 151.9, 95% CI = 19.08–999.99) increased risk for OSF compared with abstainers.

Table 5 Synergistic effect of cigarette smoking, alcohol drinking, and areca nut chewing for leukoplakia by logistic regression

Variable	*Number*	*Parameter estimate*	*Standard error*	*Wald chi-square*	*P-value*	*ORs*	*(95% CI)*
Intercept		−3.99	0.48	69.63	<0.0001		
BSA	17	2.72	0.44	37.52	<0.0001	15.12	(6.34, 36.05)
BS	5	2.15	0.61	12.38	0.0004	8.54	(2.58, 28.23)
BA	2	1.76	0.85	4.29	0.0384	5.82	(1.10, 30.84)
B	1	2.15	1.19	3.28	0.0702	8.60	(0.84, 88.19)
SA	11	1.60	0.45	12.54	0.0004	4.96	(2.05, 12.04)
S	14	1.30	0.42	9.56	0.0020	3.69	(1.61, 8.43)
A	7	0.86	0.49	3.13	0.0770	2.36	(0.91, 6.13)
Man	65	0.50	0.39	1.63	0.2017	1.64	(0.77, 3.51)
Age		0.01	0.01	0.76	0.3819	1.01	(0.99, 1.02)

B, areca quid chewer; S, cigarette smoker; A, alcohol user.
Reference group: woman and no habits.

Table 6 Synergistic effect of cigarette smoking and areca quid chewing for OSF

Variable	*Number*	*Parameter estimate*	*Standard error*	*Wald chi-square*	*P-value*	*ORs*	*(95% CI)*
Intercept		−6.01	1.29	21.896	<0.0001		
BS	10	5.02	1.06	22.52	<0.0001	151.95	(19.08, 999.99)
B	1	4.18	1.44	8.41	0.0037	65.86	(3.89, 999.99)
S	5	3.39	1.11	9.38	0.0022	29.68	(3.39, 259.90)
Age		−0.02	0.02	0.70	0.4023	0.985	(0.95, 1.02)

B, areca quid chewer; S, cigarette smoker; A, alcohol user.
Reference group: no areca quid chewing and cigarette smoking.

Discussion

House-to-house surveys have been employed in India (2) and in the Sudan (15) to examine the oral cavities of randomly selected population samples based on cluster analysis of households. Most published studies on the use of tobacco in developing countries, however, have been either hospital-based or drawn from convenience samples. House-to-house surveys based on random sampling provide more accurate population data but need dedicated teams for fieldwork and considerable networking to arrange visits for the convenience of the villagers.

The terminology and nomenclature for oral leukoplakia varies considerably. Most researchers use WHO (12, 13) and Axell et al. criteria (14). On otherhand 'oral lesions associated with betel quid habits' (16) may need special consideration if the examiner is able to record that the lesion is located where an areca quid is habitually placed by the examined subject. This was not attempted in this study.

The prevalence of oral precancerous lesions varies in different countries, and representative studies suggest a variance from as much as 25% to as little as 0.2% (17). Two separate research findings in mainland China (18) and Hong Kong (19) reported the prevalence of leukoplakia as 2 and 0.6%, respectively. Yang et al. (11) reported the prevalence of leukoplakia was 24.4% among the aborigines in southern Taiwan. This study showed that the prevalence of leukoplakia was 7.44%, significantly lower than Yang's report. This may be due to differences in habits practised by population groups; particularly the aboriginal people are known to have higher risks due to their lifetime areca chewing habits.

In this study, homogenous leukoplakia (6.05%) was found to be more prevalent than non-homogenous leukoplakia (1.40%). These results are comparable to those of Axell (20) (3.5% vs. 0.3%) from Sweden and of Gupta et al. (2) from Eranakulam District, India (1.26 vs. 0.21) though of higher magnitude for both clinical types. A rationale for the diagnosis of subtypes of leukoplakia exists due known variations in their prognosis (2, 4).

A statistically significant association between leukoplakia and reported risk habits has been demonstrated in many studies (21), though remarkable regional differences exist (22). In Asia, leukoplakia is known to be associated with smoking (bidi and cigarette), smokeless tobacco and chewing habits (paan, areca quid, and miang) (23), and a synergistic effect also was found (24); In the latter study (24), relative risk for males with leukoplakia rose from 5.3 for quid chewers to 15.0 for those who added tobacco to their quid and further rose to 24.7 who in addition smoked. Chewing of areca/betel quid is widespread in the orient (25). A large variety of ingredients, including tobacco, may be used along with areca nut as the main constituent of a betel quid. The composition and method of chewing can vary widely from country to country and the prevalence of leukoplakia can vary too. Tobacco is mostly added as a constituent of betel quid in India (23) and in Thailand (26). In India, the prevalence of oral leukoplakia among betel quid chewers with tobacco ranged from 0.4 to 1.8% and among betel quid chewers without tobacco ranged from 0.3 to 0.7% in India (23). In Thailand, the habits of chewing included use of areca quid with tobacco and Maing chewing. For the latter group the prevalence of leukoplakia was 1.1% and not strongly correlated by logistic regression. In Melanesia, like in Taiwan, people do not add tobacco to areca quid chewing. The prevalence of leukoplakia was 4.6–17% in Papua New Guinea (27, 28). In Taiwan, Shiu et al. (3) showed that the OR for leukoplakia in a current areca quid, cigarette, and alcohol users were, respectively, 25.85, 5.42, and 8.66. Our study determined a prevalence of leukoplakia of 7.44% and that in current areca quid users, this could rise to more than 20%. The stratification of subjects by chewing/smoking habits allows examination of risks attributable to a single habit, though numbers in each category would be small. The study confirmed areca quid chewing without the use of tobacco is an important risk factor for leukoplakia in Taiwan.

The synergistic effect of areca quid chewing, cigarette smoking, and alcohol drinking on leukoplakia has been reported. In Lee et al.'s study (29), the risks of oral leukoplakia for smokers who also chewed areca quid increased from 10.0 to 40.2-fold compared with a non-smoking areca quid chewer. In our study, the risks of oral leukoplakia for both groups were lower, in the order of 9, but the subjects who chewed areca quid, smoked cigarette, and drank alcohol were 15-times more likely to have leukoplakia than abstainers. Similar synergistic effects of these habits contributing to the causation of oral cancer were documented from Taiwan (1).

In cross-sectional studies, the prevalence of OSF among subjects around the world is from 0.03 to 3% (30). Two separate studies in southern China reported the prevalence of OSF as 3 and 3.03%, respectively (18, 31). In our study, the prevalence of OSF was found to be 1.58%. Diagnostic criteria vary in different studies and we adopted the clinical criteria agreed at the consensus conference held in Malaysia in 1996 to define OSF (15). This is the first report from Asia to use these criteria for the detection of OSF. A female preponderance of OSF is found in many Indian studies (32). In this study, all OSF cases were male and this reflects the significantly high areca chewing habit among Taiwanese male compared with females. Areca quid chewing is reported as the major etiologic agent for OSF (33). In case-series studies, the frequency of areca quid chewing reported among cases of OSF cases is close to 100% (30). In the first study on OSF conducted in late1970s in Taiwan, the frequency of areca quid chewing reported among OSF was 60% (34). Some underreporting due to lack of recognition of the importance of this behaviour at the time is likely. In our study, among cases of OSF the frequency of current areca quid chewing was 64.7% (11/17) and others with OSF not reporting the habit may have quit the habit following the development of the condition. In case-control studies, the relative risk of

OSF among areca nut chewers was computed to range from 32 to 109.6 (33, 35, 36). The relative risk of OSF among smokers or drinkers was not significantly elevated in the present study.

By univariate analysis, 79 subjects, whose life style habits were limited to alcohol drinking, did not exhibit OSF; alcohol habit was therefore excluded in the logistic regression model for further analysis. The subjects who were both current areca quid and cigarette smokers exhibited a 151-fold increase in risk of OSF than among abstainers, while those who only currently used areca quid only showed a 66-fold increased risk of OSF. It is likely that those who both smoked and chewed areca quid probably started their habits at a much younger age or their frequency of chewing was higher. This needs to be tested. While OSF is not linked to smoking, in Taiwan a synergistic effect of cigarette smoking and areca quid chewing cannot be disregarded.

The verrucous lesion described as an exophytic growth with irregular sharp or blunt projections (37), included verrucous leukoplakia and verrucous hyperplasia but some lesions seen in Taiwan do not fit the recognised criteria for both these conditions. Shear and Pindborg (37) reported that out of 28 patients with verrucous lesions 24 (86%) used tobacco and one was an areca quid chewer. Tobacco appears to be a major factor in the causation of verrucous lesions. In Chen et al.'s study (38) on verrucous carcinomas from Taiwan, areca quid chewing was reported by 97.3%. In this study, the prevalence of verrucous lesions (not carcinomas) was 0.84% and the frequency of current areca quid chewing in this subgroup was 55.6% (5/9). The data indicate that, in Taiwan, areca quid use could be a major risk factor for verrucous lesions. In collaboration with several regional centres and the WHO Collaborating Centre for Oral Cancer in the UK we are conducting further research to define the newly identified 'verrucous lesion' in this population.

The prevalence of oral lichen planus in our study was found to be 2.98%. This is much higher than that reported by Pindborg et al. (39) (0.1–1.5%) in India, and Axell and Rundquist (40) (1.9%) in Sweden. The prevalence of oral lichen planus in the general population on a global scale had been reported to be 0.02–3.8% (41). Life style habits are not implicated in its aetiopathogenesis and is considered an immunopathological disorder (42). Axell and Rundquist (40) reported that oral lichen planus was less prevalent among smokers than non-smokers, with the exception of the plaque type. In this survey, we found that the prevalence of oral lichen planus was 3.57% (8/224) in smokers and 2.82% (24/851) among non-smokers ($P = 0.713$). The relatively high prevalence of oral lichen planus in the present study may be attributed to the difficulty in distinguishing oral lichen planus and areca quid-induced lichenoid lesions due to their closely similar clinical presentations (15).

Erythroplakia is a rare oral precancerous lesion found in the oral cavity. 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% (43). Ikeda et al. (22) found only one subject (0.03%) with erythroplakia among 3131 Japanese people. Zain et al. (44) also reported only one subject with erythroplakia among 11 707 people in Malaysia. It is noted that there is a relatively high prevalence of erythroplakia (1.95%) in this study. To accurately diagnose erythroplakia it is necessary to distinguish this lesion from non-specific mucositis, candidiasis, or vascular lesions by biopsy. This difficulty is apparent in another study from Asia, which described 100 erythroplakias without biopsy confirmation in a single survey (45). In our study, chewing areca quid was the most significant risk factor for erythroplakia in Taiwan, but no synergistic effect with cigarette smoking and alcohol drinking was found.

In conclusion, this study demonstrated several associations for oral precancerous disorders and life style habits in southern Taiwan. Although the areca quid of Taiwan does not contain tobacco, areca quid without tobacco was recognised as a major risk factor for oral precancerous lesions/conditions. These findings are of significance for the evaluation of carcinogenic risks of areca nut without tobacco on human populations. At present there is no systematic approach to provide any intervention for areca chewers in Taiwan. As life style is an adaptation to ones social environment and that these risk factors are deeply entrenched in the society, any interventions should go beyond the individual to include the family and the sociocultural framework.

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