Association of Carcinogenic Oral Habits with Oral Squamous Cell Carcinoma

Nazish Fatima BDS, MDS
Sidra Mohiuddin BDS, MDS
Salim Hosein MBBS, DABGS
Mervyn Hosein BDS, FDS RCSE, FDS RCS, FFD RCSI

OBJECTIVE: To determine the association among betel nut, betel quid or smoking alone, and betel quid combined with smoking in subjects reporting with oral sub mucous fibrosis, oral submucous fibrosis with malignant transformation to cancer and oral squamous cell carcinoma.

METHODOLOGY: An analytical cross sectional, multi centric study of n = 1009 cases collected through non-probability convenience sampling. These n=1009 subjects were subdivided into four groups: group 1, who consumed areca nut only; group 2, who chewed betel quid along with areca nut; group 3, who used betel quid and smoked; and group 4, who had no chewing habits history but were smokers. These changes were further confirmed with the help of biopsy reports of the subjects with OSMFca and OSCC. Chi square test was performed to find out association of chewing habits with the progression of disease state. Level of significance was kept at p≤0.05.

RESULTS: The mean age of the sample (n=1009) were 42.79±1.31 years (range: 10-70 years). Statistically significant difference was (p<0.00) found among all four groups in terms of initiation, propagation and progression of oral squamous cell carcinoma. Furthermore, statistically insignificant difference (p=0.40) was found between group 2 and group 3 as similar number of cases (OSCC) was seen among them.

CONCLUSION: Current study concluded that patients who have combined habits of chewing betel quid with areca nut and betel quid with smoking were at highest risk of initiation and progression of oral cancer. However, smoking cigarettes alone was the weakest risk factor.

KEYWORDS: Betel quid; Areca nut; Smoking; Oral squamous cell carcinoma, Oral submucous fibrosis


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INTRODUCTION

Cancer is a global burden because of its high incidence and death rates.1,2 Amongst all cancers, oral cancer is the second most common cancer reported from developing countries.3,4 Evidence has shown that cancer is proven to be a disease of multifactorial origin, associated with varying risk factors among different population sub groups.5 However, factors that are primarily considered as established risk factors are: tobacco usage; areca nut; heavy intake of alcohol; infection with human papillomavirus; and existence of oral potentially malignant disorders Since Pakistan is a developing county where people are suffering from oral cancer are mostly belong to low socioeconomic status.6 As this high risk group of the population; in addition to oral cancer is also suffering from nutritional deficiencies such as vitamin B12, folic acid and antioxidants therefore they get easily effected by the disease.7 Many epidemiological studies have reported consumption of tobacco to be the major etiology behind oral cancer.6,8 In addition; deaths caused by tobacco hardly make headlines, but tobacco kills one person in every six seconds.9,10 Many studies within the South Asian region report the frequent exchange and/or sharing of tobacco products as a way to promote relationship ties and friendship.12,13 Furthermore, some studies have suggested that consumption of tobacco in combination with betel quid is also linked with relieving...
stress and/or help keep chewing workers awake because of the presence of pharmacologically active ingredients.12,14

Globally, tobacco is available in two major forms: smoked and smokeless. The common smoked form includes cigarettes, cigars, e-cigarettes and hookahs whereas the smokeless is further divided into chewing (betel quid, pan masalas, Gutka), and snuff forms (dry/moist).8 Betel quid (BQ) with tobacco and gutka (processed and packaged areca nut with added tobacco and other ingredients) are the most widely used smokeless tobacco (ST) products in the south Asian region (i.e. Pakistan, Bangladesh, India, Sri Lanka, Taiwan etc.) and are the one among four most commonly used psychoactive substances consumed by about six million people around the globe.8,12,15,16,17

Gender wise prevalence of smoking reported by WHO (2013) among Pakistani population was found to be 31.8% of men, 5.8% of women, and 19.1% of adults are currently use tobacco in one form or another. Furthermore, of these overall adult population 17.9% of men, 1% of women and 9.6% of the adults were found to be users of cigarette smoking on daily basis whereas water pipe smokers were 4.4% of men, 1% women and 2.7% were adults. On the other hand, adult’s consumption of smokeless tobacco on daily basis was found to be 10.5% men, 3.5% women and 7.1% of adults. However, among young generation 13.3% of boys, 6.6% of girls and 10.7% of all youth were consuming either tobacco in direct form or its derived products.13 Moreover, it is also reported by the World Bank that unless urgent action is taken to control the situation, the annual deaths from tobacco will rise more than 8 million by 203018 if these trends are not over looked then it will lead to an estimated 500 million people’s death associated with tobacco alone.11

There is scarcity of data in countries like Pakistan, India, and Bangladesh regarding association of OSMF, its malignant transformation and OSCC with tobacco users in forms i.e chewing & non chewing (areca nut and betel quid, betel quid and smoking) as well as combination of these habits and their association in causing oral malignancies. Furthermore, there is an utmost need to find out the synergistic effect of combination of chewing and non-chewing habits. These findings could be helpful for further evaluation of rate and progression of OSCC, and will possibly allow high authorities to allocate more resources towards prevention and management of oral cancer.

Therefore, the objective of current study was to evaluate the association among betel nut, betel quid or smoking alone, and betel quid combined with smoking in subjects reporting with oral sub mucous fibrosis, oral sub mucous fibrosis with malignant transformation to oral cancer and oral squamous cell carcinoma.

METHODOLOGY

A cross sectional, multicentric study of histologically confirmed n=1009 cases of OSCC were selected and examined by the principal investigator; from both private and public tertiary care units through a non-probability convenience sampling technique. The age ranges of the subjects were 10 to 70 years of age. Selection criteria was as follow:- all those subjects who had habit of consuming betel nut, tobacco and its derivatives, were agree to be the part of study. However, subjects that were habitual eaters and came to the OPD for other dental procedures, pregnant and lactating females were excluded.

Sample size was determined by WHO sample size calculator.19 Clinical details included age, gender, 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), smoking tobacco etc.

Data collection was performed by subdividing the total n=1009 subjects into four groups: group 1, who consumed areca nut only; group 2, who chewed betel quid along with areca nut; group 3, who used betel quid and smoked; and group 4, who had no chewing habits history but were smokers only.

Clinical grading of OSMF was based on the classification proposed by Haider SM and Merchant AT et al.20 Clinical oral examinations was performed to detect malignant transformation related to pre-existing OSMF. These transformations were further confirmed with the help of biopsy reports of the subjects with OSMFCA and OSCC. Data were assembled and entered in SPSS version.18 Frequencies and percentages were calculated for gender and group wise chewing patterns and chi square test was performed to find out association of chewing habits with the progression of disease state. However, mean and standard deviation was calculated for quantitative. Findings were considered significant with a p-value of less than 0.05.

RESULTS

Of the total n=1009 subjects, 57.3% (n=578) were females and 42.7% (n=431) were males. The mean age of the sample (n=1009) were 42.79±1.31 years (range: 10-70 years). Moreover, 2.2% (n=22) of subjects were of ages below 25 years, 54.9% (n= 554) were within 26 to 50 years of age and about 42.1% (n= 433) were aged 51 years and above.

The subjects were divided into four groups according to usage of habits, first group was taking areca nut (AN) only, second group was taking areca nut plus betel quid
(AN + BQ), third group was taking betel quid along with smoking (BQ + Smoking), while the fourth group had no chewing habit they were only smokers.

Out of 1009, 21.8% (n=220) were in group 1 who were consuming AN only; 22.7% (n=229) in group 2 reported a habit of eating AN plus BQ; group 3: 32.8% (n=331) reported that they consumed BQ along with a smoking habit; while 22.7% (n=229) of the subjects in group 4 were smokers only.

Out of total n=1009 subjects, 22.5% (n=227) were diagnosed with OSMF alone, 23.2% (n=234) with OSMFCa while 54.3% (n=548) were diagnosed with OSCC without pre-existing OSMF.

The descriptive analysis of chewing habits with the type of oral disease is described in table 1. The relationship of the type of oral habits and type of oral disease is represented in table 2.

**Table 1: Descriptive analysis of oral habits and types of oral disease**

<table>
<thead>
<tr>
<th>Oral habits</th>
<th>Diagnosis</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OSMF</td>
<td>OSMFCa</td>
<td>OSCC</td>
</tr>
<tr>
<td>Areca not only</td>
<td>11</td>
<td>97</td>
<td>68</td>
</tr>
<tr>
<td>% of oral habit</td>
<td>52.3%</td>
<td>44.1%</td>
<td>3.6%</td>
</tr>
<tr>
<td>% of Diagnosis</td>
<td>50.7%</td>
<td>41.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Areca Nut plus Betel Quid</td>
<td>20</td>
<td>25</td>
<td>181</td>
</tr>
<tr>
<td>% of oral habit</td>
<td>8.7%</td>
<td>10.9%</td>
<td>80.3%</td>
</tr>
<tr>
<td>% of Diagnosis</td>
<td>8.8%</td>
<td>10.7%</td>
<td>33.6%</td>
</tr>
<tr>
<td>Betel quid plus smoking</td>
<td>21</td>
<td>45</td>
<td>265</td>
</tr>
<tr>
<td>% of oral habit</td>
<td>6.3%</td>
<td>13.6%</td>
<td>80.1%</td>
</tr>
<tr>
<td>% of Diagnosis</td>
<td>9.2%</td>
<td>19.2%</td>
<td>48.4%</td>
</tr>
<tr>
<td>Smokers</td>
<td>71</td>
<td>67</td>
<td>91</td>
</tr>
<tr>
<td>% of oral habit</td>
<td>21.0%</td>
<td>29.2%</td>
<td>39.7%</td>
</tr>
<tr>
<td>% of Diagnosis</td>
<td>31.3%</td>
<td>28.6%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Total</td>
<td>227</td>
<td>234</td>
<td>548</td>
</tr>
<tr>
<td>% of oral habit</td>
<td>22.5%</td>
<td>23.2%</td>
<td>54.3%</td>
</tr>
<tr>
<td>% of Diagnosis</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Statistically significant
Chi-square Test

**Table 2: Association of oral habits and type of oral disease**

<table>
<thead>
<tr>
<th>With respect to oral habits</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 vs group 2</td>
<td>0.00</td>
</tr>
<tr>
<td>Group 1 vs group 3</td>
<td>0.00</td>
</tr>
<tr>
<td>Group 2 vs group 3</td>
<td>0.400*</td>
</tr>
</tbody>
</table>

*Statistically significant

**DISCUSSION**

In the current study we have reported the disease trend among chewers (users of areca nut, betel quid and tobacco), non-chewers (i.e smokers only) and also among subjects who had a combination habit of chewing and smoking tobacco. Furthermore, we have found that subjects who were consuming either areca nut alone or habit of tobacco smoking; reported with increased numbers of oral sub mucous fibrosis as well as malignant transformation of oral sub mucous fibrosis. On the other hand, subjects who were consuming betel quid in combination with areca nut and betel quid in combination with smoking; reported with increased numbers of oral squamous cell carcinoma. We had found statistically insignificant association among the subjects who had habit of chewing betel quid along with areca nut and chewing betel quid along with smoking with progression of oral malignant conditions i.e OSMF, OSMFCa and OSCC.

Oral carcinogenesis is a progressive, multistage process in which genetic and phenotypic molecular markers are involved in enhancing the function of several proto-oncogenes, oncogenes by deactivating tumor suppressor genes, thus causing over activity of the growth factors and its cell surface receptors, which can lead to increase messenger signaling intra-cellularly and leads to increase release of transcription factors. Thus oncogenes alone are not responsible for causing cancer however, genes having tumor suppressor activities can result in cellular phenotypic changes and these changes are responsible for increased cell proliferation, loss of cellular cohesion, are able to infiltrate in to local tissue so they can spread to distant sites.

In current study we have found that smoking alone is the weakest cause for developing oral cancer as compare to combination of chewing tobacco habits. This finding is similar to the studies reported by Balaram P et al and Znaor A et al from India as well as in some case control studies reported by Bundgaard T et al and Madani et al. The reason is as chewing tobacco and its product may have a stronger effect than smoking tobacco because of the direct contact of the carcinogenic substances with the oral epithelium.

In this study we have found that chewing tobacco is strongly related to develop oral cancer. This finding is in corroboration with aforementioned studies. The reason was may be the duration of keeping the chewing tobacco and its products with in the oral cavity either with or without lime. Another similar finding was reported by Muwonge et al that smokeless tobacco users were at higher risk of developing oral cancer, along with some other oral abnormalities as compare to smokers alone.

Moreover similar to current studies evidences have suggested that chewing betel quid with tobacco, tobacco consumed by chewing with lime, betel quid with or without tobacco, and areca nuts are human carcinogens. However current study has reported that in addition to the carcinogenicity of these products, combination of chewing tobacco habits are more potent cause of oral cancer among
Pakistani population. It has been suggested that both dental and medical health care professionals should work together for initiation of chewing tobacco cessation awareness among high risk groups. There is also a need for designing and implementation of polices; regarding either to reduce availability or increase taxation over all kinds of tobacco products. In addition, mass media campaigns will be needed to spread awareness about the harmful effects of tobacco and its derivatives. Strategies suggested for the control of betel quid may include: elimination of carcinogenic constituents from the products as well as motivating teenagers through public education and law enforcement not to take up these habits while enhancing the intake of antioxidant containing green vegetables and beta-carotene.

**CONCLUSION**

Current study concluded that subjects who have combined habits of consuming betel quid with areca nut and/or betel quid with smoking were at highest risk of initiation and progression of oral cancer. However, smoking tobacco only was found the weakest risk factor for developing oral cancer.

**CONFLICT OF INTEREST**

None to declare

**REFERENCES**

1. World Health Organization. Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018. [https://www.who.int/cancer/PACGlobocanFinal.pdf](https://www.who.int/cancer/PACGlobocanFinal.pdf)


