RESEARCH COMMUNICATION

Reassessment of Risk Factors for Oral Cancer

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Abstract

A total of 140 cases of histologically confirmed oral cancer were evaluated for their demographic details, dietary habits and addiction to tobacco and alcohol using a pre-designed structured questionnaire at the Mahatma Gandhi Institute of Medical Sciences, Sevagram, in Central India. These cases were matched with three sets of age and sex matched controls. Oral cancer was predominant in the age group of 50-59 years. Individuals on a non-vegetarian diet appeared to be at greater risk of developing oral cancer. Cases were habituated to consuming hot beverages more frequently and milk less frequently than controls. Consumption of ghutka, a granular form of chewable tobacco and areca nut, was significantly associated with oral cancer cases. Cases had been using oral tobacco for longer duration than controls, and were habituated to sleeping with tobacco quid in their mouth. Most cases were also addicted to smoking tobacco and alcohol consumption. Bidi (a crude cigarette) smoking was most commonly associated with oral cancer. On stratified analysis, a combination of regular smoking and oral tobacco use, as well as a combination of regular alcohol intake and oral tobacco use were significantly associated with oral cancer cases. Synergistic effects of all three or even two of the risk factors - oral tobacco use, smoking and alcohol consumption- was more commonly seen in cases when compared to controls.

Key Words: Oral cancer - epidemiology - oral tobacco - smoking - risk factors

Introduction

Cancers of the oral cavity accounted for over 274,000 cases in 2002 and were the cause of death in over 127,000 cases (Parkin et al, 2002). In India, cancer of the oral cavity is one of the five leading sites of cancer in either sex. It is estimated that 75,000-80,000 new oral cancer cases develop in India annually. Only 15% of patients are diagnosed when the disease is in a localized stage (Gupta and Nandakumar, 1999).

Over 90% of oral cancer among men in India could be attributed to tobacco (WHO, 1997). Tobacco is smoked, chewed, sucked or applied to gums in diverse ways (Bhonsle et al, 1992). Chewing of betel-quid with tobacco is widespread and a dose response relationship has been established as measured with duration of chewing, frequency of chewing and period of time chewed (Sankaranarayanan et al, 1989).Smoking of cigarettes or bidi (a crude cigarette with about 0.2 gm coarsely ground tobacco wrapped in a specific tree leaf) have also been shown to be risk factors (Bhonsle et al, 1992).

However, the emergence of newer, chewable flavoured tobacco preparations, called ghutka, which are packaged attractively and easily available in the market has changed the scenario and their role in oral cancer needs to be assessed. The present study was carried out to ascertain the newer epidemiological risk factors involved in causation of oral cancer and to emphasize the role of each risk factor individually. The study also seeks to determine the statistical association and synergistic effect of various known risk factors like oral tobacco use, smoking and alcohol consumption.

Materials and Methods

This hospital based study was carried out in 2001-2002 in the Department of Pathology, Mahatma Gandhi Institute of Medical Sciences (MGIMS), Sevagram. The study area mainly comprised of Wardha and adjoining districts, in the state of Maharashtra in central India, where majority of the population is rural.

Epidemiological evaluation of 140 adult cases with histologically confirmed oral cancer (ICD- OC02 to ICD-OC 069) was carried out. The anatomical sites included in this study were: buccal mucosa, alveolus and gingival, palate, tongue (excluding base of tongue) and floor of mouth. Patients with carcinoma of the lip, tumours of the salivary gland and sarcomas were excluded from this study.

These 140 cases of oral cancer were age and sex matched with three sets of controls: Control Group 1: 140 'healthy' subjects i.e. persons with no apparent clinical disease. These subjects were recruited from visitors to the hospital, blood donors and people outside the hospital

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area.Control Group 2: 140 subjects who were diagnosed with cancers other than oral cancers. These controls were taken from patients admitted in various wards of the hospital. Control Group 3: 100 subjects who were habituated to tobacco consumption in any form were recruited. These subjects were visitors to the hospital and subjects from outside the hospital.

All the cases and controls were interviewed in depth according to a pre-designed structured questionnaire. Complete demographic details were obtained. The oral cavity was thoroughly examined in good illumination for the carcinoma site in cases and for any other possible pathological lesion in all the three sets of controls. Tobacco chewers in all groups were specifically asked about the site of placing tobacco or betel quid in their mouth.

Detailed information was obtained about dietary habits and tobacco use according to the questionnaire format (Table 1). All data was compiled, quality checks were carried out for consistency of information, and analysis was done using EPI Info 6 software

Table 1. Questionnaire used to obtain Dietary and Addiction Information

A. Dietary Habits:
1. Food:
   1. Vegetarian   2. Non-Vegetarian
If non-vegetarian, how frequently do you take non-vegetarian food:
   1. Regular   2. Occasional
Staple food: 1. Rice   2. Wheat   3. Coarse Grains
2. Seasonings frequently used:
   1. Green chillies   2. Red chillies   3. Pepper
   4. Garlic   5. Onion   6. Ginger
   7. Cloves   8. Tamarind
3. Nature of cooking utensils.
   1. Iron   2. Aluminium   3. Copper
   4. Brass   5. Copper-zinc coated 6.Zinc
4. Do you take milk?
   1. Daily   2. Occasionally 3. No.
5. Do you take hot beverages? :
   1. Tea   2. Coffee

B. Addictions/Habits:
6.Do you use tobacco:
   1. Yes   2. Occasionally 3.No
7. Type of tobacco:
   1. Mainpuri   2. Pattiwala   3. Ghutka
   4. Kharra   5. Pan Parag   6. Zarda
8. Age at which started chewing tobacco:………years.
9. Quantity daily consumed: …packets.
10. Do you sleep with tobacco quid in mouth:
   1. Yes   2.No.
11.Do you smoke:
   1. Yes   2. Occasionally 3. No.
12. Type:
   1. Bidi   2. Cigarette   3. Hukkah
   4. Cigar   5. Chilum
13. Age at which started smoking:………years.
14. Do you drink alcohol:
   1. Regularly   2. Occasionally 3. No.
15.Do you use:
   1. Pan   2. Betel Nut   3. Lime
16.Do you use:
   1. Opium   2. Ganja   3. Bhang
   4. Charas

Results

Most cases of oral cancer (77.1%) as well as control groups belonged to rural areas. Maximum cases (30.7%) were present in the age group of 50-59 years (Table 2). Males were twice as commonly affected by oral malignancies than females in the ratio of 2.1:1. The most common site of occurrence of oral cancer was the cheek mucosa (34.28%), followed by floor of mouth (17.85%) and gums (11.42%)

On analysis, the consumption of non vegetarian food was found to be significantly higher in oral cancer cases compared to controls (p value = 0.03 between cases and control group 1, p value = 0.00004 between cases & control group 2, p value = 0.0000 between cases and control group 3). It was observed that though regular milk consumption was not frequent in all the categories, oral cancer cases had least frequent (4.3%) habit of milk consumption. This was found to be statistically significant (p value < 0.04).

All subjects of the study group consumed hot beverages regularly, with tea drinkers being the most predominant (99.6%). Oral carcinoma cases were habituated to consuming hot beverages more frequently (more than 4 times a day) than the controls and the difference was found to be highly significant (p value < 0.002)

It was observed that cases and control group 3 (these were selected for their habit of tobacco consumption) regularly used oral tobacco (Table 3). Ghutka chewing was more common (74.3%) in cases than controls. Ghutka is a generic name for a product which contains tobacco, areca nut and several other substances in a powdered or granulated form. It is sold in commercially prepared attractively coloured sachets. It is generally chewed, sucked and spat out or sometimes swallowed.

It was observed that most cases had been using oral

Table 2. Age Distribution of Cases with Oral Cancer

Age group	No. of cases	Percentage
0-29	05	3.6%
30-39	06	4.3%
40-49	28	20.0%
50-59	43	30.7%
60-69	39	27.9%
> 70	19	13.6%
Total	140	100%

Table 3. Correlation of Study Group with Oral Tobacco Use

Category	Regular user	Occasional user	No habit	Total
Cases	136 (97.1%)	4 (2.9%)	0 (0.0%)	140 (100%)
Control 1	18 (12.9%)	26 (18.6%)	96 (68.6%)	140 (100%)
Control 2	0 (0.0%)	24 (17.1%)	116 (82.9%)	140 (100%)
Control 3	95 (95.0%)	5 (5.0%)	0 (0.0%)	100 (100%)
Total	249 (47.9%)	59 (11.3%)	212 (40.8%)	520 (100%)

Table 4. Criteria for Division into Groups

Group A: Occasional or no use of any one of the risk factors
  i.e. oral tobacco use, smoking, alcohol intake.
Group B: Regular use of one of the risk factors. It includes
  the following 3 subgroups:
  1) a) Occasional or no oral tobacco use.
      b) Occasional or no habit of smoking.
      c) Regular habit of alcohol intake.
  2) a) Occasional or no oral tobacco use.
      b) Regular habit of smoking.
      c) Occasional or no habit of alcohol intake.
  3) a) Regular habit of oral tobacco use.
      b) Occasional or no habit of smoking.
      c) Occasional or no habit of alcohol intake.
Group C: Regular use of two out of three risk factors. It
  includes the following three subgroups:
  1) a) Regular habit of oral tobacco use.
      b) Regular habit of smoking.
      c) Occasional or no habit of alcohol intake.
  2) a) Regular habit of oral tobacco use.
      b) Occasional or no habit of smoking.
      c) Regular habit of alcohol intake.
  3) a) Occasional or no habit of oral tobacco use.
      b) Regular habit of smoking.
      c) Regular of habit of alcohol intake.
Group D: Regular use of all the risk factors i.e. oral tobacco
  use, habit of smoking and alcohol intake.

Table 5. Synergistic Effects of Oral Tobacco Use, Smoking and Alcohol Intake

Category	Group A	Group B	Group C	Group D	Total
Cases	01 (0.7%)	51 (36.4%)	49 (35.0%)	39 (27.8%)	140
Control 1	80 (57.1%)	51 (36.4%)	09 (6.4%)	0 (0.0%)	140
Control 2	120 (85.7%)	19 (13.6%)	1 (0.7%)	0 (0.0%)	140
Control 3	2 (1.41%)	75 (53.6%)	22 (15.7%)	01 (0.71%)	100
Total	203 (39.0%)	196 (37.7%)	81 (15.6%)	40 (7.69%)	520

and oral tobacco use, showed that regular alcohol intake and regular oral tobacco use was the commonest combination in patients with oral cancers. In control groups 1 and 2 the commonest combination was regular alcohol intake and no oral tobacco use. In control group 3 commonest combination was regular tobacco use and no habit of alcohol intake. Highly significant difference was seen between cases and control groups 1 & 2 (p value = 0.0000).

To study the synergistic effect of important risk factors in oral cancer, all the subjects of the study were divided into 4 groups (Table 4). It was observed that regular use of all the three risk factors was significantly seen in patients of oral cancer. Even regular use of two risk factors was associated with increased risk of developing oral cancer (Table 5). The synergistic effect of risk factors was highly significant.

Discussion

Oral cancer is the fifth most common cancer worldwide (Parkin et al, 1993). The age standardized rates per 100,000 population in India were estimated to be 12.8 in men and 7.5 in women. An increase in the incidence of mouth cancer was reported among those aged less than 50 years (Gupta, 1999). This is consistent with the hypothesis of an increase in oral cancer among young people due to increased consumption of the alternative chewing products like ghutka and pan masala. The consumption of these newer forms of flavoured oral tobacco has widespread social sanction, and hence in this study, we have tried to refocus on the role of all tobacco products which are available in market and their association with oral cancer.

Most of the cases and control subjects were from rural areas. The present study has a rural bias since Wardha district has a predominantly rural population. This may also indicate that the urban lifestyle influences may not play a major role in the causation of oral cancers.

The disease was predominantly seen in middle aged persons (50-59 years) and was common in males (67.5%). Other studies from India (Padmavathy and Reddy, 1960; Gandagule and Agarwal, 1969) have reported highest incidence in the fourth and fifth decades. A comparison of age specific incidence rates during 1983-87 and 1995 in Ahmedabad, India, shows that the incidence has

tobacco for 20 - 49 years. Controls in group 3 were also regular tobacco users, but had been using oral tobacco for 1-29 years. This difference was found to be highly statistically significant between the cases and control group 2 and was also significant with the other control groups. It was observed that a very high number of cases (42.9%) had the habit of keeping quid in mouth and falling asleep as compared to control groups and this finding was found to be highly statistically significant (Odds Ratio = 18 (CI 5.88 < OR < 61.65)).

Most of the cases (62.9%) were regular smokers, whereas more than 50% of controls in all groups did not smoke. Bidi smoking was most common in cases and control groups 1 and 2, whereas cigarette smoking was commonly seen in control group 3.

It was observed that alcohol intake, whether occasional (22.1%) or regular (30.0%), was more common in cases as compared to all the controls.

Further analysis was done to observe the effects of multiple risk factors. On stratified analysis between the habit of smoking and oral tobacco use, it was observed that regular smoking and regular oral tobacco use was the commonest combination in patients with oral carcinoma; whereas in control group 1, the commonest combination was regular smoking with no oral tobacco use. In control group 2, the commonest combination was occasional smoking without oral tobacco use; whereas in control 3, the commonest combination was non smoker with oral tobacco use. The difference was highly significant in all subgroups between cases and control groups 1 and 2. On comparing cases and control group 3, no statistical significance was found in non smokers, whereas in regular, occasional smokers, the difference was minimally significant with p value = 0.21 and 0.30 respectively.

Stratified analysis between the habit of alcohol intake

significantly increased in the younger population (Gupta, 1999). We found a significant number of cases of oral cancer presenting at younger ages. Since oral cancer is a disease related to environmental influences, early exposure to these influences may lead to development of malignancy at an early age. The fact that a large incidence of oral cancer is being observed in younger age groups, it is definitely a matter of great concern as it stems from increasing use of tobacco by adolescents, youth and women.

The high incidence of oral cancers in males in this study and those of other authors (Padmavathy and Reddy, 1960; Gandagule and Agarwal, 1969) can be attributed to high prevalence of tobacco chewing, smoking and alcohol intake in them. However, a large number of women (30.7%) in our study were housewives who were accustomed to oral tobacco use.

The commonest site of occurrence of oral cancer in the present study was cheek mucosa, (34.28%) followed by floor of mouth (17.85%). In countries such as Australia, the USA, Denmark, tongue is the commonest site of oral cancer (Pinholt et al 1997, Hibbert et al 1983, Oliver et al, 1996). However, the buccal mucosa is the commonest site of oral squamous cell carcinoma in countries where the use of oral tobacco is more common such as India, Malaysia and New Guinea (Ng et al 1985, Thomas and MacLennan, 1992). This is probably due to the fact that location of cancer in oral cavity has direct bearing by the type of tobacco use, the majority of the lesions corresponding with the site of maximum exposure to betel quid and also to other related habits.

This study showed a significant association between oral cancer cases and non vegetarian food. In a hospital based case control study done in China, Zheng et al (1993) found that dietary fibre derived from food and vegetables had a strong negative association with risk of oral cancer. They also observed that dietary fibre had protective effect on both leukoplakia and oral submucous fibrosis. Analysis obtained from three simultaneous case control studies conducted in the USA, Italy, China (MacFarlane et al, 1995) has observed that high consumption of vitamin C and dietary fibre leads to lower risk.

While non-vegetarians appeared to be at greater risk than vegetarians in developing oral cancer, other factors like staple food and seasonings were not significantly associated with cancer. Macfarlane et al (1995) did not observe any consistent effect of levels of intake of micronutrients, fats, proteins and carbohydrates on risk of developing oral cancer. However, Nandakumar et al (1990) observed that there was markedly elevated risk of oral cancers in persons who consumed ragi as a staple cereal in their diet. As this particular cereal is not used in diets of the local resident population of Wardha district, we did not observe any association of staple food with oral cancer.

Regular milk consumption was not frequent in all the categories of study group. However, the cases of oral cancer consumed milk least frequently and this was statistically significant. Findings of our study are similar to Levi et al (1998) who showed that milk has some protective effect in development of oral cancer.

Most of the subjects in the present study were habituated to hot beverage consumption, especially to drinking tea (99.6%). We observed that oral carcinoma cases were habituated to consuming hot beverages more frequently than the controls. Chutta is a kind of cigar often smoked in a reverse pattern, where the burning end is placed inside the mouth. This pattern of smoking, seen in certain coastal districts of Andhra Pradesh (India), is commonly associated with squamous cell carcinoma of palate and dorsum of tongue. This is because the mucosa is exposed to pyrolyzed tobacco products and intense heat. It has been shown that heat functions as co-carcinogen and accelerates the neoplastic process (Daftary et al, 1992). Although there are no studies in available literature which have observed the association of hot beverages in oral cancer, a similar mechanism maybe responsible for statistically significant association of oral cancer with frequent intake of hot beverages observed in our study.

We observed highly significant association of oral tobacco use with oral cancer when cases were compared with controls from groups 1 and 2. However, the difference was not of statistically significant when cases were compared with control group 3, as these subjects were selected because of their habit of tobacco consumption. Padmavathy and Reddy (1960) observed that the habit of chewing tobacco alone or with betel was seen more commonly in oral cancer cases when compared to controls. Samuel et al (1969), Gandagule and Agarwal (1969), Nandakumar et al (1990), Ko et al (1995), Wasnik et al (1998), Hayes et al (1999) and Dikshit and Kanhere (2000) demonstrated the association of oral tobacco use with carcinoma of oral cavity. However, the absence of a statistically significant difference between controls and cancer patients having history of regular use of tobacco indicates that there are additional factors which may also be involved in the development of oral cancers.

We observed that consumption of ghutka was significantly high in cases of oral cancer when compared with control groups 2 and 3. The findings of our study are significant as ghutka, which is a preparation without betel quid, is significantly associated with malignancy when compared to other forms which are consumed along with betel quid. This is probably due to the fact that the betel leaf (paan) contains compounds such as eugenol, and hydroxychavicol. These compounds are probably anti-mutagenic or anti-carcinogenic (Amonkar et al, 1986; Padma et al, 1989). The findings of our study do substantiate earlier observations regarding partial protection given by paan which may negate the carcinogenic effects of areca nut, tobacco and lime mixture.

Oral cancer cases were found to have been using oral tobacco for longer duration than the controls in this study. Gandagule and Agarwal (1969) and Nandakumar et al (1990) also observed a statistically significant dose response based on duration of tobacco consumption. Muscat et al (1996) observed that cumulative life time measure of exposure to cigarette is associated with linear increase in the risk of oral cancer. We also found that history of sleeping with tobacco quid in the mouth was a highly significant risk factor in development of oral cancer.

We observed that most cases (62.9%) of oral cancer were regular smokers, whereas more than 50% of controls did not smoke. The difference between cases and controls was highly significant. Padmavathy and Reddy (1960) observed that smoking was seen in highly significant number of cases than controls. Graham et al (1977) observed high risk of developing oral cancer associated with heavy smoking. Nandakumar et al (1990) found only slightly elevated risk of developing oral cancer with smoking. MacFarlane et al (1995) observed high risk for smokers having smoked more than 33 pack years as compared to smokers having smoked less than 33 pack years.

We observed that bidi smoking was more common in patients of oral cancer and control groups 1 and 2; whereas cigarette smoking was more common in control group 3. The statistical difference was found to be highly significant on comparison between control groups 2 and 3. Rao and Desai (1998) observed that bidi smoking was a significant risk factor for cancer from the base of tongue, whereas tobacco chewing was risk factor for cancer from anterior portion of tongue. Bidis are the most popular form of tobacco consumption, accounting for 34% of tobacco produced in India (Lee, 1975). The mainstream smoke of bidi contains much higher concentration of toxic agents as compared to cigarettes. Thus smoking bidi is even more hazardous than cigarette smoking in the development of tongue and oral cancer (Jayant and Pakhale, 1985). The findings of our study also corroborate the increased risk associated with bidi smoking when compared with cigarette smoking. Control group 3 subjects who were regular oral tobacco users used cigarettes more frequently than bidis.

Alcohol intake, whether occasional (22.1%) or regular (30%), was more common in cases when compared to controls in this study and this difference was found to be highly significant. Padmavathy and Reddy (1960) and Graham et al (1977) observed that alcohol has a role in development of oral cancer.

We found that the combination of regular smoking and regular oral tobacco use was a significant risk factor on comparing cases with control groups 1 and 2. However, there was no statistically significant association on comparison with control group 3. No studies in available literature have performed stratified analysis in relation to smoking and use of oral tobacco in comparison with the controls who are regular tobacco users. Our findings indicate that though this association is significant in comparison with groups who may be regular oral tobacco users or non users (control groups 1 & 2), it is not a statistically significant association in comparison with the group having regular or occasional oral tobacco users (control group 3). Therefore the habit of smoking may not have significant association with oral cancer.

Another factor which may be more important than this combination of habits is our observation that controls had been using oral tobacco for a lesser duration than cases. So, the duration of oral tobacco use is perhaps more important than the association of oral tobacco use with smoking.

On stratified analysis, we found that regular alcohol intake with regular oral tobacco use caused significant risk to cases compared to all the control groups. According to Sankaranarayanan et al (1990), although alcohol consumption alone is not independently associated with oral cancer, it did seem to enhance the risk of developing disease when used in combination with tobacco chewing and cigarettes smoking. The findings of our study have also shown that in patients of oral cancer, all non-alcoholics were regular oral tobacco users. Similarly it was also observed that none of the cases were non-tobacco users but regular alcoholics. This indicates that alcoholism itself may not be an independent risk factor in the development of oral cancer, but may enhance the risk of developing disease.

To study the synergistic effect of important risk factors i.e. oral tobacco use, smoking and alcohol consumption in development of oral cancer, we divided the study subjects into four subgroups based on regular, occasional or no use of the risk factors. It was observed that regular use of all the three risk factors was significantly seen in oral cancer cases and even regular use of two risk factors was common in cases as compared to controls. Similar observations were made by Sankarnarayanan et al (1990), Ko et al (1995) and Hayes et al (1999). Our findings indicate that the combination and regular use of important risk factors shows a significant synergistic effect on development of oral malignancy.

In last few decades, small, attractively packed commercial preparations of tobacco and non-tobacco betel quid substitutes have become widely available. These are being aggressively marketed by the concerned companies, often claiming to be safer products. These are being consumed widely by people of all ages and sexes as well from all social strata of society. Hence the consequences of these habits are expected to be significant and intense in the future. Although recently some attempts have been made to curb the sale of these products, urgent action is needed to permanently ban these products

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