Consumption of areca quid, cigarettes, and alcohol related to the comorbidity of oral submucous fibrosis and oral cancer

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Objective. Oral submucous fibrosis (OSF) is defined as a precancerous condition, and it is also commonly seen in clinical practice, coexisting with oral cancer. The aim of this study was to identify the effects of areca quid, cigarette, and alcohol on the coexistence of oral cancer and OSF.
Study design. This is a case-control study. One hundred four histologically confirmed male OSF subjects were included, which consisted of 65 OSF subjects without oral cancer (control group) and 39 OSF subjects with oral cancer (case group).
Results. The cigarette consumption in the case group was significantly higher than the control group. In drinking habits, the mean consumption of alcohol in the case group was significantly higher than the control group. Logistic regression analysis was used to identify these risk factors. Age and alcohol consumption showed a significant effect, and the odds ratios were 1.07 in age and 1.5 in alcohol consumption.
Conclusion. Alcohol drinking could be a risk factor associated with an increased risk of malignant transformation and coexistence with oral cancer in OSF patients, but cigarette and areca quid were not risk factors in our study. For oral cancer prevention from OSF, more attention should be paid to the importance of public health strategies targeted toward preventing and reducing alcohol consumption. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:647-52)**

Oral submucous fibrosis (OSF) is a chronic progressive disease leading to marked limitation of mouth opening and is characterized by the oral mucosal becoming stiff due to fibroelastic transformation of the juxtaepithelial and deeper connective tissue.[1] Some previous studies have proved that the areca quid chewing habit (with/without tobacco) is causal to triggering changes that lead to OSF in susceptible individuals.[2-8] Oral submucous fibrosis is an oral mucosal lesion commonly seen in Southeast Asia; reports have shown that the prevalence of OSF in this area ranges from 0.04% to 24.4%.[6,9,10] The highest rate of 24.4% was reported from a study collected from an aboriginal community of southern Taiwan, with a 69.5% areca quid chewing prevalence rate.[6] In oral cancer patients, OSF is also commonly coexistent with oral cancer lesions, which coupled with the comorbidity rate is more than 40%.[11] In 1984, Pindborg indicated that the coexistence of OSF with oral cancer could actually be considered an expression of malignant transformation of OSF because of the relatively short duration and rapid spread of oral cancer, compared with the chronicity of submucous fibrosis.[11] The malignant transformation rate of OSF is reported as 2.3% to 7.6%.[12,13] In most Southeast Asia countries, areca nut is used with tobacco, and it has been difficult to identify the risk effect in areca nut use only. In Taiwan, tobacco-free areca quid chewing is a popular habit and provides a suitable area to establish the OSF risk from areca nut use only. From previous studies in Taiwan, areca quid chewing is a major etiology of oral cancer and OSF.[6,14-17] It was estimated

The study was supported by grant NSC93-2314-B-037-054 from the National Science Council, Taiwan [to P.-S.H.], Republic of China.
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Received for publication Jul 11, 2006; returned for revision Dec 11, 2006; accepted for publication Dec 27, 2006.
1079-2104/$ - see front matter
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doi:10.1016/j.tripleo.2006.12.032

Table I. Distribution of OSF with and without oral cancer, according to smoking and drinking exposure

	OSF with oral cancer (n = 39)		*OSF without oral cancer (n = 65)*			
	n	*%*	*n*	*%*	*Crude OR (95% CI)*	*P value*
Smoking						
No	7	17.95	6	9.23	1.00	.2281*
Yes	32	82.05	59	90.77	0.47 (0.14-1.50)	
Drinking						
No	5	12.12	23	35.88	1.00	.0120
Yes	34	87.18	42	64.62	3.74 (1.28-10.83)	
Areca quid type						
Betel quid	12	30.77	25	38.46	1.00	.5889
Lao-hwa quid	15	38.46	19	29.23	1.65 (0.63-4.32)	
Combined use	12	30.77	21	32.31	1.19 (0.44-3.20)	

OSF, oral submucous fibrosis; *OR,* odds ratio; *CI,* confidence interval.
*Fisher exact test.

that there are about 2 million areca quid chewers in Taiwan.[15] With the increasing consumption of areca quid in Taiwan,[17] the prevention of occurrence and malignant transformation of OSF will become more important in the future.

There have been several studies concerning the epidemiological risk factors of OSF, but none focusing on the etiologies related to the coexistence or malignancy of OSF. The major risk factor of OSF is areca quid chewing, so in this study only areca quid chewers were included. The aim of this study was to simultaneously quantify the effects of chewing, smoking, and drinking on malignant transformation of OSF to oral cancer.

MATERIAL AND METHODS

This study is a hospital-based case-control study. All subjects were consecutively collected from the Division of Oral and Maxillofacial Surgery, Department of Dentistry, Kaoshiung Medical University Hospital from 1998 to 1999. All cases were diagnosis confirmed by histopathology. There were 104 new histologically confirmed OSF cases included in our study. Of all the OSF cases, 65 subjects had OSF without oral cancer (control group), and 39 subjects had OSF with oral squamous cell carcinoma (case group). All subjects were male and areca quid chewers. All patients were interviewed to complete a structured questionnaire by a trained interviewer. The questionnaire was used to collect information on demographic characteristics, history, and quantity of smoking, drinking, chewing habits, and type of areca quid. The average amount of per day use of cigarettes, alcohol, and areca quid was reported by the subjects. The starting and quitting age (if one has quit) of these 3 habits were also collected to estimate the use duration. The type of betel material chewed was recorded as areca nut with betel leaf and white lime paste (betel quid), or areca nut with betel inflorescence and red lime paste (Lao-hwa quid), or both combinations.

Using the original usage in pack per year for the analysis model may result in parameter estimates by each pack per year. In our data, the average consumption for areca quid, cigarette, and alcohol beverage was 37.9, 30.4, and 13.5 units, respectively. Using 10 as a unit is considered more practical in terms of interpreting the dose-response effect.

Statistical analysis

The chi-square test and the 2-sample *t* test were used to examine the difference of risk factors among OSF patients without oral cancer and with oral cancer.

Adjusted odds ratios (ORs) with 95% confidence interval (CIs) were calculated to estimate the risk of the suspected risk factors in the questionnaire. All OR estimates were examined by logistic regression analyses. SAS computer package 8.0 (SAS Institute Inc., Cary, NC) was used for the analysis of collected data in the study.

RESULTS

Of the 104 male patients with OSF, 39 (37.5%) were comorbid with oral cancer. When comparing the smoking and drinking habits between the case and control groups (Table I), it was found that the smoking prevalence in the case group was 82.05% and the control group was 90.77%. The smoking rate in the case group was slightly lower than that of the control group, but the difference was not statistically significant. The drinking prevalence in the case group was 87.18%, which was significantly higher than the control group, 64.62%. The duration and amount of chewing, smoking, and drinking habits are compared in Table II. In the case group, the mean consumption of areca quid was 4.76 (SD, 7.43) 10-packs per year, which was higher

Table II. Duration and amount of areca quid, cigarettes, and alcoholic beverages

	OSF without oral cancer (n = 65)		*OSF with oral cancer (n = 39)*		
Variables	*Mean*	*(SD)*	*Mean*	*(SD)*	*P value*
Areca quid (10-pack/y)*	3.21	(4.36)	4.76	(7.43)	.2371
Cigarettes (10-pack/y)	2.41	(1.67)	4.09	(3.24)	.0069
Alcoholic beverages (10-liter/y)	0.67	(1.20)	2.49	(3.24)	.0016
Age (y)	40.09	(11.01)	48.72	(9.59)	<.0001

OSF, oral submucous fibrosis.
*One pack is defined as 20 pieces of areca quid.

than the control group, 3.21 (SD, 4.36) 10-packs per year. But the difference was not statistically significant. The cigarette consumption in the case group was 4.09 (SD, 3.24) 10-packs per year, which is significantly higher than the control group at 2.41(SD, 1.67) 10-packs per year. In drinking habits, the mean consumption of alcoholic beverages in the case group was 2.49 (SD, 3.24) 10-liters per year and was significantly higher than the control group, which was 0.67 (SD, 1.2) 10-liters per year. In the case group, the mean age was 48.72 (SD, 9.59) years, but only 40.09 (SD, 11.01) years in the control group. The difference of mean age between the case and control group was statistically significant.

There were 3 logistic regression models used in our study (Table III). In model 1, only consumption status of areca quid and age were included in the logistic regression analysis. However, only the age variable had a significant effect on the comorbidity with oral cancer in OSF patients (OR, 1.08; 95% CI, 1.03-1.12). The consumption amount of cigarettes was added in model 2. In this model, age still had a statistically significant OR 1.07 (95% CI, 1.02-1.11). The borderline significant effect (OR, 1.20; 95% CI, 1.00-1.46; $P = .0559$) was found in cigarette consumption. In model 3, except for consumption of areca quid and cigarettes, the consumption of alcoholic beverages was considered in the logistic regression model. Age and consumption of alcoholic beverages showed a significant effect, and the OR was 1.07 (95% CI, 1.02-1.12) in age and 1.50 (95% CI, 1.11-2.01) in alcoholic beverage consumption. It was found that older age and increasing consumption might be important malignant risk factors of OSF. The type of areca quid chewed was considered in the 3 models; the Lao-hwa quid chewers seemed to have a higher malignant risk (OR, 1.3) when compared with betel quid chewers but was not statistically significant. To compare the estimated parameters in the 3 models, the ORs of consumption in areca quid, cigarettes, and alcoholic beverages did not show a variation in different models. This pattern suggests that the interaction effect is not found in the 3 habits.

DISCUSSION

Areca quid chewing is the most important etiologic factor for OSF.[3,6,7,14,16,18,19] From previous studies, it was indicated that OSF is hardly ever found in non–areca quid chewers.[2,16] In India and Southeast Asian countries, areca quid is usually chewed with tobacco.[7,20] Some studies from Taiwan have also demonstrated that the type of areca quid used in Taiwan is strongly related to OSF.[6,14,16,18] However, in Taiwan the areca quid is used without tobacco.[6,14-17] The exact etiologic effect of areca quid in OSF is not well understood. It is most often stated that arecoline, the most abundant alkaloid in areca quid, has been observed—experimentally—to stimulate collagen synthesis by fibroblasts in vitro[21] and even stimulates double-stranded polynucleic acid synthesis in human buccal fibroblasts.[22] Not only in OSF, areca quid chewing in Taiwan has also been defined as a major etiologic factor in oral cancer, which has been proved in several studies from Taiwan.[15,17] In the study of Ko et al.,[15] the risk of oral cancer for areca quid chewers is much higher than that of cigarette smokers or alcohol drinkers. The coexistence of OSF with oral cancer could actually be considered an expression of malignant transformation of OSF.[11,23] To compare the difference of risk factors between OSF with and without oral cancer may help to identify the etiologic factors related to malignancy transformation of OSF. From the present results, the malignant risk of OSF was not found to increase with the consumption amount of areca quid. In previous studies, it was indicated that even a relatively short exposure is sufficient to induce OSF.[2,3,14] Therefore, we cannot find a dose-response effect of areca quid on OSF malignancy. Another explanation of the present data is that the carcinogenic process is multiple staged, and the major effect of areca quid might be in the relatively early phase or initial stage of carcinogenesis.

There are 3 major types of areca quid in Taiwan: betel quid, Lao-hwa quid, and stem quid.[16] But stem quid is only used by Taiwanese aboriginal groups.[6] The betel quid and Lao-hwa quid are the major types chewed by the general population of Taiwan.[15] There is

Table III. Logistic regression analysis of risk factors for OSF without and with oral cancer

	Model 1			Model 2			Model 3		
Variables	*OR*	*95% CI*	*P value*	*OR*	*95% CI*	*P value*	*OR*	*95% CI*	*P value*
Areca quid (10-pack/y)	1.03	(0.95-1.12)	.4559	1.01	(0.94-1.11)	.7558	1.01	(0.91-1.13)	.8000
Cigarettes (10-pack/y)	—			1.20	(1.00-1.46)	.0559	1.10	(0.89-1.36)	.3613
Alcoholic beverages (10-liter/y)	—			—			1.50	(1.11-2.01)	.0076
Areca quid type									
Betel quid	1.00			1.00			1.000		
Lao-hwa quid	1.35	(0.47-3.85)	.5746	1.34	(0.46-3.89)	.5916	1.29	(0.41-4.03)	.6651
Combined use	1.17	(0.40-3.41)	.7763	1.10	(0.37-3.32)	.8586	1.03	(0.33-3.22)	.9591
Age (y)	1.08	(1.03-1.12)	.0007	1.07	(1.02-1.11)	.0048	1.07	(1.02-1.12)	.0042

OSF, oral submucous fibrosis; *OR,* odds ratio; *CI,* confidence interval.

a higher risk of oral cancer with chewing Lao-hwa quid than with chewing betel quid.[15] In the present study, a higher OR was found in Lao-hwa quid when compared with betel quid, but it was not statistically significant because of the small sample size. The different malignant effects among various areca quid types require further study.

Of Taiwanese areca quid chewers, 86% to 87% are cigarette smokers and 75% are alcoholic beverage drinkers.[24] Hence, the effects of drinking and/or smoking should not be ignored in the malignant transformation of OSF. In the present paper, the association of alcohol and malignancy of OSF was evident after adjusting for smoking habit; a dose-response trend was observed for alcohol drinking and the malignant risk of OSF. Alcohol drinking has been associated with an elevated risk of oral cancer in several previous studies.[15,25-29] In publications from Scotland and Denmark, it was indicated in cohort-based studies that increasing changes of oral cancer are probably a result of the increased consumption of alcoholic beverages.[30,31] Although alcohol drinking also plays a role in the etiology of oral cancer in Taiwan, the risk of drinking only was thought to be less than that of cigarette smoking or betel quid chewing.[15] In other studies about OSF or leukoplakia, an independent or synergistic effect of alcohol use was not identified.[6,14,16]

Although the occurrence of precancerous lesions was reported to be mainly related to chewing and smoking habits in Taiwan, our study showed little relationship in the 2 habits. In our study, the malignant risk of OSF seemed to increase with consumption of alcoholic beverages. In an Indian study, 2003,[32] it was indicated that alcohol drinkers have a higher risk of multiple oral premalignant lesions. The effect of alcohol beverage drinking on the malignant potential of oral precancerous lesions has also been found in leukoplakia.[33] The mechanism by which alcoholic beverages induce oral cancer is not clear. The most likely explanation is that alcohol or its metabolites are human carcinogens. Ethanol is a common ingredient in alcoholic beverages, which has been recognized as a solvent that may damage the oral cells and increase the mucosal penetration of certain oral carcinogens.[34] On the other hand, acetaldehyde, the first metabolite of ethanol,[35] is the suspected carcinogen in alcoholic beverages. Acetaldehyde in saliva has been suggested to act directly to damage the oral mucosa. It is supposed that alcohol drinking may act as a promoter for facilitating the malignant transformation from oral precancer to cancer.

For oral cancer, cigarette smoking is not only an independent risk factor but may also act synergistically with areca quid chewing.[15] However, the independent effect of smoking was not seen on the pathogenesis of OSF, and only the synergistic effect was found in some studies.[2,16] In our study, the effect of cigarette smoking was significant when the drinking habit was not included in the model (Table III, model 2). Cigarette smokers are usually also alcohol drinkers.[24] Hence, when considering the drinking habit, the effect of smoking on the malignant effect is not significant. Similar results were found in other studies regarding other precancer lesions such as leukoplakia.[33,36] It is thought that the smoking habit may not be a main contributory cause for malignant transformation.[33,36] In a study from India, smoking did not appear to be a risk factor for multiple oral premalignant lesions.[32] It is not very clear why the smoking habit is not associated with a greater risk of malignant potential in precancer lesions or conditions. It is speculated that if the use of tobacco is suppressed, other factors of greater importance contribute to the initiation or promotion of carcinogenesis.[37]

Age is an influencing factor in the incidence of oral cancer, as was also found in this study. The average age of the OSF patients with oral cancer in our study was 48.72 years, which is similar to the average diagnosis age of oral cancer cases collected from the same hospital in Taiwan.[15] But in our study, the subjects with

OSF, without oral cancer, had a younger diagnosis age. The age difference between subjects with and without oral cancer should be supposed as evidence that the coexistence of oral cancer with OSF is a malignant transformation from OSF.

Significant sex differences have been reported in oral cancer cases in Taiwan. As with oral cancer, OSF in Taiwan is also a male-predominant disease. From previous studies in Taiwan, of all OSF patients, 97% to 99% were males.[14,18] It is because areca quid chewing is not acceptable for women in the general population of Taiwan. Except for aborigines, the chewing prevalence in females is less than 2%.[24] To avoid the confusing etiologic effect between sexes, only males were included in the present study.

In conclusion, tobacco smoking and area quid chewing do not appear to be associated with an increased risk of malignant transformation in OSF, whereas alcohol drinking may possibly be a risk factor. Most studies regarding oral mucosal lesions underscore the importance of public health strategies targeted toward preventing and reducing exposure to alcohol. The public should be aware of the high risk of oral malignancy in oral precancer lesions induced by consumption of alcoholic beverages. Further studies are necessary to clarify the relationship of alcohol drinking to malignant transformation of OSF.

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