INTRODUCTION

Oral cancer is one of the most common cancers in the world and shows marked geographic differences in occurrence. Oral cancer affects as many as 274,000 people worldwide annually, and its frequency around the world is often indicative of the patterns of use of tobacco products. It has been established that there is a dose–response relationship between the amount of tobacco product used and the development of oral cancer. Thus it is a common cancer in Southeast Asia, where more than 100,000 new cases are reported every year. Oral cancer ranks number one among men and number three among women in India. Surveys in various cancer hospitals in India reveal a frequency ranging from 15% to 20% for oral cancer among all cancers. The high incidence of oral cancer in India has been attributed to widespread tobacco usage among the population either in chewable or smoked form. Tobacco has traditionally been chewed in India as an ingredient of betel quid or pan, which is a combination of betel leaf, areca nut, and lime, although in recent time an increase in consumption of other forms, such as gutka, khaini, mawa, and so on, has been on the rise. Smoking in the form of cigarettes is usually restricted to the urban and socioeconomically higher strata of the population, whereas in the rural areas and low socioeconomic groups tobacco is smoked mostly in the form of bidi (a native cigarette of coarse tobacco hand-rolled in a dry tembhruni leaf) and other crude indigenous forms, such as chutta, chillum, and others.

The majority of oral cancers consist of oral squamous cell carcinomas (OSCC), malignant tumors, which arise from the epithelium of the oral mucosa. Most OSCCs are preceded...
for several months or years, by clinically visible alterations of the oral mucosal surface, most often having a white appearance (leukoplakia) with or without a red component. Such changes are referred to as precancerous lesions.[1] It is well known that leukoplakia is the most prevalent precancerous lesion of the oral mucosa. Oral leukoplakia has been defined as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease and should be differentiated from Smoker’s palate (leukokeratosis nicotina palate), cheek and lip biting, frictional white lesion, and snuff dipper’s lesion. Epidemiological data on the prevalence of oral leukoplakia have shown ranges from 0.7% to 24.8%.[3] The prevalence estimates were 0.37% for homogeneous and 0.06% for nonhomogeneous oral leukoplakia. Malignant transformation rate of leukoplakia is 3-6%.[4]

Erythroplakia is defined as “A fiery red patch that cannot be characterized as clinically or pathologically as any other definable lesion”; it is characterized as a high-risk lesion (HRL) for the subsequent development of carcinoma.[5]

Oral submucous fibrosis (OSMF) presents as a whitish yellow change that has a chronic, insidious biologic course.[6] OSMF is a chronic disease of oral mucosa characterized by inflammation and progressive fibrosis of lamina propria and deeper connective tissues, followed by stiffening of an otherwise yielding mucosa resulting in difficulty in opening the mouth.[7] The association of OSMF and oral cancer is profound with the rate of malignant transformation estimated to be 3-19%.[8] The reported prevalence rate in India varies from 0.2-1.2%.[2]

In the current study, we retrospectively analyzed 191 cases of potentially malignant oral lesions (PMLs), which had been biopsied in our hospital, in order to assess their relationship with tobacco usage. The aim of this study is to assess the relationship between tobacco usage with age, gender, frequency, and duration of habit either in chewable or smoking form and to find out the correlation of these with high-risk level.

MATERIALS AND METHODS

In order to assess the clinicopathological correlations of oral premalignancy, we reviewed 191 cases of lesions having potential for malignant transformation. Only those cases in which biopsy had been performed to confirm the clinical diagnosis were included. The case histories and clinical notes were retrieved from our Medical Records Department. Clinical data such as age, gender, tobacco history without the use of alcohol (present/absent) along with type (chewers, smokers, and both), frequency, and duration were recorded. Clinically, site of the lesion, color (white/red/mixed), clinical sign, and symptoms (e.g., reduced mouth opening, burning sensation, palpable bands, striation, and induration) were obtained from the medical records along with clinical diagnosis (hyperkeratosis, leukoplakia, erythroplakia, leukoedema, lichen planus, OSMF, candidiasis, carcinoma). The histopathological diagnoses (hyperkeratosis/hyperplasia, leukoedema, candidiasis, lichen planus, OSMF, mild, moderate, or severe epithelial dysplasia, carcinoma in situ, OSCC) were reviewed by one of the authors using hematoxylin and eosin–stained sections. Based on the histopathology those lesions exhibiting moderate or severe epithelial dysplasia or frank carcinoma were classified as HRLs, whereas those showing benign hyperplasia/hyperkeratosis or mild dysplasia were classified as low-risk lesions (LRLs) and lesions diagnosed as lichen planus, OSMF, and candidiasis were classified as questionable risk lesions (QRLs).[8] The data obtained were then analyzed to find out the correlation between the occurrence of HRL with various demographic parameters such as age and gender as well as with type, frequency, and duration of tobacco habit without the consumption of alcohol.

RESULTS

A total of 191 cases of PMLs, which had been biopsied in our hospital were taken from the data of 3 years (2007-2009). Out of these 191 patients, 175 were males and remaining 16 females. Tobacco history was reviewed for all the patients both from the biopsy requisition forms and the patient records retrieved from the medical records department. It was observed that tobacco-related history was documented in 141 cases, whereas there was no documentation of the habit history in the remaining 50 cases [Table 1]. Out of these 141 cases, 19 reported no tobacco history, 52 were purely chewers, 45 purely smokers, and 25 cases were both chewers and smokers of tobacco [Table 1, Figure 1]. The patients included in these categories were those with a habit but without consumption of alcohol.

Table 1: Proportion of habits

| Habit not known | 50 |
|-----------------|----|
| Habit present   |    |
| Chewers         | 52 |
| Smokers         | 45 |
| Both            | 25 |
| Habit absent    | 19 |
| Total           | 191|

Figure 1: The proportion of habits in potentially malignant oral lesions
Based on the clinical diagnosis it was observed that 50 cases could not be grouped in any specific group as more than one provisional diagnosis for the same lesion were mentioned in the records. Of the remaining 141 cases, 75 were leukoplakias (both homogenous and nonhomogenous), 23 OSMF, 15 lichen planus, 14 carcinomas, 6 were hyperkeratosis, 4 candidiasis, 2 erythroplakia, and 2 leukoedema [Table 2, Figure 2].

Based on the histopathological diagnosis and risk levels out of the 191 patients, there were 55 cases of LRL, 101 HRL, and 35 cases of QRL. The correlation of various clinical and tobacco-associated parameters with the risk level of the lesions has been shown in Table 3 and Figures 3-5.

DISCUSSION

Oral cancer is one of the 10 most common cancers in the world and shows marked geographic differences in occurrence. Oral cancer ranks number one among men and number three among women in India[2] and predominate in cancer morbidity figures in the subcontinent. The social customs, habits, nutritional state, and the climatic conditions vary remarkably in different parts of the globe, and even in different sectors of the big country in India. Local habits are thought to play a distinct role in the high rate of oral and pharyngeal cancer in India. An increased frequency of cancer in the oral cavity was more often associated with the habit of the chewing of tobacco with betel leaf, betel nut, and slaked lime than with other habits, whereas in persons suffering from carcinoma of the oropharynx and of the hypopharynx there was evidence of an increase in the frequency of tobacco smoking.[9] The Indian data suggest that the relative risk of developing oral cancer is 2.82 for smokers and 5.98 for chewers.[10]

The use of tobacco in various forms is widespread in India, with between 47% and 73% of population indulging in the habit, compared with approximately 36% in United States. The rate of transformation of precancerous lesions into oral cancers is similar to that seen elsewhere, suggests that the high incidence of oral cancer in India is not a reflection of a unique susceptibility but simply of the very high prevalence

| Clinical diagnosis | Leukoplakia | Erythroplakia | Lichen planus | Leukoedema | OSMF | Candidiasis | Carcinoma | Hyperkeratosis | Total No diagnosis | Multiple diagnosis |
|--------------------|------------|--------------|---------------|-------------|------|-------------|-----------|---------------|------------------|-------------------|
| Total              | 75         | 2            | 15            | 2           | 23   | 4           | 14        | 6             | 141              | 19                | 31                |

OSMF: Oral submucous fibrosis

Figure 2: Various clinical diagnosis

Figure 3: Agewise distribution in various risk levels

Figure 4: Gender wise distribution in various risk levels

Figure 5: Proportion of risk level on the basis of histopathology
Table 3: Proportion of risk levels

| Category | LRL | HRL | QRL | Total |
|----------|-----|-----|-----|-------|
| All patients | 55  | 101 | 35  | 191   |
| Those patients whose tobacco history was documented | 39  | 70  | 32  | 141   |
| Age | | | | |
| <30 years | 16  | 13  | 20  | 49    |
| >30 years | 43  | 89  | 10  | 142   |
| Gender | | | | |
| Female | 6   | 4   | 7   | 16    |
| Male | 49  | 97  | 28  | 175   |
| Tobacco history (available for 141 cases) | | | | |
| No history of tobacco consumption | 9   | 4   | 6   | 19    |
| History of tobacco habit present | | | | |
| Chewers | 13  | 20  | 20  | 53    |
| Smokers | 13  | 30  | 2   | 45    |
| Both (No history of tobacco consumption + History of tobacco habit Present) | 4   | 16  | 4   | 24    |
| Total | 39  | 70  | 32  | 141   |

Habit frequency (available for 109 cases)

| Chewers (packets/day) | 2 | 1 | 0 | 3 | 109 |
|-----------------------|---|---|---|---|-----|
| <5                    | 8 | 17| 19| 44|     |
| Total                 | 18| 19| 47|    |     |

| Smokers (Cigarettes or bisdis/day) | 1 | 9 | 0 | 10 |
|------------------------------------|---|---|---|----|
| <5                                 | 10| 20| 1 | 31 |
| Total                              | 29| 1 | 41|    |

| Both | 0 | 6 | 1 | 7 |
|------|---|---|---|---|
| <5   | 4 | 7 | 4 | 14|
| Total| 4 | 13| 4 | 21|

Habit duration (available for 99 cases)

| Chewers (years) | 9 | 6 | 4 | 19 | 99 |
|-----------------|---|---|---|----|----|
| <5              | 7 | 11| 6 | 24 |    |
| Total           | 16| 17| 10| 43 |    |

| Smokers (years) | 2 | 3 | 2 | 7 |
|-----------------|---|---|---|---|
| <5              | 7 | 22| 0 | 29|
| Total           | 9 | 25| 2 | 36|

| Both (years) | 2 | 3 | 1 | 6 |
|--------------|---|---|---|---|
| <5           | 2 | 10| 2 | 14|
| Total        | 4 | 13| 3 | 20|

LRL: Low-risk lesion, HRL: High-risk lesions, QRL: Questionable risk lesions

Relation of tobacco habit in potentially malignant lesion

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Leukoplakia is the most common PML, but its conversion to malignancy is highly unpredictable. The malignant transformation rates have been found to vary between 0.13% and 36.4%.[12] Similarly other potentially malignant clinical entities such as erythroplakia, lichen planus, and OSMF show a wide variation in their malignant transformation rates. It has been proposed that histological demonstration of dysplastic changes in the oral epithelium may be a better predictor of probability of malignant change in a PML than its clinical type. Hence we divided the cases into HRLs and LRLs depending on the severity of dysplastic changes in the oral epithelium. Certain lesions and conditions such as lichen planus, OSMF, and candidiasis, where the malignant potential is still debatable were classified as a separate group.

It was observed that the prevalence of HRL was considerably higher in those patients with tobacco consumption with 66 of 70 (94.3%) patients diagnosed as having HRL gave a history of consuming tobacco in some form. Only 5.7% patients having HRL did not give any history of tobacco consumption as compared with 23.1% and 18.8% patients having LRL or QRL, respectively. These data suggest that changes in oral tissues developing in tobacco consumers have a greater potential for malignant transformation than those developing in non-consumers. Polycyclic aromatic hydrocarbons, aldehydes, aromatic amines, nitrosamines, and so on present in tobacco are thought to be carcinogenic[10] and have been shown to cause mutations in oral mucosal cells.[1] As an early sign of damage to oral mucosa, tobacco smokers and chewers often develop precancerous lesions, such as leukoplakia. These lesions are easily accessible to diagnosis and can be considered as an indicator of oral cancer risk.

In our study we reviewed cases of PMLs, which had been biopsied in our institution in past 3 years. Only those cases with undisputable diagnosis of dysplasia and other PMLs, such as OSMF, lichen planus, and others, were included. A total of 191 cases satisfied these criteria and were included in the study. Out of these, tobacco-associated history was available for 141 patients, whereas there was no mention of either a positive or a negative history in the remaining 50 cases both in the biopsy requisition forms and in the medical records of the patients as shown in Table 1. It was observed that the lesions studied were almost equally prevalent in patients consuming chewable form of tobacco as well as smoked form. Out of a total of 141 patients with known tobacco history, 77 were tobacco chewers either alone or in combination with smoking. On the other hand, there were 70 cases of tobacco smokers with or without chewing habit. Only 19 cases (13.5%) developed oral PMLs in the absence of any tobacco habit. It is evident from these data that PMLs were seen more commonly in patients with tobacco habit as 122 of 141 (86.5%) cases of these lesions occurred in those individual having a habit of some form of tobacco consumption [Table 1].

Studies have shown that almost 80% of oral cancers progress from precancerous lesions and about 2-12% of precancers are transformed into cancer.[11]
On assessing the type of tobacco habit we found that the higher percentage of patients developing HRL were smokers as compared with those who used chewable form. The risk of development of oral leukoplakia has been shown to be greater in exclusive smokers as compared with exclusive tobacco chewers,[10] but whether the risk of conversion of leukoplakia into oral cancer is higher in smokers or chewers is still not clear. Our data suggest a slightly greater risk in smokers and this could be because of the synergistic effect of localized elevation in the temperature of the oral cavity, which may make the epithelium more susceptible to genotoxic effect of tobacco products. Benzopyrene and other polycyclic aromatic carcinogenic agents in tobacco smoke are considered to increase the prevalence and spectrum of TP 53 mutations and smokers have more p53 mutations than non-smokers.[13,14]

When the frequency of tobacco habit was reviewed, it was seen that out of the 109 patients for whom tobacco frequency was known, 81.7% consumed tobacco more than five times per day. Of these more than half had HRL and in less than one fourth of the lesions seen were LRL. This shows that increase in the frequency of tobacco increases the risk of developing lesions, which may have a higher potential to convert to malignancy. When the type of habit was analyzed individually it was seen that most of the lesions in purely chewers were seen in those who had a frequency of more than five times per day with only 6.8% of lesions seen in those who chewed tobacco less than five times per day. On the other hand, smoking even at lower frequency was seen to have a higher tendency for the development of these lesions as almost one fourth of the lesions seen in pure smokers were those individuals who smoked less than five times per day. Combining the two types of habits was found to be more harmful as almost one third of the lesions seen in this group were patients who consumed tobacco less than five times daily. When the risk level of the lesions developing in those individuals who consumed tobacco less than five times per day was assessed it was observed that about 33% of lesions in purely chewer group were HRL, whereas almost 90% in pure smokers and 86% lesions in mixed habit group were HRLs [Table 3]. This suggests that individuals using smokable form of tobacco had a much higher risk of developing lesions with a greater malignant potential even if the frequency of consumption was low.

The data regarding the duration of tobacco habit was available for 99 patients and it was seen that out of these two thirds had a history of tobacco use for more than 5 years. In these patients almost two thirds of the lesions seen in longer duration group were HRL as compared with only one third lesions in the short duration group. This suggests that along with frequency even the duration of tobacco consumption increases the risk of developing oral cancer. When the risk levels were correlated with duration of habit it was seen that in the short duration, group lesions seen in purely chewers and those having mixed habit had a greater proportion of HRL (35% and 23%, respectively) as compared with those seen in purely smokers (12%). This probably is the effect of prolonged exposure as tobacco in chewable form where tobacco is kept in contact with the mucosa for a longer time leading to leaching and concentration of carcinogens at a localized area. In these cases longer individual chewing cycle even at short duration may be hazardous. Strong association between cancers of the oral cavity and pharynx with tobacco use is well established. Epidemiological studies show that the risk of developing oral cancer is five to nine times greater for smokers than for nonsmokers, and this risk may increase to as much as 17 times greater for extremely heavy smokers of 80 or more cigarettes per day. The percentage of oral cancer patients who smoke (approximately 80%) is two to three times greater than that of the general population.[15,16] In addition, treated oral cancer patients who continue to smoke have a two to six times greater risk of developing a second malignancy of the upper aerodigestive tract than those who stop smoking.[17] Banoczy et al., reported higher prevalence rate of leukoplakia among smokers, and intervention studies show a regression of the lesion after stopping the smoking habit.[18]

CONCLUSION

We found that lesions developing in individuals were more in males, over 30 years of age; smoking tobacco to be of higher risk potential than those with chewing tobacco and both the frequencies and duration of smoking habit are directly correlated with malignant transformation. To conclude, the results of our study are supportive of the fact that tobacco consumption is one of the major etiological factors in development of OSCC and the PMLs developing in individuals with tobacco habit show a greater tendency for structural changes in the oral epithelium and hence may be at a higher risk of getting converted to malignancy. Also we found that lesions developing in individuals with habit of smoking tobacco to be of higher risk potential than those with chewing habit.

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