

## High risk of malignant transformation of oral submucous fibrosis in Pakistani females: A potential national disaster

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### Abstract

**Objective:** To determine the relationship of age, gender and other associated risk factors linked with malignant transformation of oral submucous fibrosis into oral squamous cell carcinoma.

**Methods:** This cross-sectional, multi-centre study was conducted at both public and private tertiary care hospitals and clinics of Karachi, Pakistan, from 2004 to 2012, and comprised patients with oral submucous fibrosis and/or oral squamous cell carcinoma. Out of the total sample, malignant transformations of oral submucous fibrosis to oral squamous cell carcinoma were included. Cases of oral squamous cell carcinoma without clinical evidence of pre-existing oral submucous fibrosis were excluded. Sample selection was based on non-probability convenience sampling. SPSS 18 was used for data analysis.

**Results:** Of the 1774 cases, 765(43.12%) were of oral submucous fibrosis alone, 472(26.60%) were reported as malignant transformation of oral submucous fibrosis into oral squamous cell carcinoma and 537(30.27%) were of oral squamous cell carcinoma without clinically visible oral submucous fibrosis. Of the malignant transformation cases, 370(78.4%) involved women and 102(21.6%) men. Besides, 5(1.1%) patients were aged below 25 years, 266(56.4%) were 26-50 years and 201(42.6%) were aged 51 years or above, with the mean age of  $21.80 \pm 3.1$ ,  $34.02 \pm 2.1$  and  $40.28 \pm 13.1$  years, respectively ( $p=0.001$ ). Moreover, 228(48.3%) patients used betel quid with tobacco, 108(22.9%) consumed areca nut only, 55(11.7%) chewed betel quid without tobacco, 36(7.6%) used naswar, while 45(9.5%) had no chewing habits ( $p=0.001$ ).

**Conclusion:** The risk of developing oral squamous cell carcinoma was high, especially women.

**Keywords:** Malignant transformation, Oral submucous fibrosis, Betel quid, Tobacco. (JPMA 66: 1362; 2016)

### Introduction

The World Health Organisation (WHO) has categorised oral pre-cancers as precancerous lesions and conditions.<sup>1</sup> Oral submucous fibrosis (OSMF) is a precancerous condition chiefly associated with consumption of areca nut alone or in betel quid and its derivatives. It is one of the most prevalent premalignant conditions across South Asia.<sup>2</sup> Progressive fibrosis of the oral soft tissues results in limited mouth opening and diminished oral function. Mortality, or extreme morbidity, frequently occurs as OSMF has a significant transformation rate to oral squamous cell carcinoma (OSCC).<sup>1</sup> The incidence of OSMF has significantly risen due to increased consumption and common availability of areca nut, often mixed with chewing tobacco and other chemical constituents.<sup>3</sup>

In OSMF, the oral epithelium becomes atrophic and more vulnerable to injury. This is compounded by the nutritional deficiencies frequently associated with the

population afflicted where an impaired inflammatory repair response leads to scarring and fibrosis.<sup>4</sup> Since the alkaloid and other chemical irritants in betel quid and tobacco are crucial for tumour initiation, promotion and progression, exposure to these, especially when in combinations, has been shown to markedly potentiate oral cancer. Most cases with malignant transformation occur gradually and over time.<sup>5</sup>

Once fibrosis has set in, OSMF does not regress spontaneously on cessation of the chewing habit.<sup>6</sup> There are essentially two outcomes of established OSMF: persistence without significant progression of disease or eventual malignant transformation. OSMF is strongly associated with a risk of oral cancer, although the biology underlying this association is still unresolved.<sup>7</sup> Studies suggest that dysplasia is seen in about 25% of biopsied OSMF cases and the rate of transformation to malignancy varies from 3% to 19%.<sup>8</sup>

It is documented, as well as frequently observed in clinical practice, that OSCC cases are often associated with, or preceded by, precancerous lesions or conditions for varying lengths of time.<sup>9</sup> Interestingly, these share the same aetiological factors with oral cancer, particularly the

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use of tobacco, and exhibit the same site and habit relationships. These precancerous lesions and conditions can serve as a good model to investigate the chemopreventive approach for controlling oral cancer. The recognition and early management of pre-cancers, therefore, constitute vital control measures.<sup>9</sup> Global estimates of OSMF show an essential confinement to Indians and Southeast Asians, with an overall prevalence rate in India of about 0.2% to 0.5 % and a gender-based prevalence varying from 0.2-2.3% in males and 1.2-4.57% in females across a wide age range of 20 to 40 years.<sup>10</sup> Given the widespread use of areca nut / betel quid products in this demographic and with expanding global migratory trends over the past several decades, this is no longer a disease confined to developing countries and is set to pose a significant burden on healthcare systems in numerous Western countries.<sup>4</sup>

OSMF is well recognised for its significant malignant potential the incidence of which varies from one region to another.<sup>8,11-13</sup> Currently, with OSCC associated with OSMF increasingly being reported in clinical practice in the Asian-Pacific region, the incidence of malignant transformation in OSMF seems to be much higher than that reported in the literature.

The current study is unique and the largest cross-sectional study to come out of this country. Additionally, the type of chewing products consumed and their association with malignant transformation need to be studied for various reasons. Firstly, the content of these products are obviously not similar throughout the world; there are considerable variations in contents and additives. Secondly, due to changing chewing habits in different phases of life as well as varying ingredients in these chewing products, it is important to quantify the size of association between different chewing products and malignant transformation. Thirdly, there is no significant literature in our population on this particular topic so it is worth reporting.

The current study was planned to determine the relationship of age, gender and other associated risk factors linked with malignant transformation of OSMF into OSCC.

## Patients and Methods

This cross-sectional, multi-centre study was conducted at both public and private tertiary care hospitals and clinics in Karachi, Pakistan, from 2004 to 2012, and comprised patients with OSMF and OSCC. Some of the OSMF patients had been followed up over the years and had subsequently developed OSCC. Out of the total sample, malignant cases of OSMF transformed into OSCC (OSFCa)

were included. Cases of OSCC without clinical evidence of pre-existing OSMF (Ca-OSF) were excluded. Sample selection was based on non-probability convenience sampling. All cases were diagnosed and documented by the corresponding author.

Sample size was determined by WHO sample size calculator,<sup>(14)</sup> estimating a population proportion with specified absolute precision, keeping 95% confidence interval (CI), 0.05 anticipated population proportions, 0.02 precision and 5% margin of error. Clinical details included: age, gender, socioeconomic background, associated habits of eating areca nut alone, as well as variants in the form of betel quid with or without tobacco, naswar, etc.

SPSS 18 was used for data analysis. Frequencies and percentages were calculated for qualitative variables while means and standard deviations for quantitative variables. Associations between dependent and independent variables were observed by applying chi-square test.  $P \leq 0.05$  was considered significant.

## Results

Of the 1774 cases, 765(43.12%) were of OSMF alone, 472(26.60%) were reported as malignant transformation of OSMF into OSCC (OSFCa) and 537(30.27%) were of OSCC without clinically visible OSMF (Ca-OSF) (Figure). Of the OSFCa cases, 370(78.4%) were of women and 102(21.6%) were of men. The mean age was  $36.66 \pm 9.36$  years (range: 8 to 80). Moreover, 5(1.1%) patients were aged below 25 years, 266(56.4%) within 26 to 50 years and 201(42.6%) were aged 51 years or above, with the mean age of  $21.80 \pm 3.1$ ,  $34.02 \pm 2.1$  and  $40.28 \pm 13.1$  years, respectively. Besides, 228(48.3%) patients used betel quid

**Table:** Descriptive analysis of OSMF cases with malignant transformation into OSFCa.

Variable	Frequency (n=472)	Percentage (%)
<b>Age ranges</b>		
0-25 years	05	1.1(21.80±3.1)
26-50 years	266	56.4(34.02±2.1)
51 and above	201	
	42.5(40.28±13.1)	
<b>Gender</b>		
Female	370	78.4
Male	102	21.6
<b>Chewing habits</b>		
Areca nut only	108	22.9
Betel quid with tobacco	228	48.3
Betel quid without tobacco	55	11.7
Naswar	36	7.6
No habits	45	9.5

OSMF: Oral sub mucous fibrosis

OSFCa: Malignant transformed cases of oral sub mucous fibrosis in to oral squamouscell carcinoma.

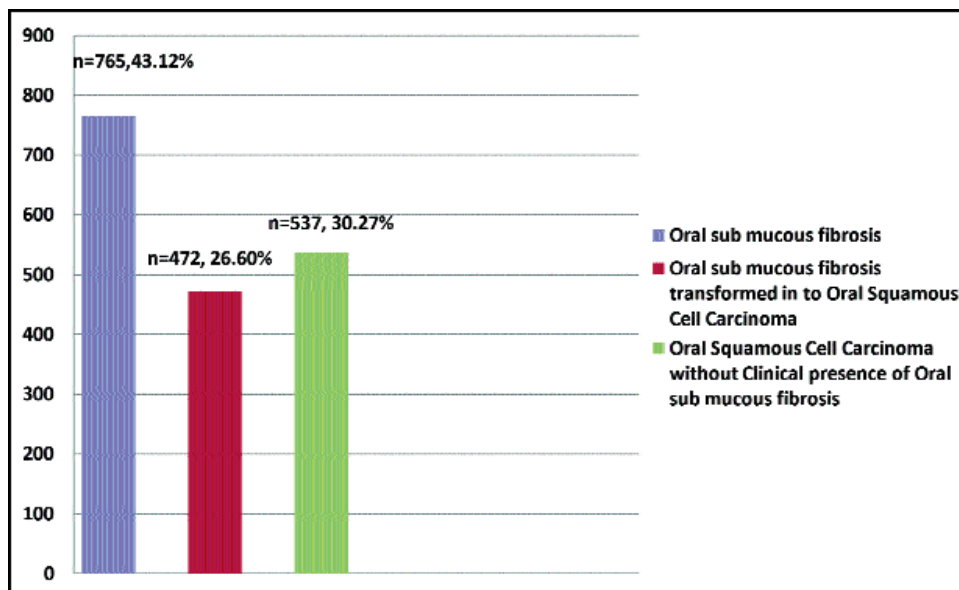


Figure: Descriptive analysis of total cases (n=1774).

with tobacco, 108(22.9%) consumed areca nut only, 55(11.7%) chewed betel quid without tobacco, 36(7.6%) used naswar, while 45(9.5%) had no chewing habits (Table).

Statistically significant difference was found for the differences of age ranges and chewing habits ( $p=0.001$ ). The difference in chewing habits of males and females was also significant ( $p=0.001$ ).

The differences between various chewing habits and the diagnosis of OSMF transformed to OSFCa was also significant ( $p=0.001$ ). However, difference within each gender associated with chewing habits was not significant ( $p=0.709$ ).

## Discussion

It is documented that younger females consumed betel nut alone graduating into more toxic variants as they grew.<sup>15</sup> Therefore, in the current study a large number of cases with OSMF and OSCC were included. Of them, malignant transformations of OSMF into OSFCa were found in more than one-third of the study cases, with females showing higher malignant transformation compared to males. This finding has not been reported previously in any locally published study.

Transformation was found across an age range of 26 to 50 years with the mean age of  $34.02 \pm 2.1$  years. They exhibited an increased consumption of betel quid with tobacco and its associated locally available variants. Furthermore, age and gender were found to be

statistically associated with chewing habits; and the association between those chewing habits and confirmed malignant transformation was also significant. Most importantly, the male-to-female ratio among OSFCa cases at 4F:1M was significantly higher than reported elsewhere, and constituting a distinctly younger age group, i.e. (10+) years less than the non-clinically obvious Ca-OSF which fits the known trend of 2M:1F. In a culture where females are socio-economically deprived, this is extremely significant and should ring major alarm bells.

The pathogenesis of this malignant transformation is in the atrophic oral epithelium which is more susceptible to the continuous attack by genotoxic agents present in the composition of betel quid.<sup>16</sup> Repetitive and continued exposure of epithelial cells to antioxidants, enzymes and reactive oxygen species (superoxide anion, peroxide, hydrogen peroxide, hydroxyl radical) impairs the cellular defence system leading to deoxyribonucleic acid(DNA) damage. These damaged cells can mutate to cancer initiation cells.<sup>17</sup> Further promotion and progression of such initiated cells can lead to oral pre-cancerous lesions / conditions or directly to frank malignancy.<sup>4,18</sup> One of the most common and widely acknowledged, potentially malignant conditions, is OSMF.

Paymaster first described the malignant potential of OSMF in 1956: the currently evaluated rate of which is 7-13%. Many follow-up studies have been conducted to identify the important aspects of malignant transformation in OSMF.<sup>11</sup> This current study reports more than one-third of the subjects with OSMF that transformed to OSFCa. The distinction between the two presenting groups of OSCC was made on the basis of mouth opening and blanching/ bands, etc, and not on histologic evidence.<sup>18</sup>

According to Chaturvedi et al., most malignant transformations occur in younger males but having better prognostic features: better grade of tumour differentiation, lower incidence of nodal metastases and less extra-capsular spread.<sup>19</sup> Although not assessing these

histo-pathological aspects, the current study, however, suggests a change in trend with 78.4% females presenting with malignant transformation. This may be due to additional contributing factors: multiple pregnancies, aggravating nutritional deficiencies, and lack of awareness or access resulting in late reporting of the disease.<sup>20</sup>

The majority of females in the current study were of a young and potentially productive age group. The findings concur with those of Sumathi et al. where the majority of patients with OSMF were from the 15-30 years age group.<sup>21</sup> The underlying aetiology of this disease occurring in the early decades is the routine consumption of areca nut initiated in childhood and associated with a low socioeconomic status. Early development of OSMF accelerates progression towards malignant transformation to OSFCa.<sup>14,22,23</sup>

A recent household survey involving 16,000 women from a low socioeconomic background living in a Karachi Slum Township showed that an alarmingly large number were addicted to tobacco, with an overall prevalence of more than half. A study entitled 'Prevalence of tobacco use among women: a cross sectional survey from a squatter settlement' was conducted by the Aga Khan University in collaboration with the All Pakistan Women's Association and the National Alliance of Tobacco Control.<sup>22</sup>

According to current WHO statistics, while the prevalence of tobacco consumption is declining in developed countries, it is steadily increasing in developing countries where women and youth are the target of tobacco advertising strategies.<sup>24</sup> Furthermore, it was reported in 2014 that the Asia-Pacific region was one of the fastest growing markets for tobacco and its variants, with the top four affected countries being Malaysia, Indonesia, Pakistan and Vietnam.<sup>25</sup>

Additional factors may be associated with the increased female predilection in Pakistan. There is a lack of distinction between the transition from plain areca nut to the various more toxic products such as gutka, pan masala and tobacco /chemical additives. In addition to smoking, which is considered taboo in certain areas of the country, a significant majority of women habitually consume betel quid and/or tobacco in its other forms. Minimal signs and non-crippling symptoms in the early stages and/or a lack of awareness about the disease potential result in lower reporting rates of the true incidence of OSMF. Multiple pregnancies are often found associated with low socio-economic and poor nutritional status: all related to a lack of empowerment of females. Malnutrition promotes the development of OSMF by

impairing repair of inflamed mucosa leading to defective healing by scar tissue. All these factors contribute to lowering the body's innate resistance and can act as promoting factors in the presence of these chewing habits.<sup>23</sup>

The habitual use of betel products from childhood, with duration, frequency and cumulative amount all being factors, enhances the risk of early development of OSMF and, with progression to more lethal variants, increases the probability of transformation to frank OSCC. With a rapid and poorly planned population growth, Pakistan has a disproportionately high number of socio-economically disadvantaged, illiterate and disempowered women. Early marriages, repeated pregnancies and the production of stunted children create a vicious cycle where, among other disasters, OSMF and its transformation to OSFCa are likely to rise exponentially.<sup>26</sup>

Finally, this paper opens up an area of research into factors and reasons why the other patients, roughly 55% of the malignancies, with essentially the same patterns of habits developed cancers at a later stage and without clinical signs and symptoms of OSFCa.

The findings of this study are of great potential demographic importance in much of the Asia-Pacific region where the status of females is lower than males. It raises research questions of chance element non-probability sampling. It also queries possible additional biological differences between men and women which make women more prone and susceptible to malignant transformation. Secondly, females have a vital role in development and training of future generations, so this study further highlights the potential group which needs to be targeted by future interventions to reduce both their risk of malignant transformation and also to spare future generations of children from hazardous effects of these chewing habits. Therefore, the study has many implications, both for further scientific studies as well policy and practice.

## Conclusion

With increasing global migratory population trends, a widespread demographic catastrophe is in the making. Regional governments with populations most affected urgently need to address this issue and institute immediate measures to restrict the use of these hazardous substances while simultaneously raising awareness through community-oriented oral health education. A concerted health and education outreach including primordial mode of prevention is required to cut the greater risk of developing OSCC, especially among

females already compromised by a low socio-economic status and with superimposed multiple pregnancies.

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