

# Prevalence of Areca Nut Eating Habits and its Association with Oral Submucous Fibrosis in Preuniversity College-going Adolescents of Raichur in Karnataka, India: A Prospective Cross-sectional Survey

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## ABSTRACT

**Introduction:** Oral submucous fibrosis (OSMF) is a well-known premalignant condition. Use of areca nut is a known cause of OSMF. More and more adolescents are becoming habitual to the use of areca nut and thus become prone for oral cancer.

**Objective:** To assess the prevalence of areca nut eating habits and its association with OSMF in the preuniversity college-going adolescents of Raichur in Karnataka, India.

**Materials and methods:** A prospective cross-sectional study was conducted among the preuniversity college-going adolescents. A questionnaire was asked to be filled by them with regard to areca nut eating habits. All of them were examined by a single examiner for the detection of OSMF.

**Results:** Among the total of 1,208 adolescents included in the study, 527 were males and 681 were females. A total of 358 (29.64%) people accepted that they have the habit of eating areca nut. There was a significant association between areca nut eating habit and OSMF. There exists a significant relationship between the frequency and duration of areca nut eating habit with the presence of OSMF ( $p < 0.0001$ ).

**Conclusion:** Areca nut eating habit is increasingly becoming prevalent among college-going adolescents. This needs to be addressed promptly by all concerned to prevent the occurrence of oral cancer.

**Keywords:** Areca, Carcinogen, Fibrosis, Oral, Precancerous condition, Tobacco.

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## INTRODUCTION

Oral submucous fibrosis (OSMF) is defined as the chronic, insidious disease affecting the oral cavity and sometimes pharynx, although occasionally preceded and/or associated with vesicle formation and is always associated with juxtaepithelial inflammatory reaction followed by fibroelastic changes in the lamina propria with epithelial atrophy leading to stiffness of oral cavity and thereby leading to trismus and inability to eat.<sup>1</sup> Oral submucous fibrosis is also known as "diffuse OSMF," "idiopathic scleroderma of mouth," "idiopathic palatal fibrosis," "sclerosing stomatitis," "juxtaepithelial fibrosis," etc.<sup>2</sup> Oral submucous fibrosis is a well-recognized, potentially premalignant condition. Malignant transformation rates as high as 7.6% have been reported from the Indian subcontinent over a 17-year period.<sup>3</sup> The World Health Organization (WHO) defines OSMF as "a generalized state of the oral mucosa associated with a significantly increased risk of oral cancer."<sup>4</sup> This chronic progressive scarring disease that predominantly affects the people of Southeast Asian origin was first reported by Schwartz in 1952, who described it as "atrophica idiopathica mucosa oris."<sup>5</sup> In India, 30 to 40% of all reported cancers is oral cancer.<sup>6</sup> It has been suggested that consumption of chillies, nutritional deficiency, chewing of areca nut, genetic susceptibility, altered salivary constituents, and autoimmunity and collagen disorders may be involved in the pathogenesis of this condition.<sup>7</sup> The use and dependence on areca nut in the form of so-called pan-masala/gutkha is rapidly increasing especially among youth in India. The main constituent of pan-masala is areca nut with tobacco, areca lime, catechu (kattha), tannin, etc., and some flavoring agents as additives in the preparation. These additives have an enhancing effect on carcinogenic properties of areca nut and because of its addictive properties leads to physical dependency on the product.<sup>8</sup> Recently, the WHO evaluated and announced areca nut as a<sup>8</sup> carcinogen in the light of results of a recent exercise.<sup>9</sup> Use of areca nut has become increasingly prevalent among adolescents and thus our young generation is alarmingly becoming prone to oral cancer. So this study was undertaken to assess the prevalence of OSMF and its association with

the use of areca nut among college-going adolescents of Raichur city.

## MATERIALS AND METHODS

A prospective cross-sectional survey was conducted among the preuniversity college-going students through health checkup camps at their colleges in Raichur city during June 2014 to December 2014. The sample size was calculated using WHO sample size calculator by keeping the prevalence of areca nut eating habit at 16.4% referenced from previous studies.<sup>10</sup> With 5% level of significance (95% confidence interval), 15% relative error, 10% design effect, and 20% nonresponse rate, the recommended sample size was calculated to be 1,132. Ethical committee clearance was taken from the institute's ethical clearance committee. Eight colleges were visited over a period of 6 months. Initially, a questionnaire was given to the students that contained open and closed questions related to the habit of areca nut chewing. The frequency, duration, reason, and the preferred method of eating areca nut were inquired. Specific questions linked with the symptoms of OSMF were also asked. The history on questionnaire was recorded by the second author, while all the clinical examinations were performed by the first author. The subjects showing vesiculation, burning sensation of mucosa of mouth and tongue, irritation while consuming spicy food, blanching and stiffness and/or palpable bands of oral mucosa, labial mucosa, buccal mucosa, fauceal pillars mucosa and palatal mucosa (Figs 1 and 2), partial or total restriction in mouth opening, restriction in ability of protruding tongue, restricted movement of soft palate, inability to protrude tongue, and feeling of restriction in blowing cheek, etc., were regarded as having OSMF.<sup>11-13</sup> Cases complaining of difficulty in opening the mouth due to other reasons like inflammation, acute infections,

habit of smoking form of tobacco, etc., were excluded from the study. Histopathology of the patients was not done, because both controls and OSMF cases refused to undergo biopsy. A brief awareness campaign was organized immediately after the checkup camp regarding hazards of areca nut chewing and OSMF. Students diagnosed to be having OSMF were referred to our department and were treated by behavioral therapy, oral multivitamins, antioxidants, and mouth opening exercises. Parents of the patients were also made aware regarding the bad effects of chewing areca nuts. Data collected from the survey were analyzed statistically. The descriptive analysis and inferential analysis using chi-square test was performed.

## RESULTS

Among the total of 1,208 adolescents surveyed in the study, 527 were males and 681 were females. Their age ranged between 16 and 18 years; 850 (70.36%) adolescents did not have the habit of eating areca nut. A total of 358 (29.64%) adolescents accepted that they have a habit of eating areca nut. Among them, 279 were boys and 79 were females. Oral submucous fibrosis was observed clinically in 67 adolescents (51 boys and 16 girls); 108 adolescents were eating 1 to 3 sachets of areca nut daily, and in this group none had developed OSMF (Table 1); 111 adolescents were eating 4 to 6 sachets of areca nut daily and in this group 14 had developed OSMF; 124 adolescents were eating more than six sachets of areca nut daily and in this group 53 had developed OSMF; 15 adolescents were eating areca nut weekly but not daily and in this group none had developed OSMF. When the duration of eating areca nut was analyzed (Table 2), we found that among the areca nut eaters, 107 adolescents have been eating areca nut from 1 to 6 months and in this group none had developed OSMF; 91 adolescents had been eating areca



**Fig. 1:** Oral submucous fibrosis with blanching and stiffness and/or palpable bands of buccal mucosa, fauceal pillars mucosa, and palatal mucosa



**Fig. 2:** Extensive OSMF with blanching and stiffness and palpable bands of buccal mucosa, fauceal pillars mucosa, and palatal mucosa with stiffening of uvula

**Table 1:** Frequency of usage of areca nut and presence of OSMF

Frequency effect on OSMF	Presence of OSMF			Chi-square test, p-value
	Yes	No	Total	
Frequency of usage				$\chi^2 = 395.19$ $p < 0.0001$
1–3 sachets daily	00	108	108	
4–6 sachets daily	14	97	111	
More than 6 sachets daily	53	71	124	
Weekly but not daily	00	15	15	
No usage	00	850	850	
Total	67	1,141	1,208	

**Table 2:** Duration of usage of areca nut and presence of OSMF

Duration effect on OSMF	Presence of OSMF			Chi-square test, p-value
	Yes	No	Total	
Duration of usage				$\chi^2 = 961.46$ $p < 0.0001$
1–6 months	00	107	107	
7–12 months	00	91	91	
More than a year	00	77	77	
More than 5 years	67	16	83	
No usage	00	850	850	
Total	67	1,141	1,208	

nut since 7 to 12 months and in this group none had developed OSMF; 77 adolescents had been eating areca nut since more than a year and in this group none had developed OSMF; 83 adolescents had been eating areca nut since more than 5 years and in this group, 67 people had developed OSMF. Overall, none of the noneaters of areca nut had OSMF, while OSMF was present in 18.71% of areca nut eaters. From our study, it is clear that there is a significant association between areca nut chewing habit and susceptibility to OSMF ( $p < 0.0001$ ).

## DISCUSSION

Areca nut is the seed *Areca catechu*, and it grows in much of the tropical Pacific, Asia, and parts of East Africa. It is also called as betel nut and is often chewed wrapped inside betel leaves (paan) or with tobacco (betel quid), the composition of which varies in different populations and countries.<sup>14,15</sup> It is one of the most widely consumed addictive substances in the world after nicotine, ethanol, and caffeine, and is consumed by approximately 10% of the world's population.<sup>16</sup> Many reports suggest that chewing areca nut starts at a young age, and it is being consumed freely by children.<sup>17,18</sup> The proponents of areca nut say that areca nut helps in digestion and has got mild euphoric effects,<sup>17</sup> although the effects vary from person to person.

The areca nut contains the tannins arecatannin and gallic acid; a fixed oil gum; a little terpeneol; lignin; various saline substances; and four main alkaloids, namely arecoline, arecaidine, guvacoline, and guvacine that have vasoconstricting properties. The major parasympathetic and muscarinic effects of areca nut are due to arecoline. It has been presumed that both arecoline and arecaidine undergo glutathione conjugation as they form mercapturic acid in rats. The major metabolite of arecoline is arecoline 1-oxide. The main mode of arecoline metabolism appears to be hydrolysis to arecaidine and N-oxidation combined with double bond reduction

of the arecaidine.<sup>19,20</sup> The N-oxidation of arecoline to arecoline 1-oxidase takes place by flavin-containing monooxygenase 1, flavin containing monooxygenase 3, and not by P-450, which strongly suggests that this reaction may occur in tissues other than the liver, especially the kidneys, where flavin-containing monooxygenase 1 is found in abundance.<sup>20</sup> This points to a possible role of the kidneys in the metabolism and toxicology of arecal alkaloids.<sup>20</sup> The urinary metabolites of arecoline 1-oxidase are 50% arecoline 1-oxidase itself, 30% mercapturic acids and their catabolic products, and the remaining 20% are its N-oxide derivatives.<sup>20</sup> A number of nitrosamines are also formed from the arecal alkaloids in the mouth, which play an important role in the causation of oral cancer, especially methylnitrosaminopropionitrile, which is the most carcinogenic among them.<sup>17,19,20</sup>

Areca nut has wide-ranging effects on the human body. It is associated with central obesity and type II diabetes.<sup>17</sup> According to the International Agency for Research on Cancer (IARC) review,<sup>14</sup> areca nut is carcinogenic in humans and is linked to cancers of the oral cavity, pharynx, esophagus, liver and biliary tracts, and the uterus.

The alkaloid arecoline due to its parasympathomimetic properties stimulates both muscarinic and nicotinic receptors. Habitual users of areca nut claim euphoria, a sense of well-being, warmth, increased alertness, salivation, palpitation, antimigraine, and enhanced capability to work.<sup>21</sup> Also, areca nut use causes dependency syndrome, which comprises increased concentration, mild euphoria, relaxation, postprandial satisfaction and a withdrawal syndrome associated with insomnia, mood swings, irritability, and anxiety, the severity of which can be compared with that of amphetamine use.<sup>19</sup>

Prevalence of type II diabetes, hyperlipidemia, hypertriglyceridemia, and metabolic syndromes is more common in areca nut chewers as its metabolite, arecoline, inhibits adipogenic differentiation, induces lipolysis in 3T3-L1 adipocytes, and interferes with insulin-promoted

glucose uptake.<sup>22,23</sup> Animal studies have shown that arecoline in acute administration causes an increased release of triiodothyronine, thyroxine, and suppression of thyroid-stimulating hormone; in large doses, it activates the hypothalamic–pituitary–adrenal axis, similar to stress response, and in regular use causes hypothyroidism.<sup>24</sup> Areca nut causes platelet aggregation associated with phospholipase C activation, mobilization of Ca<sup>++</sup>, TXB<sub>2</sub>, which leads to release of growth factors, and increased fibrogenesis that plays a crucial part in its effects on the oral mucosa and cardiovascular system.<sup>25</sup> The areca nut metabolite arecoline causes aggravation of disease in asthmatics by increasing bronchoconstriction in a dose-dependent manner and decreasing the forced expiratory volume in 1 second by 30%.<sup>26,27</sup> Expectant mothers who consume areca nut have higher incidences of low birth weight, low birth length, and preterm births.<sup>28</sup>

Oral submucous fibrosis is a disease of the oral mucosa characterized by excessive accumulation of subepithelial collagen, thereby resulting in severe limitation of mouth opening. It is a premalignant condition with a malignant transformation rate of 4.5%.<sup>29</sup> The prevalence rate of OSMF in India is considered to be 0.2 to 0.5%. The disease is most common in southern parts of India, and the state of Kerala has the highest prevalence.<sup>30</sup> Epidemiological data and intervention studies suggest that areca nut is the main etiological factor for OSMF.<sup>16</sup> Arecoline modulates matrix metalloproteinases and their tissue inhibitors, as well as the activity of lysyl oxidase, which leads to the accumulation of collagen in oral mucosal fibroblasts.<sup>31,32</sup> Areca nut polyphenols inhibit collagenases and increase the cross-linkage of collagen, reducing its degradation.<sup>33</sup> These events may underlie the generation of OSMF in areca nut chewers,<sup>32</sup> which could be further enhanced by the release of copper ions, present in areca nut, catechu, and slaked lime into the oral cavity of the chewers; inorganic copper salts increased the production of collagen by oral fibroblasts.<sup>31</sup>

The studies examining the association between areca nut chewing and oral precancerous lesions undertaken before 2004 were reviewed in previous IARC Monographs (1985, 2004). The relative risk estimates for oral leukoplakia,<sup>34–37</sup> erythroplakia,<sup>38</sup> and OSMF<sup>39–44</sup> ranged from 7 to around 30. Other studies of OSMF reported high risks associated with areca nut use: Relative risk (RR) 32 [95% confidence interval (CI): 6–177] for areca nut without tobacco and RR 154 (95% CI: 34–693) for areca nut alone<sup>40</sup>; RR 75.6 among users of mawa (a mixture of areca nut, tobacco, and slaked lime)<sup>41</sup> and RR 49.2 (95% CI: 24.3–99.6) among areca nut chewers (with and without added tobacco).<sup>44</sup> In our study, OSMF was present in 18.71% of areca nut eaters and in none of those not eating

areca nuts. From our study, it is clear that there is a significant association between areca nut chewing habit and susceptibility to OSMF ( $p < 0.0001$ ).

In two cross-sectional studies from Sri Lanka and Taiwan, where areca nut quid is used without added tobacco, significant associations for areca quid chewing with oral precancerous lesions were found. The risks were 8.40 (95% CI: 5.13–13.75) in Taiwan<sup>45</sup> and 3.01 (95% CI: 2.25–4.0) in Sri Lanka (areca quid with or without added tobacco).<sup>46</sup> Yang et al<sup>47</sup> reported a significant positive association for betel quid chewing without tobacco (among nonsmokers) with OSMF from a case–control study in Taiwan [odds ratio (OR), 4.51; 95% CI: 1.20–16.94]. In a study from the People’s Republic of China, duration of areca nut quid use without added tobacco was associated with a significantly increased risk (OR for longest duration, 10.15; 95% CI: 2.72–37.79) for malignant transformation of OSMF ( $p$  for trend = 0.008).<sup>48</sup> In a further case–control study (Ahmad et al),<sup>49</sup> gutkha and other areca nut products had a highly significant association with OSMF ( $\chi^2 = 188.14$ ,  $p < 0.001$ ). Intervention studies demonstrated that reduction in the use of areca nut quid with added tobacco resulted in lowering the incidence of precancerous lesions<sup>50,51</sup> and cessation resulted in development of no new precancerous lesions.<sup>52</sup>

India has one of the highest incidences of oral cancer patients in the world. The age-adjusted rate of oral cancer in India is 20/100,000 population, which accounts for more than 30% of the total cases of cancer.<sup>53</sup> Areca nut, with its carcinogenic potential, is a contributor to the disease load. Despite contributing to numerous life-threatening diseases and carcinogenic properties, it is easily available in the country and freely consumed by all age groups. Areca nut is marketed as mouth freshener under several names, such as gutkha, paan masala, supari mix, etc. While gutkha is a combination of smokeless tobacco and areca nut, paan masala/supari mix is a pure areca nut product.<sup>16</sup> The market turnover of Indian gutkha and paan masala companies is more than 100 billion rupees, and billions more are spent on marketing.<sup>54</sup> The prevalence of areca nut consumption with or without tobacco is very high in India and is a part of the normal social culture in the society, and is chewed for various reasons. In rural areas, it is consumed by about 34.7% of the males as compared with 32.4% of the females.<sup>55</sup> In urban areas, the consumption rate among males is about 37.8% and in females it is about 29.7%.<sup>56</sup> The use of areca nut products is prevalent in adolescents, where 16.4% use it regularly and 13% use it occasionally.<sup>57</sup> In our study, 29.64% adolescents had the habit of eating areca nut. The easy availability, low cost, and friends with habits of chewing areca nut habit have an impact on the high prevalence of areca nut chewing and associated OSMF.

Even the well-educated section of the society consumes areca nut, where 12.5% do it regularly and 27.5% do it occasionally.<sup>10</sup> It is important to note that consumption is higher in lower socioeconomic groups who are illiterate and daily wage earners.<sup>58</sup>

Many state governments in India have taken a positive step by banning the production and sale of gutkha. This ban is now effective in 20 states and three union territories of India. The huge loss of human lives and finances due to the morbidity and mortality caused by areca nut and paan masala addiction is putting tremendous strain on the economy, and is much more than the revenue generated by the paan masala and gutkha industry.<sup>16</sup> The government needs to set up an areca nut control program. It is high time that stricter laws are made to regulate areca nut consumption and stern instructions are issued to the manufacturers to have pictorial warnings on the products.<sup>59</sup> Also the selling of areca nuts to people below 18 years should be banned completely so that the young pool of India can be saved from the hazards of ill effects of areca nut.<sup>60,61</sup>

## CONCLUSION

Areca nut being used for consumption in various forms plays an important role in the etiology of OSMF. People take to areca nut chewing at a comparatively younger age and more and more number of adolescents become victims of this health hazard. The easy availability, low cost, and friends with habits of chewing areca nut habit have an impact on the high prevalence of areca nut chewing and associated OSMF. Steps are absolutely essential to decelerate the rapid evolving epidemic of OSMF and oral cancer due to use of areca nut products in the country. The adolescent population should be properly educated on this topic and oral health awareness should be included in the school education curriculum besides the efforts from the government to curb the menace of areca nut usage.

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