Proceeding S.Z.P.G.M.I. Vol: 29(1): pp. 47-54, 2015.

Risk Factors of Oral Cancer in Lahore, Pakistan: A Case Control Design

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ABSTRACT

Increase in incidence of oral cancers associated with tobacco and smokeless tobacco products in South Asian countries, especially in Pakistan, is creating an alarming situation. **Objectives:** Study investigated the association of tobacco, smokeless tobacco and alcohol with oral cancer. **Methods:** A case control design was used. 118 cases of oral cancer were selected from hospital, matched with 354 controls during April to June 2015. Case to control ratio was 1:3. **Results**: Mean age of cases was 48.91±13.24 years, 77.1% being males and 22.9% females. Most of the participants belonged to low socioeconomic status. The association of pan with oral cancer was very significant ($p<0.05$, OR= 9.755, 95% CI 5.7-16.5). However, 62/118 cases were non-chewers and developed oral cancer. Pan chewing showed the strongest risk for oral cancer. We also found an increased risk for oral cancer in the consumption of Niswar ($p<0.05$, OR= 3.941, 95% CI 1.6-9.8), gutka ($p<0.05$, OR= 4.133, 95% CI 3.5-4.9), supari/chalia ($p<0.05$, OR= 3.291, 95% CI 1.6-6.7) and alcohol ($p<0.05$, OR=4.789, 95%Cl: 1.7-13.6). Cigarette Smoking habit was present in both case and controls ($p>0.05$, OR= 1.291, 95% CI 0.8-1.9) indicating the cultural habit prevalent in Pakistan. **Conclusion**: Our study thus proved strong association between these predisposing factors and the development of oral cancer and the strength of association found to be stronger than in other studies.

INTRODUCTION

The incidence of malignant neoplasm of oral cavity is increasing with the uniformly low survival rates for the past years which reach approximately 50% in the best treatment centers[1]. Even though the oral cavity is a potentially approachable site for examination but half of the oral cancers are not noticed until the disease is highly developed[2]. Among all risk factors tobacco related products and alcohol are considered highly related to the oral cancer[3]. As a result of strong promotion of tobacco products, the prevalence of precancerous condition and lesions has increased significantly and there is concern that the rate of oral cancer would further increase[4].

According to WHO (world health organization) there will be a marked increase in trends of oral cancer patients specially in South Asian countries where incidence of oral cavity cancers are found highest in all urban cancer registries, in comparison to global data[5]. In American and European countries alcohol and tobacco are documented as the high risk factors of oral cancer[6] but in developing Asian countries the main carcinogenic influence are betel quid areca nut and its substitutes. WHO also states that alcohol consumption, tobacco and other risk factors have 43% role in all cancer deaths[7]. In 2012, 300 new cases of lip and oral cavity cancer were diagnosed which was 2.1 percent of all cancers. Of these 199 were men and 101 women[8].

According to Shaukat Khanum cancer registry Lahore in Pakistan oral cavity malignant neoplasm is the second most common cancer after breast in females and lung cancer in males[9].

Socioeconomic status is also considered to be linked with the incidence of oral cancer[10]. People especially young adults in low socioeconomics area who are more prone to bad habits, and are more addicted to pan, chalia and tobacco related products mainly because of education lack and less access to health services are more at risk[7].

The most common forms of smokeless tobacco (ST) available and used in Pakistan include:

- Pan/betel with tobacco – a chewed mixture of areca nut (Areca catechu), tobacco, slaked lime (calcium oxide and calcium hydroxide) and catechu (Acacia catechu) wrapped in a betel leaf (Piper betel) with sweetening agents.
- Niswar – a mixture of sun-dried, sometimes only partially cured, powdered local tobacco (Nicotianarustica), ash, oil, flavoring agents (*e.g.* cardamom, menthol), coloring agents (indigo) and lime.
- Chalia/supari – areca nut (used plain, flavored with essences or coated with tobacco).
- Gutka – sun-dried roasted, finely chopped tobacco, areca nut, slaked lime and catechu mixed with flavors and sweeteners.

The predisposing risk factors of oral cancer under study include pan (betel quid) which is either with tobacco or without tobacco, supari, chalia, niswar, gutka, cigarettes, alcohol, and oral hygiene. IARC have grouped these agents in IA as definite carcinogenic. Numerous studies have been conducted in many countries on the risk factors and their association to clinical and pathological features of Oral Cancer, in order to define the pathways of carcinogenesis[11]

The use of smokeless tobacco is socially and culturally supported in Pakistan[5]. The usage of these products is increasing day by day which is leading to the increase in number of oral cancer patients in Pakistan. Majority of Pakistani population suffers at the hand of various addictions even after knowing their fatal effects. There is not much sound scientific literature available on risk of oral cancer related to pan and other tobacco products in Pakistan and without which it is difficult to comment on changing strength of association of known risk factors with increasing incidence of oral cancer. Hence, there is a need to re-evaluate the changing epidemiological trends.The objective of this case-control study was to measure the association of risk factors with oral cancer in Pakistan.

METHODS

A case-control study was conducted from April to June 2015 recruiting cases of oral cancer (biopsy-proven cases of oral squamous-cell carcinoma) from Oncology Department, King Edward Medical University / Mayo Hospital, Lahore (KEMU) and Institute of Nuclear Medicine and Oncology Lahore (INMOL). These 2 hospitals are tertiary care hospitals located in Lahore, Pakistan catering patients from all over Pakistan and especially Punjab.

Sample Size

It was calculated with the help of Epi Info™ 7.1.5. It was calculated as 118 cases and 354 controls by using 95% Confidence Interval, 80% Power of test with expected frequency of persons using Niswar among Oral cancer patients and Controls 16.5% and 6.7% respectively[12]. Allotment ratio was kept as 1:3, hence for every case, three controls were selected.

Definition, source and selection of cases

A case was defined as a person aged between 18-80 years with laboratory confirmed diagnosis of oral cancer (ICD-10 Version 2015 C00-C14). All the cases histopathologically diagnosed as oral cancer, either admitted or visiting the Out-Patients Department during the study period were included from the specified 2 hospitals. Our visiting days were 3-4 times a week spending 3 hours in these hospitals, with 6-7 average patient per visit, until our sample of cases completed. We enrolled them in the study after taking written informed consent.

Definition, source and selection of controls

We defined a control as a person aged between 18-80 years. 3 controls were matched with each case either admitted to the same hospital at that time but with some other disease or were accompanying their patients (attendants/relatives). Matching was done for gender, age group and socio-economic status. We excluded control subjects with any history of past or present malignancy, chronic

diseases (diabetes, hypertension) and any apparent congenital deformity. The controls were approached in a similar manner to the cases.

Assessment of exposure/ risk factors

After obtaining verbal consent, the cases and controls were interviewed personally by the researcher using a self-structured questionnaire developed using extensive literature search and expert advice. The questionnaire included socio-demographic information such as age, gender, marital status, District, literacy, occupation, in the personal profile of both cases and controls. The subsequent part of the questionnaire included questions on many known and unknown risk factors of oral cancer including exposure to pan, niswar, gutka, supari/chalia, smoking and alcohol intake. The exposure of pan chewing was rated as never chewed, ex-chewer or current chewer.

We defined users of niswar, pan or gutka as someone who had ever indulged in the habit daily for a month. Smokers were persons who had ever smoked cigarettes, bidis, hookah, cigar, or a pipe daily for at least one month[12]. For each of the substances we asked the date of starting, current use and average quantity used per day. The questionnaire mapped both the daily consumption and the duration of consumption. In case of missing or incomplete information the subjects were contacted by telephone.

Statistical method

The data analysis was carried out using the SPSS version 19 (licensed to: team EQX 6th birthday 1337). Cross-tabs were made with all variables and Chi-Square test applied. The p value, odds ratio (OR) and 95% Confidence Interval (CI) calculated.

Human participant protection was ensured following principles of Helsinki's declaration. Scientific and ethical review of this research was done by Department of Public Health and Community Medicine at Shaikh Zayed Medical Complex, Lahore.

RESULTS

In our matched case-control analysis, there were 118 cases and 354 controls from 2 different hospitals in Lahore, Pakistan. The mean age of the oral cancer patients was 48.9068±13.24 years and of controls was 48.2684±13.63 years, while ranging from 19-78 years. Table 1 shows the frequencies of individuals in each age group. Table 2 shows the Socio-demographic characteristics of both cases and controls. Majority of the participants were males. Of the 118 cases 77.1% were males and 22.9% were females. Of the 354 controls, 72.06% were males

Table 1: Distribution of cases and controls by their age.

Age group (years)	Frequencies (%)		
	Cases	Controls	Total
18-30	15 (12.7)	46 (13.0)	61 (12.9)
31-40	23 (19.5)	72 (20.3)	95 (20.2)
41-50	23 (19.5)	71 (20.1)	94 (19.9)
51-60	37 (31.4)	104 (29.4)	141 (29.8)
61-70	15 (12.7)	44 (12.4)	59 (12.5)
71-80	5 (4.2)	17 (4.8)	22 (4.7)
Total	118(100)	354(100)	472(100)

Table 2: Characteristics of case and controls

Variables	Category		Total
	Case	Control	
Sex			
Male	91 (77.1%)	258(72.9%)	349(73.9%)
Female	27 (22.9%)	96(27.1%)	123(26.1%)
Total	118 (100%)	354(100%)	472(100%)
Education			
Illiterate	46(38.9%)	101(28.5%)	147(31.1%)
Under-metric	46(38.9%	66(18.6%)	112(23.7%)
Metric	18(15.3%)	94(26.6%)	112(23.7%)
Graduation	8(6.8%)	93(26.3%)	101(21.4%)
Total	118(100%)	354(100%)	472(100%)
Occupation			
Official worker	18(15.3%)	108(30.5%)	126(26.7%)
Non-official worker	69(58.5%)	154(43.5%)	223(47.2%)
Housewife	28(23.7%)	78(66.1%)	106(22.5%)
Student	3(2.5%)	14(11.9%)	17(3.6%)
Total	118(100%)	354(100%)	472(100%)
Socioeconomic status			
Poor	67(56.8%)	86(24.3%)	153(32.4%)
Lower middle class	51(43.2%)	254(71.8%)	305(64.6%)
Upper middle class	0(0%)	13(3.7%)	13(2.8%)
Upper class	0(0%)	1(0.3%)	1(0.2%)
Total	118(100%)	354(100%)	472(100%)

Table 3: Distribution of risk factors among cases and controls.

Variables		Intake	Category		Level of significance of chi square*	Odds ratio	95% confidence interval	
			Case	Control			Lower limit	Upper limit
Pan	Yes	<5 years	17	18	0.000**	**9.755**	5.799	16.409
(Years intake)		>5 years	9	12				
	No		62	324				
Niswar	Yes	<5 years	4	4	0.002**	**3.941**	1.591	9.763
(Years intake)		>5 years	7	5				
	No		107	345				
Gutka	Yes	<5 years	3	0	0.000**	**4.133**	3.520	4.852
(Years intake)		>5 years	2	0				
	No		113	354				
Smoking	Yes	Current	6	83	0.243	**1.291**	0.840	1.983
(Smoking intake)		Ex-Smoker	41	37				
		<5 years	7	24				
		>5 years	40	96				
	No		71	234				
Supari / Chalia	Yes	<5 years	9	5	0.001**	**3.291**	1.556	6.690
(Years intake)		>5 years	6	10				
	No		103	339				
Alcohol	Yes	<5 years	7	3	0.001**	**4.789**	1.667	13.576
(Years intake)		>5 years	2	3				
	No		109	348				
Sunlight exposure	Yes	<4 hrs	52	135	0.001**	**3.810**	1.601	9.065
(Hours / day)		>4 hrs	60	159				
	No		6	60				
Tea / Coffee	Yes	<3 cups	76	219	0.000**	0.724	0.683	0.768
(Daily)		>3 cups	42	93				
	No		0	42				
Family history	Yes		22	29	0.002**	**2.568**	1.411	4.675
	No		96	325				

* Chi-square applied (p-value)
**P<0.05 statistically significant.

and 27.12% females. Majority of cases were either illiterate (38.9%) or under-metric (38.9%). Only 6.8% were graduates. With regards to occupation, 58.4% were non-official workers and 15.3% were official workers, while the remaining were housewives and students (23.7% and 2.5% respectively).

The frequency of 'pan chewing' in cases was 56/118 vs. 30/354 for controls (p<0.05, OR= 9.755, 95% CI 5.7-16.5). Among both genders, 'Niswar chewers' were 11/118 cases vs. 9/354 control subjects (p<0.05, OR= 3.941, 95% CI 1.6-9.8). Of 118 cases only 4.2% had the habit of 'Gutka' consumption but no consumers of 'Gutka' were found among controls (p<0.05, OR= 4.133, 95% CI 3.5-4.9). Among total 118 cases, 15 consumed 'supari/chalia' and out of 354 controls, 15 consumed it (p<0.05, OR= 3.291, 95% CI 1.6-6.7) (Table 3).

Smoking habits showed that 6/118 cases and 83/354 controls were current smokers, whereas

41/118 cases and 37/354 controls were ex-smokers (p>0.05, OR= 1.291, 95% CI 0.8-1.9). Majority of the participants were those who smoked for more than 10 years (85.1% cases and 80% controls). 9/118 cases and 6/354 controls were alcohol consumers, whereas rest of the participants were non-consumers (Table 3).

Sunlight exposure, tea/coffee and family history association is shown in detail in table 4. 46.4% cases had sunlight exposure for less than 4 hours daily and 53.6% cases for more than 4 hours/day (p=0.001, OR 3.810, 95% CI: 1.601-9.065), indicating an approximately 4 times increased odds of exposure/ risk factors among cancer patients. Tea and coffee habit is also highly seen in cases, among all cases 64.41% take less than 3 cups daily and 35.59% of the cases take 3 cups or more of tea/coffee daily which shows highly significant association (p=0.000, OR 0.724, 95% CI: 0.683-0.768).The prevalence of Family history in cases is 18.64% and in control subjects is 8.19% (p=0.002, OR: 2.568, 95% CI: 1.411-4.675), indicating a strong association.(Table 3)

DISCUSSION

The burden of oral squamous Cell Carcinoma (OSCC) is on the rise not only in Pakistan but also in the rest of Asian subcontinent[13]. The International Agency for research on cancers is expecting an Epidemic of Oral cancer by 2030, if this rise in incidence goes unabated. This can be largely attributed to the culturally used risk factors, like pan and tobacco. The present study throws light on the association of pan and its related products, smoking and alcohol in the development of oral cancer.

The unadjusted odds ratio of 'pan' in our study is 9.75 (95% CI=5.799-16.409). A study conducted in Pakistan shows 'pan' with tobacco OR 12.45 and 'pan' without tobacco OR 5.17 with confidence interval ranging from 4.86-31.93 and 2.04-13.11 respectively, which is proximate to our study findings[12]. The reason behind this increased strength of association is that 'pan' is very much culturally backed up in Pakistan and many demographic groups do not consider it a risky habit. The statistically substantial dose response with respect to 'pan chewing' practice in our study proposes that certain variations in 'pan chewing' habits could significantly decrease the risk of developing oral cancer. In another study conducted in Southern India, OR of chewing tobacco is 8.77 with 95% CI 7.56-10.17[14]. Regarding different types of 'pan', in agreement with our results, a systemic review with meta-analysis was done in the South Asian countries which showed the OR (both adjusted and unadjusted) varying from 3.1 to 15.7[15]. The results of all these studies show a great association between the risk factor 'pan' and the development of oral cancer.

According to our study, 'Gutka' consumption had a significant association with oral cancer. Analysis showed that the odds of 'Gutka' consumption was 4 times (p=0.000, OR = 4.133, 95% CI = 3.5-4.9) more in oral cancer cases than controls. Previous studies have found 'Gutka' to be a leading cause in the development of cancer, as 'Gutka' consumers were 5.1 (95% CI: 2.0--10.3; P < 0.001) times more likely to get oral cancer compared to non-consumers[16]. These results are very similar to our findings. 'Gutka' can be highly addictive, than ordinary chewing tobacco[16].

The frequency of development of oral cancers increases with increasing the years of consumption of 'Niswar'. Our analysis showed that the participants who used 'Niswar' had an approximately 4 times greater risk of developing oral cancer (p=0.002, OR=3.941, 95% CI=1.6-9.8). A study carried out in Pakistan, in 2007, indicated that 'Niswar' was the most frequently used form of smokeless tobacco (O.R: 4.203 [2.279–7.751] [17].

The odds of getting oral cancer among cigarette smokers are 1.291 times (95% Cl: 0.81-1.983 P=0.243) higher than those who do not smoke cigarettes. Similar findings were reported in a study conducted in Mahapatra (OR: 1.1, 95%Cl: 0.7-2.0 p=0.659)[16]. There is no significant relationship of oral cancer and the habit of smoking (p>0.05), indicating the increased local custom of smoking habits prevalent in this part of Subcontinent (39.9% in cases vs. 33.9% in controls). Majority of the cases were found to be ex-smokers, as opposed to controls, which had more number of current smokers. Larger proportion of smokers was chronic users (5-20 years or more) highlighting the easy availability and low cost of cigarettes in our society.

There is well established association between oral cancer and the use of alcohol. This habit is a widely accepted cultural practice in West, but in most parts of Southern Asia, this beverage is not much socially and culturally accepted. In our study alcohol was found to be one of the determinants in development of oral cancer in Pakistan (p=0.001, OR=4.789, 95% CI: 1.7-13.6). A similar study shows an OR value of 1 indicating a strong association between the two[14]. The p-value in our study is highly indicative of the association of alcohol with oral cancer, as illustrated by a similar study (OR=4.5)[18].

As for 'supari/chalia', we found out a 3.2% increased risk of developing oral cancer among the users (OR=3.291, 95% CI: 1.556-6.690). Similar results have been shown by a study done on high school students in Karachi (OR:1.5, 95% CI:1.0-2.2)(19). Areca nut without tobacco is assumed of being linked with oral cancer, but studies have not clearly confirmed its independent effect[20].

Our study identified change in the strength of risk involved with known risk factors in our population and this is attributed to the fact that over last one or two decades there is increase in the frequency of known risk factors in our population along with increasing incidence of oral cancer. Although many previous studies have been conducted on this subject globally, but only few have been carried out in this part of the Asian Subcontinent, especially in this metropolitan city Lahore. Current study findings recommend and highlight the high time to address reduction in these risk factors with high odds through sustained, targeted efforts to prevent the on-going increased incidence of oral cancer in Pakistan.

In case-control studies, we cannot exclude the role of recall bias, selection bias and confounding bias but we tried to minimize the selection bias by defining criteria for selection. We matched known confounders in this study to minimize confounding bias.

CONCLUSION

In conclusion, our study shows the current image of major risk factors of oral cancer in Pakistan. It seems that different forms of smokeless tobacco used in Pakistan should be considered as a very strong risk factor. Pan chewing, cigarette smoking, use of gutka, niswar, supari/chalia and alcohol also shows increased association with the oral cancer. Our study also found significant association of sunlight exposure, tea/coffee and family history with oral cancer. Although patterns of these effects are noticeable but these effects are overall weaker than are those of pan and other forms of smokeless tobacco consumption. There is a need to construct an insights obtained from efforts of such similar studies to decrease smoking associated damage and to explore strategies to reduce use of smokeless tobacco and decrease significantly the associated burden of harm.

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