

ORIGINAL ARTICLE

SOCIO-ECONOMIC IMPLICATIONS OF A YOUNGER AGED FEMALE PREDILECTION IN MALIGNANT TRANSFORMATION OF ORAL SUBMUCOUS FIBROSIS

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Background: This study was conducted to determine the age, gender and pattern of associated chewing habits among cases of oral squamous cell carcinoma (OSCC) presenting with, (OSMFCa) and without, (Ca-OSMF) pre-existing clinical oral submucous fibrosis in Karachi, Pakistan. **Method:** A cross sectional, multi centric study of (n=1009) cases with histologically confirmed oral squamous cell carcinoma seen at both public, private tertiary care hospitals and clinics over a period of eight years. A non-probability convenience sampling was used for selection of cases. Of these n=472 cases were reported as malignant transformation of clinical OSMF into OSCC: (OSMFCa) and n=537 were of OSCC without clinical evidence of OSMF: (Ca-OSMF). Qualitative analysis for gender and chewing patterns as well as chi square was performed for association. Age comparison between the OSMFCa and Ca-OSMF groups were performed by independent t test. **Results:** A total of n=1009 cases presenting with OSCC were examined. Of these 46.78% (n=472) cases were reported as OSMFCa and 53.22% (n=537) as Ca-OSMF. The comparison of age differences at presentation of OSMFCa and Ca-OSMF cases by independent t test was statistically significant ($p<0.049$). Both gender and chewing habits showed significant association with OSMFCa and Ca-OSMF. **Conclusion:** Common to both affected groups was consumption of betel quid, chewing tobacco and variants with males tending to move on to more complex combinations. An overall male trend was noted in OSCC, particularly in Ca-OSMF. However, proportion of females with OSMFCa was significantly higher than males. A significantly younger female affectation in this group has significant potential socio-economic consequences.

Keywords: Malignant transformation; Carcinogenesis; Oral submucous fibrosis; Oral squamous cell carcinoma; South Asia

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INTRODUCTION

Cancer is one of the leading causes of death in both more and less economically developed countries; the global burden of cancer is increasing with ageing and growing populations, causing massive societal problems particularly in developing countries where about 82% of the world's population resides.¹ Across Asia, cancer is one of the most serious health threatening diseases with an increasing mortality rate.² According to studies cancer incidence rates were over 3 million whereas proportionate cancer mortality rates in these populations were over 2 million during year 2000. Mackay *et al.* forecast that incidence rates of cancer cases would be increased to 7.1 million by year 2020 if current cancer preventive strategies remain unchanged.³ OSMF is a recognized potentially malignant condition whose incidence is raised due to increased consumption and common availability of areca nut, often mixed with chewing tobacco and other chemical constituents.⁴ Further, at some point in time this premalignant condition can transform into malignancy especially with the persistence of those chewing habits or with the

addition of smoking or alcohol.⁵ Betel nut and variants, tobacco and alcohol consumption have documented risk increasing synergistic effects.⁶ Nutritional deficiencies frequently associated with this population may impair inflammatory repair responses leading to scarring and fibrosis.^{7,8}

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.⁹

Head and neck cancers constitute the sixth most common cancer worldwide.^{10,11} The most common head and neck cancer is OSCC which can either be Ca-OSMF or present as malignant transformation in OSMF. According to evidence from Taiwan, out of 2 million people about 85.4% were habitual users of betel quid with a chance of developing OSMF. Of these, about 25% later developed OSCC.¹²

In Pakistan 21% of male and 11% of female cancers are located in the head and neck region.¹³

Among head and neck cancers the most common cancer reported from South and Southeast Asian countries is oral squamous cell carcinoma (OSCC) with marked geographic variations in occurrence.¹⁴ The major risk factors for OSCC in Pakistan, India, Taiwan and other neighbouring countries are the habitual consumption of smokeless tobaccos and betel quid with or without added tobacco.^{15,16}

Globally, OSCC usually occurs in patients 60 years and over. However, during the last half century this trend has changed with the incidence found to have increased among a younger age group. Furthermore, an alarming increase in the incidence rate of the disease from 0.4 to 3.6% was seen in cases younger than 40 years of age drawing attention of epidemiologists and surgeons towards the changing face of the disease which is becoming a major health burden, especially in countries that can least afford them.¹⁷

Aforementioned studies have shown increasing incidence of OSCC in developing countries due to a socio-cultural acceptance of the practice of areca nut and betel quid consumption with or without tobacco additives. As one of the largest mega-cities, Karachi shows diverse ethnicity of population along with gender wise changing trend in consumption of areca nut and betel quid and variants recording an alarming increase in female habitual affectation. Moreover, negligible efforts are made to implement policies against consumption of betel nut and its various lethal derivatives, tobacco control and use of early detection tests and strategies targeted to high risk populations.

Objectives: To determine the age, gender, and pattern of associated chewing habits among cases with OSMFCa and Ca-OSMF attending public and private tertiary care hospitals of Karachi, Pakistan.

MATERIAL AND METHOD

A cross sectional, multi centric study of n =1009 cases with histologically confirmed oral squamous cell carcinoma seen at both public and private tertiary care hospitals and clinics over a period of eight years. A non-probability convenience sampling was used in the study for selection of both cases. Of these 472 cases were reported as malignant transformation of clinical OSMF into OSCC (OSMFCa) and 537 were of OSCC without clinical evidence of pre-existing OSMF (Ca-OSMF). All cases were diagnosed and documented by the senior author.

Sample size was determined by WHO sample size calculator, estimating a population proportion with specified absolute precision, keeping 95% confidence interval, 0.05 anticipated population proportions, 0.02 precision and 5% margin of error.⁴ Clinical details included age, gender, clinical grading of OSMF;

associated habits of eating plain or packaged areca nut alone or with its combinations in the form of betel quid (*paan*) with or without tobacco, *naswar* (moist powdered tobacco snuff), etc.

Assessment of clinical grading of OSMF was based on the classification proposed by Rose and Balan in 2007.¹⁸ Clinical oral examinations were performed to detect malignant change associated with pre-existing OSMF.

Data were assembled and entered in SPSS version 18. Frequencies and percentages were calculated for gender and chewing patterns and chi square test was performed to find out association among these variables. However, mean and standard deviation was calculated for quantitative variable such as age. Independent *t*-test was performed for comparison of age between the OSMFCa and Ca-OSMF groups. Level of significance was kept at $p \leq 0.05$.

RESULTS

A total of 1009 cases with oral squamous cell carcinoma were examined of which 46.78% (n=472) cases were reported as malignant transformation of OSMF into OSCC (OSMFCa) and 53.22% (n=537) were of OSCC without clinically evident OSMF (Ca-OSMF). Of the total, 57% (n=578) were females and 43% (n=431) were males with an age range from ten to seventy years and an overall mean age of 42.78±13.11 years. The mean age of the OSMFCa cases was 36.66±9.36 and of those with Ca-OSMF was 48.18±13.57. (Table-1)

Out of 472 OSMFCa patients 90.5% (n=427) had various chewing habits. Only 10% (n=45) denied consumption of any form of chewing substance. On observing the pattern of chewing the majority, 53% (n=228) consumed betel quid with tobacco, 25 % (n=108) consumed areca nut only, 13% (n=55) chewed betel quid without tobacco, and 8% (n=32) used *naswar* while only 0.23% (n=01) had other chewing habits. (Table-2)

Of the 537 Ca-OSMF patients about 76% (n=408) reported similar chewing habits while 24% (n=129) denied any form of habitual consumption. On observing the pattern of chewing in these cases 45% (n=185) used betel quid with tobacco, 21% (n=84) chewed betel quid without tobacco, 11% (n=47) consumed areca nut only, and 23% (n=92) used *naswar*. (Table-2)

The comparison of age differences in OSMFCa and Ca-OSMF cases by independent t test (mean difference = 0.014, 95% of CI -0.051–0.081) was statistically significant ($p < 0.049$). (Table-3)

Both gender ($p \leq 0.001$) and chewing habits ($p \leq 0.001$) showed significant association with OSMFCa and Ca-OSMF.

Table-1: Descriptive analysis of the total study cases

Cases	Frequency (n)	Percentage (%)
Oral Squamous cell carcinoma (OSCC)	1009	100
	Female 578 (57%)	
	Male 431 (43%)	
Oral Squamous cell carcinoma with oral submucous fibrosis (OSMFCa)	472	47
Oral squamous cell carcinoma without oral submucous fibrosis (Ca-OSMF)	537	53

Table-2: Descriptive analysis of pattern of chewing habits among OSMFCa&Ca-OSMF

Cases n=835	Areca nut	Betel quid without tobacco	Betel quid with tobacco	Naswar	Other chewing
OSMFCa	108 25.29%	55 12.88%	228 53.40%	35 8.20%	01 0.23%
Ca-OSMF	47 11.52%	84 20.59%	185 45.34%	92 22.55%	0 0%

n=835 involved in chewing habits. n=174 no chewing habits

Table-3: Comparison of age in OSMFCa vs.Ca-OSMF

Variables	Mean Difference	95% of Confidence Interval		p-value
		Lower Limit	Upper Limit	
Age ranges	0.014	-0.051	0.081	0.049*

(Independent sample t-test) (*statistically significant)

DISCUSSION

The current study (n=1009) had reported on two clinically different groups of oral squamous cell cancers, i.e., patients with malignant transformation in pre-existing clinical OSMF (OSMFCa) comprising of 46.78% (n=472) cases, and those with no clinical evidence of pre-existing OSMF (Ca-OSMF), 53.22% (n=537). Both groups (OSMFCa & Ca-OSMF) were found to be inclined towards habitual consumption of betel quid with tobacco; however, areca nut alone and *naswar* (powdered tobacco snuff) chewing was the second most common habit among cases of OSMFCa and Ca-OSMF respectively.

Further, factors like age, gender and chewing habits were found to be statistically significant across both groups (OSMFCa & Ca-OSMF). Cases reported with OSMFCa were more prevalent in a female majority and younger group having a mean age of 36.66±9.36 while those with Ca-OSMF had a male preponderance and were relatively older with a mean age of 48.18±13.57.

Another interesting finding was that patients in the OSMFCa group tended to have started the habit from an early age using areca nut only and progressing towards betel quid with tobacco and more complex variants later. This finding is similar to another study by the same authors in which age ranged distribution and associated chewing habits was reported.⁵

OSMF is a known oral pre-malignant condition.¹⁹ Once certain irreversible changes have occurred a significant proportion of cases will tend to transform into OSMFCa.²⁰ A study had reported that cases with OSMF are 19.1 times more likely to develop OSCC.²¹ Gender may play an important role in this. In the current study a greater proportion of

females were habitual consumers of chewing tobacco and its associated complex variants and had a significantly higher presentation with OSMFCa than their male counterparts. These findings are in concordance with the study reported by Iqbal *et al*²² but in disagreement with that reported by Gilani *et al*²³.

There are numerous possible reasons for the greater female presentation with OSMF related OSCC. Childhood stunting due to nutritional deprivation affects nearly half of all Pakistani children with females far more affected. This causes profound mental and developmental effects on growth, some of which are irreversible. At the ultracellular level these are also likely to reduce immunity and cellular resistance to injury.²⁴ Poverty, illiteracy and the additional impact of multiple pregnancies, especially in women in the lower socioeconomic groups with limited access to health and maternal care, aggravates physical and psychological stresses.²⁵ It has been suggested that peer pressure and depression play a significant role in taking up cigarette smoking and the habitual consumption of betel nut, quid, etc., as a stress relieving mechanism.²⁶

It was noticed that even females not too exposed to outside environments had access to these addictive products via their children and this seemed to be one reason for high consumption of *chaalia* (areca nut) and associated complex variants among both females and adolescents.²⁷ Malnutrition and multiple pregnancies are associated with foetal growth restriction resulting in low birth weight and increased risk of childhood infections and mortality. Furthermore, if the new-born child is female the cycle will repeat possibly increasing susceptibility to disease.²⁸ The cumulative effects of all these factors

might contribute to explain the significant female bias and younger age tendency in patients presenting with OSMFCa.

Because of its cultural acceptance betel products and quid are often served to guests in social gathering and marriage ceremonies. Women are even gifted *Paandaans* (traditional betel quid storage receptacles) as a part of their bridal goods/dowry.²² According to the WHO Report on the Global Tobacco Epidemic, the 2011 Pakistan scores in terms of compliance with smoke-free legislation for public places was found to be very poor.²³

Slightly more than half of the total sample in the current study presented with OSCC without clinical evidence of pre-existing OSMF (Ca-OSMF) and with clear male predominance. These findings are in agreement with other studies.²⁹ Males were noted to indulge in progressively increased consumption of more complex variants of betel nut, i.e., betel quid with and without tobacco, as well as *naswar*. Conducted at three different sites the current study sample largely comprises of the lower- and mid-socio economic strata of Karachi and is representative of the city's multi-ethnic population.²⁷ Despite common backgrounds and habits and the overall significant deleterious effects of childhood stunting, it is tempting to suggest that because male children, especially in our society, receive better nutrition than their female counterparts they may have greater innate resistance to early OSMF change and its transformation into OSMFCa.

Over time and with habit progression the cumulative damage to the oral tissues may directly lead to Ca-OSMF. Evidence suggests that increased number of cases among young females could be due to genetic susceptibility, hormonal imbalance, altered immune response and viral infections.³⁰

With the far-reaching implications of childhood stunting there is an urgent need to address issues of maternal and child health, including population spacing. Concerted public health efforts are needed to curtail all forms of tobacco advertisement, sponsorship and marketing strategies as well as to implement policies and enforce strict laws on availability and consumption of smoked and smokeless tobacco products. Since the majority of cases (OSMFCa & Ca-OSMF) had limited education there is great need for awareness programs through community outreach, mass media and schools.

CONCLUSION

In our study we found that the proportion of females with OSMFCa was significantly higher than affected males and presented at a significantly younger age. Since the vast majority of affected patients were from middle and low income groups a lack of knowledge,

awareness and access to healthcare play important promoting roles.

AUTHORS' CONTRIBUTION

NF: Write up and data Collation. SM: Design of study, write up and data analysis. SH: Revision and addition in concept. MH: Concept and data collection

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