

Oral submucous fibrosis: a case-control study in Chennai, South India

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BACKGROUND: Oral submucous fibrosis (OSF) is a pre-cancerous condition caused by the use of areca nut in various forms. There are very few published reports on areca nut use and OSF from Chennai, South India.

METHODS: A hospital-based case-control study on habits and OSF was performed in Chennai over a 3-year period. A total of 185 consecutive patients with OSF were matched with age- and sex-matched controls. History was recorded in a pre-determined format by qualified dental surgeons.

RESULTS: The male to female ratio of OSF cases was 9.9:1. All areca nut products were associated with OSF, with the risk being greatest for pan masala. The duration of the habit was more significant than the frequency of the chewing habit.

CONCLUSION: The present study confirms the strong association between areca nut use and OSF and the increasing use of pan masala.

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Introduction

Oral submucous fibrosis (OSF) is a chronic, progressive, scarring high-risk pre-cancerous condition of the oral mucosa seen primarily on the Indian subcontinent and in South-east Asia (1). The condition is characterized by fibrosis in the submucosa, reduction in the vasculature and atrophy of the surface epithelium. Clinical features include: stomatopyrosis, oral mucosal pallor and mucosal rigidity, leading to restricted mouth opening, tongue protrusion and cheek flexibility. Dysphagia occurs in severe cases. Epidemiological and *in vitro* experimental studies have shown that chewing areca nut (*Areca catechu*) is the major aetiological factor for OSF (2, 3).

Areca nut is consumed in various forms such as betel quid (areca nut + slaked lime + betel leaf) with or without tobacco, pan masala (powdered areca nut with additives, flavouring agents and tobacco) and raw areca nut (seval flakes and kotta pakku granules). In India, there are regional variations in the type of areca nut product used. The nut contains many alkaloids, arecoline being the most abundant, which have been shown to stimulate collagen synthesis by fibroblasts (3).

There has been an increase in the use of areca nut, particularly pan masala, in the younger age groups in India, leading to increasing incidence of OSF (4). Many patients with OSF have other habits concurrently, which may also play a role in the initiation and the progress of this pre-malignant condition.

Epidemiological studies on OSF have been reported from different regions in India. However, very few reports have originated from Chennai, South India. Given this paucity of information, a hospital-based case-control study performed to ascertain the association of different oral habits in the pathogenesis of OSF is reported here.

Materials and methods

One hundred and eighty-five patients diagnosed with oral submucous fibrosis in the outpatient department of Ragas Dental College and Hospital, Chennai, Tamil Nadu were included in the study. These patients had either reported for treatment of OSF or been diagnosed with OSF during routine oral examination. The period of study was 3 years from April 2000 to February 2003. Criteria for diagnosis of OSF were the presence of fibrous bands in the labial and/or buccal mucosa, loss of elasticity of the buccal/labial mucosa and inability to open the mouth (1, 5). The clinical diagnosis was confirmed by biopsy in every case, using established criteria – submucosal dense and avascular collagenous connective tissue, variable number of chronic inflammatory cells and epithelial atrophy (1).

The controls were chosen from the outpatient department of Ragas Dental College and Hospital, Chennai, Tamil Nadu. The hospital records an average of approximately 100 patients per day, of which 60 are new patients and 40 are present for follow-up treatment. A random selection method was used in which every fifth patient of the outpatient

Table 1 Age and gender distribution of OSF cases and controls

Age groups (years)	Male		Female	
	Case n (%)	Control n (%)	Case n (%)	Control n (%)
<21	11 (6.5)	9 (5.4)	–	–
21–40	124 (73.8)	125 (74.4)	14 (82.4)	14 (82.4)
41–60	30 (17.9)	31 (18.5)	3 (17.6)	3 (17.6)
>60	3 (1.8)	3 (1.8)	–	–
Total	168	168	17	17

Male:female ratio, 9.9:1.

department was included in the study. Patients included in the study were those who had no oral lesions other than periodontal disease associated with chewing/smoking habit, and consented to take part in the study. One control was then selected for each case matched by age (± 2 years) and gender.

Patients' consent was obtained for all cases and controls, and a comprehensive clinical history was taken and recorded by trained dental surgeons (K. Ranganathan and M. Uma Devi) in a pre-determined form. Complete history, including the various oral habits – the frequency (number of times per day), duration (years of consumption) and type (areca nut raw or cured, pan masala, betel quid) – along with tobacco and alcohol use, was recorded. All chewers in cases and controls used some form of areca nut at least once a day. There were no occasional users (infrequent chewing usually once or twice a month).

Statistical analysis

Data entry and analysis was performed using SPSS® 10.0. Descriptive statistics was used to ascertain the frequency, percentages, mean, median, SD and range. The habits of cases and controls were classified into various categories (12) without any overlap. The Mann–Whitney *U*-test was used to find out significant difference in the duration, frequency and intensity of all habits between cases and control, while for

non-normal data, Kruskal–Wallis test was performed. Univariate binary logistic regression, with each variable separately entered into the model, yielded the odds ratio (OR), and 95% CI was determined to ascertain the significance of risk factors for the cases.

Results

One hundred and eighty-five cases of OSF were recorded during the 3-year period of this study. For each case, the age- and sex-matched controls were randomly selected.

Table 1 gives the age and gender distribution of cases and controls. 90.8% males and 9.2% of females had OSF giving a male to female ratio of 9.9:1. Age and gender distribution of cases and controls were more or less same because of matching. The mean age of cases and controls was 32.4 ± 10.4 years, and the median age was 29 years. The youngest and oldest ages of occurrence of OSF in our cohort were 16 and 76 years in males and 24 and 57 years in females, respectively. There was no statistically significant difference in the age of occurrence of OSF among males and females ($P = 0.36$).

Table 2 lists the OR of the various habits for the cases. In the controls, the predominant habits were smoking tobacco and alcohol use. Use of pan masala was associated with the highest OR of 81.5. This was followed by areca nut along

Table 2 Habits and OR

Habits	Case n (%)	Control n (%)	OR	95% CI	P-value
AN	9 (4.9)	3 (1.6)	3.10	0.83–11.65	0.078
Pan masala	33 (17.8)	0	81.50	4.95–1341.12	0.00*
AN/PAN + Tob	17 (9.2)	3 (1.6)	6.14	1.77–21.32	0.00*
AN/PAN + Alc ^a	29 (15.7)	0	69.93	4.24–1153.86	0.001*
AN/PAN + Tob + Alc	43 (23.2)	9 (4.9)	5.92	2.79–12.56	0.00*
BQ ^a	13 (7.0)	0	29.03	1.71–492.17	0.00*
BQ + Tob ^a	14 (7.6)	0	31.37	1.86–529.88	0.00*
BQ + Alc ^a	7 (3.8)	0	15.59	0.88–274.97	0.00*
BQ + Tob + Alc ^a	19 (10.3)	0	43.45	2.60–725.30	0.008*
Smoke ^a	0	15 (8.1)	0.03	0.00–0.50	0.00*
Alc ^a	0	9 (4.9)	0.05	0.00–0.87	0.00*
Smoke + Alc ^a	0	71 (38.4)	0.0	0.00–0.07	0.002*
					0.00*

AN, areca nut; PAN, pan masala (processed areca nut without betel leaf); Tob, tobacco (smokeless); Alc, alcohol; BQ, betel quid: a combination of betel leaf with slaked lime and areca nut; Smoke, tobacco smoking.

^a0.5 added to each cell frequency to calculate OR.

*Significant at 1% level of significance.

Table 3 Comparison of chewing habit frequency, duration and intensity^a between cases and controls

	Case		Control		P-value
	Mean	SD	Mean	SD	
Frequency/day	7.44	6.17	7.43	9.51	0.113
Duration/year	6.41	11.07	2.93	3.12	0.002**
Intensity	17706.74	21766.62	6326.67	9192.22	0.005**

^aFrequency × duration × 365.

**Statistically significant.

with alcohol use, with OR of 69.9. Use of areca nut alone was not statistically significant as there were only nine patients in the cases, and three in the controls also chewed areca nut. Use of tobacco and alcohol in addition to the areca nut habit increased the risk for OSF. Logistic regression analysis showed that the age, sex, smoking alone, alcohol use alone and smoking + alcohol use alone were not associated with the development of OSF.

Comparison of all the habits among males and females having OSF showed that one female patient did not give history of any habit. This patient gave a history of use of 'Kesari dal' (*Lathyrus sativus*), and she had some features suggestive of lathyrism. Use of areca nut and pan masala was equal in females as opposed to higher percentage of males using pan masala (16.7%). Areca nut with tobacco and alcohol habit was higher in males (25.6%), while betel quid with tobacco was higher in females (23.5%). There were no statistically significant differences in the percentage of other habits between males and females. Smoking and/or alcohol did not show any correlation with the occurrence of OSF; however, their concurrent use with processed areca nut increases the risk of OSF ($P < 0.05$).

The mean frequency of areca nut use, among the cases, was similar in the different age groups (seven to eight chews). Table 3 compares the frequency (number of times/day), duration (number of years) and intensity (frequency × duration × 365) of habits between the cases and controls. As the habits frequency, duration and intensity were not normally distributed, Kruskal–Wallis test was used. Both duration and intensity of habit showed a statistically significant difference between the cases and controls ($P < 0.002$ and $P < 0.005$, respectively).

Discussion

Oral submucous fibrosis is a pre-malignant condition, which has been described in detail in Asians or Asians settled in other countries. Describing this condition in five Indian women from Kenya, Schwartz (6) called it 'atrophia idiopathica mucosae oris'. Subsequently, it was called submucous fibrosis by Joshi (7). Various aetiological factors have been suggested for OSF. These include local irritants such as capsaicin (8), pungent and spicy food (9) and areca nut use (2). In addition to the local factors, systemic factors have also been suggested to play a role in the development of OSF. These include anaemia, chronic iron and vitamin B complex deficiency (10) and genetic pre-disposition (11).

Chewing areca nut in its various forms is widely prevalent in the Indian subcontinent. The prevalence of OSF is increasing in India, from an estimated 250 000 cases in 1980 (12) to an estimated 2 million cases in 1993 (13). The rapidly increasing prevalence of this habit can be judged from the reports that the Indian market for pan masala is worth 2000 million (US\$116 million) (2).

Given the wide use of areca nut in its various forms, this study was performed to ascertain the various habits, including chewing and OSF in a selected hospital-based population, in Chennai, South India. This is the first report of a large cohort from this part of South India. Although these types of studies have an inherent problem of selection bias, they have been proved to be very useful in population-based studies to identify disease association with habits (14, 15).

Our study showed a high preponderance of OSF in males (9.9 : 1): similar to a male preponderance reported by Shah & Sharma (16) from a large cohort in Delhi, India. However, the number of males in our study was around five times higher. A case-control study from Pakistan reports a higher female prevalence (14).

In the present study, there was one case with no history of areca nut chewing. Seedat & VanWyk (17) have reported a similar case from South Africa. Interestingly, the 40-year-old female patient in our present study, without history of chewing habit, had history of consuming 'Kesari dal' (*L. sativus*) and had been diagnosed with features suggestive of mild lathyrism.

Areca nut, pan masala and betel quid were associated with OSF. The overall use of areca nut and pan masala (71%) was more widely practiced than betel quid use (29%). Areca nut and betel quid with tobacco was a more common habit in females than in males; however, more males (69%) tended to use pan masala as compared to females (35%).

Only 8% of the controls had some chewing habit. However, when the duration of the habit was considered, the controls had a mean duration of consumption of 3 years as opposed to the 6.5 years for the OSF cases. This difference in duration was statistically significant at $P < 0.005$. Interestingly, there was no statistical difference in the frequency of chews per day between the cases and controls.

The highest risk was for the pan masala chewers (OR: 81.5) followed by pan masala with alcohol users (OR: 69.9). The risk on chewing betel quid was also statistically significant. However, the OR for the betel quid chewers was less than half that of those for pan masala chewers. Other investigators have observed this decreased risk in betel quid users (16).

The risk was almost equal in males and females. The risk of OSF was almost double for those <21 years (OR: 46.1), compared to 21–40-year age group (OR: 21.9). Also, the younger patients (<21 years) developed OSF in 3.5 years, while the duration for those above 21 years was more than 6.5 years. Other investigators have observed this disturbing, rapid onset of OSF in the younger chewers (14, 16, 18).

The present study confirms the strong association between areca nut use and OSF and the increasing use of pan masala in the place of the conventionally used areca nut. Quicker onset of OSF in the younger age group and high prevalence in males is also reported. Given the morbidity of OSF, its potential to malignant conversion and absence of effective treatment in the advanced stages, the information obtained from case-control studies are important in devising specific prevention strategies in the population.

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