

Prevalence of oral squamous cell carcinoma (OSCC) in relation to different chewing habits in Karachi, Pakistan

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Abstract: The chewing habits of betel quid (*paan*), areca nut (*chaliya*), raw tobacco, *gutka*, *niswar* and *manpuri* are the most common addictions in Pakistan, India, Taiwan and China. To observe prevalence of oral squamous cell carcinoma (OSCC), a total of 170 patients of OSCC were selected from the general population for the study followed by informed consent. Among the patients, habitual chewers of betel quid (*paan*) (22), areca nut (*chaliya*) (11), raw tobacco (36), *gutka* (51), *niswar* (16) and *manpuri* users (34) were included. In betel quid chewers, 10 were males and 12 were females, betel nut users were 8 males and 3 females, with raw tobacco habits 27 were males and 9 were females, *gutka* chewers were 40 males and 11 females, all *niswar* (16) and *manpuri* users (34) were males. The age of patients, age of onset of OSCC and the duration of OSCC in all patients were noted using a structured questionnaire. Among the patients of OSCC, high percentage was found to be involved in chewing habit of *gutka* i.e., 30.0% where as the users of betel nut (*chaliya*) were least at 6.5%. The percentage of raw tobacco, *manpuri*, *paan* and *niswar* were found to be 21.2, 20, 12.9 and 9.4% respectively in the patients of OSCC. The minimum age at the onset of OSCC in patients was found as low as 16.4 years in *manpuri* users, whereas as high as 59.09 years patients with chewing habits of betel quid (*paan*). This study concludes that all of the above chewing habits lead to OSCC within the 5-10 years of exposure time. The special care is to be given to the young adults to get them rid of *manpuri* since the occurrence of OSCC was found at the age of 16.4 years in *manpuri* users, therefore these habits should be stopped immediately to secure the generation from getting OSCC.

Keywords: Oral squamous cell carcinoma, chewing habits, betel quid (*paan*), areca nut (*chaliya*), *gutka*, *niswar*, *manpuri*.

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INTRODUCTION

Non-communicable diseases have become a major public health problem in developing countries like Pakistan, concomitant with economic development. Oral squamous cell carcinoma (OSCC), the fifth most common cancer worldwide, is a major cause of morbidity and mortality in Southeast Asian countries¹. Areca nut, betel quid, leaves chewing is among the most common addictions following tobacco, alcohol and caffeine. Its usage is very popular in Pakistan, India, Taiwan and parts of Southern China. It has been estimated that more than 600 million people chew areca nut worldwide and 85% of them live in Southeast Asian countries². Its chronic use contributes significantly to the high incidence of oral cancer in these countries³.

Areca nut is present in large number of chewing products available in the country, such as *Paan* (betel quid), *gutka*, and *paan masala* consisting of a mixture of lime, areca nut (with or without tobacco), slaked lime, catechu and several condiments according to taste, wrapped in betel leaf. Use of these products can cause OSCC, oral submucous fibrosis, leukoplakia, hepatocellular carcinoma (HCC) other premalignant lesions, the potential of which is not known⁴.

In recent years, small, inexpensive and attractive sachets of betel quid substitutes (*gutka*, *mawa* and *supari*) have become widely available, are aggressively advertised in local electronic and print media, marketed and consumed by the very young and old equally without any significant discrimination of males and females (Table 1). These products have higher genotoxic and carcinogenic potential compared with conventional betel quid and leaf⁴. Chewing of these products usually starts at an early age (approx. 13-15 years) and, by adulthood, most users are addicted to the habit. Older adults are not alarmed by the fact that young children are indulging in this habit as they consider it a part of their normal life. However, this practice often leads to addiction and once the habit is formed, it persists throughout life⁵.

Although observations suggested that betel quid and areca nut and their substitutes like *gutka* and *paan* chewing habit is a major risk factor for death from circulatory, pulmonary and malignant diseases, such studies are not available from most of developing countries. By observing the progressively increasing consumption of these products and equally increasing risk of OSCC, leukoplakia, oral submucous fibrosis and other premalignant circulatory, pulmonary and metabolic derangements

this study was designed to investigate the prevalence of OSCC in members of Pakistani population with different chewing habits.

Table 1: Composition and practices of the different types of chewing substances (Auluck et al, 2009)

Local name	Contents	Habit as Practiced
<i>Paan</i>	Also known as betel quid, has 4 main ingredients: tobacco, areca nuts and slaked lime wrapped in betel leaf. May also contain cardamom, coconut, cloves and sugar.	All ingredients chewed slowly. The contents with the juices are either swallowed or spat out of the mouth.
<i>Gutka</i>	A powdered mixture of tobacco, areca nut and slaked lime with spices and flavoring agents.	The powder is placed in the mouth and slowly chewed. Contents are usually swallowed.
<i>Manpuri</i>	A powdered mixture of areca nut and slaked lime with spices and flavoring agents.	The powder is placed in the mouth and slowly chewed. Contents are usually swallowed.
<i>Niswar</i>	A thin shaving of areca nut with tobacco and slaked lime, sold in cellophane papers.	Before consumption, the cellophane pouches are rubbed to mix the contents, which are kept in the mouth in the vestibule and chewed slowly.

SUBJECTS AND METHODS

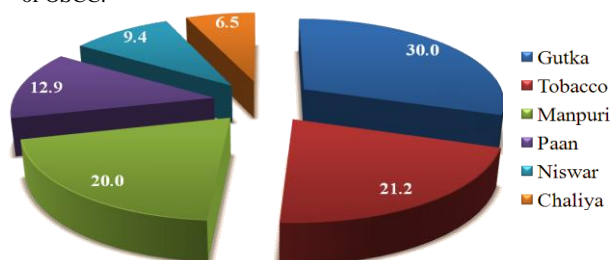
A total of 170 habitual chewers of betel quid, areca nut and their substitutes like *gutka*, *manpuri* and *niswar*, suffering from OSCC, were selected from OPDs of Jinnah Postgraduate Medical Center (JPMC), Karachi, Civil Hospital Karachi, Abbasi Shaheed Hospital, Karachi, and Darul Sehat Hospital, Karachi, Pakistan. Written Informed consent for participation was taken from the patients and individuals who were interviewed consistently. Among the patients, habitual chewers of betel quid (*paan*) (22), areca nut (*chaliya*) (11), raw tobacco (36), *gutka* (51), *niswar* (16) and *manpuri* users (34) were included. In betel quid chewers, 10 were males and 12 were females, betel nut users were 8 males and 3 females, with raw tobacco habits 27 were males and 9 were females, *gutka* chewers were 40 males and 11 females, all *niswar* (16) and *manpuri* users (34) were males. The pre-structured questionnaire used for interview containing detailed information on current and past chewing habits, onset of disease, dietary history and general demographic data. The questionnaires were

completed with the help of patients/attendant and local treating doctor. All the procedures were approved by the regulations of institutional ethical committees of hospitals and medical centers for the use of human subjects in research.

RESULTS

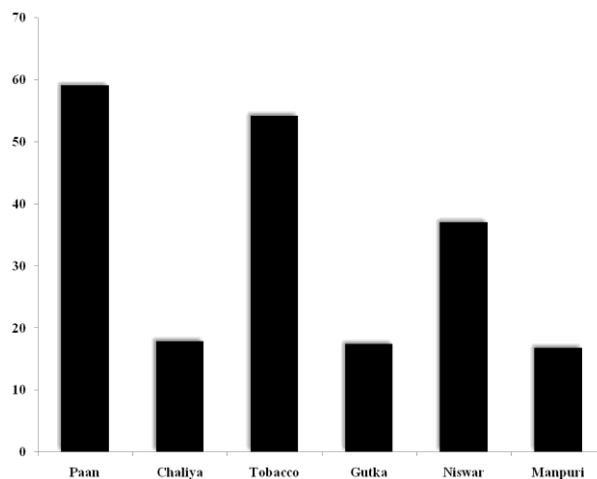
The percent frequencies of chewing habits of patients suffering from OSCC are presented in figure 1. This study finds the highest percentage of OSCC patients were found to be involved in chewing *gutka* (30%) among all the other chewing habits. The lowest percentage was found to be involved in chewing *chaliya* (6.5%). The percentages of other chewing habits among selected patients of OSCC included *raw tobacco* (21.2%), *manpuri* (20%), *paan* (12.9%) and *niswar* (9%).

Figure 1: Percent frequency of different chewing habits in patients of OSCC.



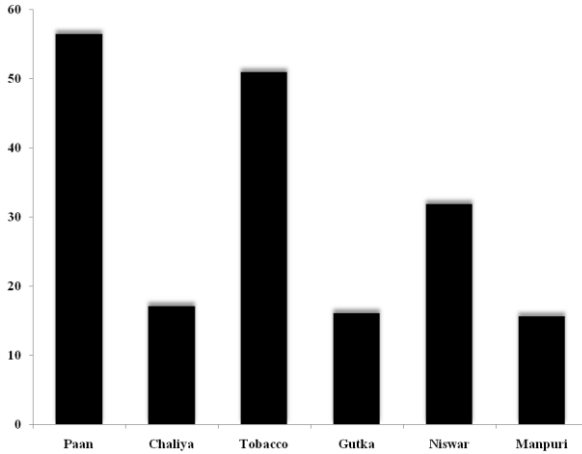
The mean age of patients suffering from OSCC in population of Karachi, Pakistan were observed as 59.09, 17.91, 54.22, 17.43, 37.07 and 16.82 years, who were found habitual of chewing *paan*, *chaliya*, *raw tobacco*, *gutka*, *niswar* and *manpuri* respectively (Figure 2).

Figure 2: The age (years) of patients suffering from OSCC having different chewing habits.



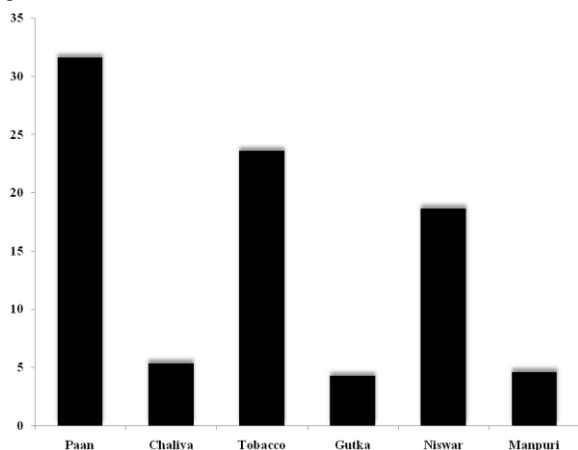
The age of onset of OSCC in patients with chewing habits of *paan*, *chaliy*, *raw tobacco*, *gutka*, *niswar* and *manpuri* were found to be 56.52, 17.17, 51, 16.16, 31.93 and 15.69 years respectively (Figure 3).

Figure 3: The age (years) of onset OSCC in patients having different chewing habits.



The total exposure time of above cited chewing habits to the onset of OSCC in patients were observed as 31.63, 5.36, 23.61, 4.27, 18.67 and 4.62 years for the habits of chewing *paan*, *chaliy*, *raw tobacco*, *gutka*, *niswar* and *manpuri* respectively (Figure 4).

Figure 4: The exposure time (years) of different chewing habits in patients of OSCC.



DISCUSSION

Chewing of betel quid, areca nut and their substitutes *gutka*, *niswar* and *manpuri*, has been an ancient custom in several parts of south-east Asia, in general, and Pakistan, India and Bangladesh, in particular. This practice dates back several thousand

years and is deeply entrenched in the culture of the populations. The betel quid is being used as a mixture of areca nut (*Areca catechu*), catechu (*Acacia catechu*) and slaked lime (calcium oxide and calcium hydroxide) wrapped in a betel leaf^{6,7}. Condiments, sweetening agents and spices may be added according to individual preferences. In most of the above mentioned populations, most habitual chewers of betel quid add tobacco, which has been related mainly to oral pharyngeal and oesophageal cancer and other premalignant and metabolic abnormalities, as observed during this study.

Areca nut (*chaliya*) chewing has not been only associated with oral cancers but also with diabetes mellitus. In this study, 70-90% diabetic patients were observed involved in these types of dietary habits. The substitutes like of *gutka*, *niswar* and *manpuri* chewing have been studied to lead the many systemic complications such as vascular diseases and hypertension⁸. Special areca nut alkaloids act as competitive inhibitors of GABA receptors and have widespread effects in the body metabolic processes regulating osmotic pressure, neurotransmission, cardiovascular rhythm, intestinal movements and normal physiology of lungs, gut and pancreas. Nitrosated derivatives of these alkaloids and alkaloid like compounds, proven carcinogens inducing tumor risks in human being these nitrosated compounds are also diabetogenic in CD1 mice, producing complications of diabetes type 2 with obesity and hyperlipidemia. Betel usage has also been found to increase in circulating markers of inflammatory and cardiovascular damage⁹. In addition, betel nut chewing has also been associated with increased production of reactive oxygen species and inflammatory mediators leading to increased excretion of albumin in urine and causing renal abnormalities¹⁰.

The presented study revealed 74-94% betel quid and areca nut and their substitutes chewing patients suffering from OSCC. Arecoline, a cholinergic alkaloid, is a major constituent of areca catechu nut and causes the euphoric effects. An association between betel nut chewing and bronchoconstriction in asthmatic patients is documented. In certain *in vitro* studies, areconile caused dose-related contraction of human bronchial smooth muscle strips, with one-tenth the potency of methacholine. The inhalation of arecoline has been reported to cause bronchoconstriction in subjects with chewing habits¹¹.

The chemical composition of betel quid and substitutes like *gutka* and *manpuri* is thought to be linked with sympathomimetic effects, while

cholinergic effects ensue at somewhat higher doses. Since sympathetic stimulation is a cause of atrioventricular tachycardia in susceptible patients, it is possible that betel nut in different combinations with tobacco and areca nut is a cause of supraventricular tachycardia¹². The patients who smoked tobacco are more likely to have severe occlusion of both left anterior descending and right coronary arteries. The muscarinic alkaloids of betel can induce coronary vasospasm¹³ and the concomitant ingestion of alcohol in these patients may also aggravate vasospasm hours after exposure¹⁴. However, epidemiological studies are required to clarify and justify whether there is any clinical association between betel nut chewing in different substitutes and combinations and acute myocardial infarction.

The clinical anomalies of betel quid and areca nut chewing have also implicated on liver functions¹⁵. Carcinogens derived from betel quid chewing may be involved in induction of p53 mutation¹⁶ and over expression of c-myc protein¹⁷ with activated ras oncogene and subsequent over expression of cell cycle regulatory protein. These genetic alterations may have occurred in the process of hepatocarcinogenesis¹⁸. Taken together, these observations suggests an independent effect and an additive interaction between betel quid chewing and either HBV or HCV infection on the development of HCC.

Abnormal arachidonic acid (AA) metabolism and platelet aggregation has been linked to vascular thrombus formation and hypertension¹⁹. Interestingly, water extracts of PBL inhibites platelet aggregation and induces vasorelaxation²⁰. On the contrary, AN extract evidently stimulates platelet aggregation and thromboxane B2 production²¹. Arecoline, the major areca alkaloid, is shown to induce vasorelaxation as well as suppress endothelial cell growth²². Moreover, generation of higher amounts of inflammatory mediators (such as IL-1 β , IL-6, IL-8, and TNF- α) by peripheral blood mononuclear cells isolated from BQ chewers relative to healthy persons was observed in vitro²³. This is possibly due to stimulation of the production of various inflammatory mediators such as prostaglandins, interleukin-6, and TNF-alpha by AN ingredients²⁴, because these inflammatory mediators are crucial for the pathogenesis of metabolic syndrome, DM, atherosclerosis, and other cardiovascular diseases^{25,26}.

In conclusion, betel quid, areca nut, *gutka*, *paan masala* and other substitutes chewing as a major etiologic factor of oral cancer increases the risk of premalignant, malignant, metabolic and systemic

abnormalities such as asthma, DM, metabolic syndrome, myocardial infarction, hypertension, hepatitis, acute inflammation, atherosclerosis and hepatocellular carcinoma. This highlights our attention to betel quid and nut chewing habit as a new and crucial health issue, because there are about 600 million chewers in the world. More *in vitro*, *in vivo*, and epidemiological studies are needed to further evaluate whether betel quid and areca nut chewing habits really has a health impact on the pathophysiology, development and progression of diseases and their mechanisms. It is also recommended to study risk behaviors, beliefs, knowledge levels and oral health practices in larger populations. In depth understanding is required regarding the beliefs of the people as they relate to this habit.

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