



Risk factors in oral squamous cell carcinoma – highlighting differences between various age groups

KEYWORDS

Oral Cancer, young age, risk factors, tobacco, alcohol, smoking

Abhilash Cherian

Dept of General Surgery Unit-1,
Christian Medical College and
Hospital, Vellore, Tamilnadu-632004

Rajinikanth J

Dept of General Surgery Unit-1,
Christian Medical College and
Hospital, Vellore, Tamilnadu-632004

John C. Muthusami

Dept of General Surgery Unit-1,
Christian Medical College and
Hospital, Vellore, Tamilnadu-632004

ABSTRACT *Aims and Objectives-*

1. To assess the risk factors for squamous cell carcinoma of oral cavity, and find the independent relative risk for each of the risk factors.
2. To highlight the differences in risk factors between young adults and older patients.

Methods and materials:

Hospital based case-control study with 76 cases and 76 age-matched control with structured questionnaire detailing about the habits of tobacco and alcohol. The primary outcome was oral cancer with age as an effect. Pearson's Chi-Squared tests and Likelihood ratios were measured. Multiple logistic regression analysis was performed to account for confounding factors and to effects of multiple risk factors.

Results:

Out of 152 patients, chewing tobacco, combination of tobacco + betel nut and amount consumed/day were significantly associated with oral cancer. Alcohol consumption and smoking were not associated with oral cancer. When all the three habits were combined, chewing and alcohol consumption had a odds ratio of 27.38 to cause oral cancer. 17 pts were aged less than 40 yrs and chewing tobacco was associated with oral cancer in this group. Of these 17 pts, 1 patient did not have any risky habits, but had oral cancer.

Conclusion:

Tobacco Chewing in any form, especially in combination with betel nut or alcohol carried significant risk to cause oral cancer. There was no difference in risk factors in patients who are aged less than 40 years.

Introduction:

In India, head and neck cancer is the most common cause of cancer in India among males and one of the top three cancers overall. Of the various subsites in head and neck region, oral cancer accounts for 80,000 cases annually. Traditionally oral cancer was known as a cancer of the older age groups with predominance in the fifth and sixth decades of life, which was similar to most cancers related to environmental factors. However, of late, there has been a steady increase in incidence among younger age groups. There is growing interest in this topic as this recent trend could reflect change in the traditional risk factors of tobacco and alcohol. Our hypothesis is that the odds of developing oral cancer are different in the young and elderly for the given risk factors of smoking, alcohol and chewable tobacco. Even though tobacco and alcohol are the major risk factors overall, but exposure to these carcinogens in the younger age group would be too short for inducing carcinogenesis, and there may be in fact no risk factors at all associated, especially among females. There is no evidence to support this argument, and there are very few articles published regarding oral cancer in young adults from the Indian subcontinent.

Aims and Objectives-

1. To assess the risk factors for squamous cell carcinoma of oral cavity, and find the independent relative risk for each of the risk factors.
2. To highlight the differences in risk factors between young adults and older patients.
3. Gather clinico-epidemiological data from patients with oral cancer.

Methods and Materials:

We conducted a hospital based case-control study with 76 cases and age-matched controls. All participants in the study were recruited from the surgical outpatient department at our hospital. Informed consent was taken from the patients.

Inclusion criteria –

Cases - Patients of any age and gender presenting to the Surgery outpatient department with newly diagnosed biopsy proven squamous cell carcinoma of the oral cavity– lips, tongue, palate and buccal mucosa. We excluded patients who presented with recurrence and who were diagnosed more than 1 month ago to avoid recall bias. We also excluded non-squamous cell cancers of the oral cavity and premalignant lesions.

Controls - Patients/papaapatient visiting the Surgical OPD for diseases other than oral cancer. Controls were gender matched and age matched within 2 years.

Detailed structured questionnaire

A structured questionnaire detailing about the habits of tobacco and alcohol usage was used in the study. The questionnaire was given to the patients and the controls after obtaining the consent. The questionnaire consisted of the following five sections, namely epidemiological data, socioeconomic details, past medical history, disease specific details for cases, detailed history of habits (smoking, chewable tobacco and alcohol).

Data was entered using Epidata Manager and Epidata Entry.

The primary outcome variable measured in the study was oral cancer. Age was studied as a possible effect modifier

in the study.

Bias: The biases expected in this study are selection bias and exposure bias. This will be addressed by selecting both cases and controls from the same outpatient department and by repeated questioning during the interview respectively. Also our inclusion criteria were patients who were diagnosed oral cancer cases within 1 month of the interview.

Sample size:

Sample size calculated = 112 – 56 cases and 56 controls.

Since we analyzed 3 risk factors (smoking, alcohol, chewing tobacco), an additional 20 patients (10 patients for each additional risk factor) in each arm were enrolled.

Thus, sample size for this study = 152 which was 76 cases and 76 controls

Analysis -

All statistical analysis was done using IBM SPSS Statistics version 19.0. Significance of independent variables was measured by Pearson's Chi-Squared tests and Likelihood ratios were measured. P value of less than 0.05 was considered significant in our analysis. Odds ratios were expressed with their 95% confidence interval.

Multiple logistic regression analysis was performed to account for confounding factors and to effects of multiple risk factors. Stratified analysis was performed to look for effect modifiers in our study.

Results:

A total of 152 patients were recruited for the study (76 cases and 76 controls) over a period of 18 months. In our study 22.4% (n=17) of the cases were young adults less than 40 years of age and 22.4% (Figure 2) were women. Tongue (52%) and buccal mucosa (46%) were the most common sites of cancer in our study. There was no difference in oral cancer site with respect to participants less than 40 years of age and participants more than 40 years of age. Approximately 55% of them were moderately differentiated and 22% well differentiated cancers. Seventeen percent of the cases had a premalignant lesion prior to developing a lesion/ulcer.

SYMPTOMS OF ORAL CANCER

All patients (n=76) presented with an ulcer or a lesion. Pain was the second most common symptom followed by difficulty in chewing, trismus, difficulty in speech, swallowing and bleeding. Only 7% of the patients presented within 1 month of symptoms. Majority of our patients presented between 1-3 months of onset of symptoms. More than 20% of patients presented 6 months after onset of symptoms. The patients that presented with symptoms of more than a year had recurrent ulcers or long-standing ulcers, which were inadequately treated.

HABITS OF CHEWING TOBACCO/BETEL NUT

68% of the cases chewed tobacco or betel nut or both. Only 14.4% of the controls had chewing habit and was statistically significant. (Chi-squared value = 45.57, p value<0.01). Crude odds ratio of was 12.54(95% CI – 5.74, 29.03). There was no statistically significant difference between chewing habits between men and women.

Mean daily consumption of tobacco was 6.7 quids with median of 5.00. There was a significant relation between

the amount of tobacco consumed per day to oral cancer (Table 1). Cumulative lifetime consumption of quid was calculated by multiplying the daily number of quids to the number of years of chewing. We found that the controls were exposed to significantly fewer quids in their lifetime compared to controls. Binary logistic regression analysis revealed a significant odds ratio (Table 1).

Table 1. ODDS RATIO FOR DIFFERENT CATEGORIES OF CHEWING

	Controls	Cases	Odds Ratio	95% C.I.
DURATION OF CHEWING IN YEARS				
Less than 20 years	5	20	9.74	3.19-29.79
20 years or more.	6	32	14.16	5.21-38.49
DAILY NUMBER OF QUIDS				
4 or less quids per day	9	15	4.48	1.7-11.76
5 or more quids per day	2	37	47.72	10.48-217.18
CUMMULATIVE CON-SUMPTION IN QUIDS				
Less than 30000 in lifetime	9	20	5.76	2.26-14.65
More than 30000 in life time	2	32	41.25	9.04-188.22
Odds ratios adjusted for age, gender, socioeconomic status				
Reference category- Never chewers				

Most of the patients consumed paan, dipping tobacco and gutkha which contained both tobacco and betel nut. Both tobacco and betel nut chewing was a significant risk factor for oral cancer.

Table 2. ODDS RATIO FOR DIFFERENT COMBINATIONS OF TOBACCO AND BETEL NUT

	Con-trols	Cas-es	Odds Ratio	95% C.I.
Betel nut and to-bacco	5	28	13.87	4.7-40.99
Tobacco only	4	13	8.904	2.55-31.09
Betel nut only	2	11	14.34	2.93-70.15
Odds ratios adjusted for age, gender, socioeconomic status				
REFERENCE CATEGORY- NEVER CHEWERS				

Only 8 percent of the participants were aware that chewing tobacco and betel nut formulation could cause oral cancer.

ALCOHOL AND ORAL CANCER

There was no significant difference between cases(34%) and controls(23%) with respect to consumption of alcohol. Most of the participants preferred hard liquor (63%). Others consumed country liquor or beer. There was no significant difference between cases and controls with respect to type of alcohol preferred.

Most participants recruited, as cases were either current drinkers or stopped drinking after onset of symptoms. Awareness among cases prior to onset of symptoms was poor. Only 1 out of 26 cases who consumed alcohol was aware that drinking alcohol could predispose to oral cancer.

Monthly intake of alcohol was calculated from daily amount of absolute alcohol and frequency of alcohol in-

take. Different types of alcohol were factored in our calculation. Hard spirits was assumed to have 40% alcohol, country liquor and beer to be 10% and 5% respectively. Twenty seven percent of patient consumed than 500 ml of alcohol per month. Twenty percent consumed between 200 and 500 ml of alcohol per month. However there was no significant difference between the study categories with respect to amount of alcohol consumed.

Only duration of alcohol was found to be a statistically significant risk factor for oral cancer. Further analysis by binary logistic regression with adjustment for age, gender, BMI and socioeconomic score odds for duration of alcohol intake more than 15 years was 2.94 (95%CI 1.05-8.18).

SMOKING AND ORAL CANCER

21% of the controls were smokers whereas 32.8% of the cases smoked some form of tobacco (p value=0.100). Therefore, smoking was not a significant risk factor for oral cancer in our study.

68% of the patients among smokers consumed cigarettes (filtered/non filtered) and 32% of the study participants smoked beedi. Other forms of smoking like pipe smoking were not present in our study population. There was no significant difference between the type of smoking (cigarette vs. beedi) between cases and controls.

Ever smokers were further classified based on current status of smoking. 44% of the study participants were current smokers. Over 50 % (13/25) of the smokers among cases had quit smoking after onset of symptoms. Eight out of 25 smokers in the case category had stopped smoking more than 1 year prior to being diagnosed with oral cancer.

Smoking has been traditionally measured in pack years. Mean among cases was 8.1 pack years and among controls was 12.46 pack years. For analysis, we divided the study participants based on pack years as – upto 10 pack years and more than 10 pack years. Compared to controls, there were a higher proportion of participants smoking more than 10 pack years in the cases, which was not significant (P value =0.272)

Adjusted odds ratios were calculated for smokers based on pack years and daily tobacco dose in view of finding a dose response relationship between smoking and oral cancer by logistic regression analysis.

With respect to pack years of smoking, people who smoked upto 10 pack years had 3 times odds of oral cancer compared to never smokers. Smoking more than ten pack years increased the odds of producing oral cancer to 6.3, which was statistically significant. Daily tobacco dose of more than 10 grams predisposed to 5 times more risk of oral cancer compared to never smokers. Smoking less than 10 grams was not associated with increased risk of oral cancer.

Forty three percent of the patients were aware that smoking can cause oral cancer. There was no significant difference between cases and controls.

Odds ratio for multiple risk factors:

Multiple logistic regression analysis was used to calculate odds ratios for various combinations of habits. Combination of smoking, chewing and alcohol consumption was 9.8 times more likely to cause oral cancer than a person who does not have any of these habits. Smoking and alcohol

together had 7 times more odds whereas chewing with alcohol gave an odds ratio of 27.47 while chewing and smoking had 28 times more odds of producing oral cancer in our study.

SUBGROUP ANALYSIS (young age Vs old age pts)

In our study, even though there were more smokers among the cases, smoking was not a significant risk factor for oral cancer in young adults. Twenty three percent of the controls and 35% of the cases smoked some form of tobacco in our study (Pearson's Chi-Squared test = 0.567, p value =0.452). In the older age group, 20% of controls and 32% of cases were smokers. However this difference was also not significant (Pearson's Chi-Squared test = 2.144, p value =0.143).

There was no difference between cases and controls with respect to alcohol consumption among young adults (Pearson's Chi-Squared test = 2.861, p value =0.09). In the older age group 18.6% of the controls consumed alcohol whereas 32.2% consumed alcohol among cases.

There was significantly more number of cases with chewing habit among young adults. (Chi-Squared=17.00, p value=0.00). Odds ratio for chewing causing cancer in this group was 34.49 (95%CI | 5.071-241.559). However the small numbers for analysis resulted in wide confidence intervals. In older age group, among controls only 15% chewed tobacco or betel nut, whereas in cases 35.5% were chewers. This was statistically significant. (Chi-Squared=29.90, p value=0.00). Odds ratio for chewing habit causing oral cancer in this group was 10.05 (95% CI 4.14-24.42).

ORAL CANCER AND FREQUENCY OF RISK FACTORS

In our study 17% of the subjects with oral cancer did not have any of the traditional risk factors of smoking, chewing or alcohol. Out of these 17 % (13 cases) four males and one female had history of sharp tooth for which medical attention was sought (6.5%). Eight cases did not have any risk factor(10.5%). Among women 29% did not have any risk factor, and among males 5% did not have any risk factors in all age groups. This result was significant. (Chi square test = 8.29 p <0.05). Among the 17 cases under the age of 40 only one subject did not have any risk factor (5.8%). Whereas among the 59 cases above the age of 40 years males without risk factors were 4.6% and women without risk factors were 30%. There was no difference noted between age groups.

DISCUSSION

This study analyzes the clinical, epidemiological, and risk factor profile for patients diagnosed to have oral cancer with emphasis on age. Additionally, we focused on deriving dose-response relationships for the risk-habits and have done a literature review.

Mean age of patients in our study was 49.6 years, which was quite similar to other published studies(1). In our study 78% of the cases were males and 22% were females (Fig 1), with a ratio of 3.5:1. Data from NCBI show that oral cancer is 2-4 times commoner in males than females (2).

Tongue cancer was more common in our study(52%), as compared to available literature even though majority of our cases chewed some form of tobacco (3).The data from our study did not yield any statistical difference between age groups (less than 40 years of age and more than 40 years of age) or gender with respect to site of oral cancer

as opposed to available literature. Tongue was the most common site of cancer in all age groups closely followed by cancer of the buccal mucosa. Most recent studies have reported increase in proportion of tongue cancer in the younger age groups especially in young women. Park et al, Liao et al and Iype et al reported tongue cancer in 27%, 25.8% and 52% patients respectively in young adults. (4,5,6).

Eighty three percent of the cases were related to tobacco and alcohol in our study. From our data there is compelling evidence corroborating available literature, which suggests that chewing habit is the strongest risk factor for oral cancer with a significant dose response relationship. In our study, OR for oral cancer for chewing habit was 12.54(95% CI – 5.74, 29.03). Genderwise, OR for females was 13.75 (95 % CI, 2.32 to 81.48), for males it was 12.65(95% CI 5.14-31.13). Most of the current literature focused on males and only few have looked at women separately. A higher odds ratio in women for chewing was probably due to less smoking and drinking among women.

Emergence of chewing habit as the strongest risk factor for oral cancer is probably due to the longer duration of contact with the oral mucosa while chewing as compared to smoking. Moreover all six participants who practiced keeping the quid overnight had oral cancer. Although there is enough evidence to suggest that arecanol increasing the risk of oral cancer most studies have reported lower odds ratio for chewing betel nut as compared to chewing tobacco, our data provides convincing evidence that (10,62) chewing betel nut without tobacco is equally harmful. In our study, more than 50% of cases were from Eastern India were betel nut chewing is widespread. Even though betel nut chewing is an accepted independent risk factor for oral cancer, exact pathogenesis has not been established.

In our study there was no significant relationship between alcohol consumption, type of alcohol, total monthly alcohol and oral cancer. Although most of available evidence seems to suggest that ever- alcohol consumption is a risk factor for oral malignancy our results our data has failed to demonstrate the same. It may be argued that though alcohol is a proven carcinogen in head and neck cancers its role in oral cancer is to a lesser degree. This argument is supported by the meta-analysis by Petti et al.(7) However, total duration of alcohol intake (in years) was found to be an associated with oral cancer (p value = 0.04). Drinking habit for more than 15 years had odds ratio 2.94 (95%CI 1.05-8.18).

Smoking tobacco, type of tobacco, pack years of smoking were not statistically associated, though there were a higher proportion of smokers among cases. Multivariate analysis showed a statistically significant risk for heavy smoking and oral cancer. Odds ratio of developing cancer for more than 10 pack years was 6.37(95% CI 1.166-34.79) and for smoking more than 10 grams of tobacco per day was 4.85. (95% CI 1.01-29.90). Thus we conclude that heavy tobacco smoking is a risk factor for oral cancer.

We got significant odds ratios for all combination of smoking, chewing and alcohol consumption (p value <0.05). Odds of getting oral cancer if one is exposed to all three habits were 9.831(95% CI 1.763-54.817). Lowest risk was seen among the combinations for smoking and alcohol-odds ratio of 7.19(95% CI 1.49-34.686). Highest odds of producing cancer were for ones who had a combination of smoking and chewing habit- Odds ratio 28.014(95% CI

3.151-249.036). Based on our data and available literature there is enough compelling evidence that combination of risk factors result in multiplicative effect on oral cancer risk.

We also compared young adults with older adults by stratified analysis. Available literature suggests that the frequency of traditional etiological factors is lower in young adults and much of the current debate in literature has revolved around this. Our data indicates that in young adults less than 40 years of age alcohol was not a risk factor for oral cancer. Both cases and controls in young adults had similar drinking habits. Although among older patients consumed more alcohol this difference was not statistically significant (Chi-Squared test = 2.861, p value =0.09). We did not look for dose response relationships for this subgroup analysis because larger sample size would be needed to make meaningful conclusions. Similar results were obtained for smoking. Though the difference was not statistically significant both alcohol consumption and smoking was higher among cases in the older age group as compared to young adults. Chewing tobacco was a significant risk factor for oral cancer in both young and older adults. Among young adults 80 percent chewed tobacco or betel nut as compared to 33% in older patients. This data was statistically significant. Odds ratio for chewing in young adults was 34 compared to odds ratio of 10 in older patients. With the current evidence we could not explain why young chewers were more susceptible to oral cancer.

Limitations of the study-

1. Our participants were selected from the surgical outpatient department. Patients advanced oral cancer/inoperable oral malignancy may not have been represented adequately in our study if they were treated with primary radiotherapy.
2. Most of the participants were hesitant to reveal addictions and habits at the interview. This could have resulted in probable recall bias and underestimated the use of tobacco and alcohol even though we tried to minimize this with repeated interviewing and adequate rapport with the participants.
3. Possible confounding factors like diet, poor dentition, oral hygiene and sexual habits were not accounted for in our study.
4. Our study population represents only the patients who visited a tertiary care hospital. Like every hospital based study our sample population may not have represented the population of the community.
5. Larger series would be required for detailed stratified analysis across age groups.

Conclusion-

This study extends the available literature and evidence for better understanding of oral cancer and its risk factors. Even though our study had multiple limitations, we can confidently conclude that chewing habit, heavy smoking over ten pack years, alcohol intake for over fifteen years carry increased risk of oral cancer. Combination of smoking, alcohol and chewing has a multiplicative effect on risk of oral cancer. We did not find a significant difference between young and older subjects with respect to etiology or site of oral cancer.

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