Prevalence of Oral Leukoplakia in 9954 Central Indian Patients: a Prospective, Cross-sectional Study

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Abstract

Introduction India is one of the leading producers and consumer of tobacco. Additionally, India has one of the highest global prevalence of oral leukoplakia (OL). However, large epidemiological studies from Madhya Pradesh (Central India), the state with maximum consumers of tobacco products in India, are lacking.

Objective Thus, we assessed the prevalence of OL among individuals residing in Central India and evaluated its association with age, gender, and history of adverse habits.

Methods This was a prospective, cross-sectional study involving 9954 patients visiting the out-patient Department of Oral Medicine and Radiology over a period of 15 months (January 2019 to March 2020). The clinical diagnosis of OL was arrived by exclusion of all the lesions mimicking OL. Univariate and multivariate analyses were performed to assess the association between OL and age, sex, and history of adverse habits.

Results The prevalence of OL was 5.6% (557/9954). It was predominant in males (male-to-female ratio=3.9:1) and increased with advancing age. The odds of developing OL was higher among patients aged ≥50 years (OR=1.08; 95%CI: 1.07–1.08, p-value<0.0001), those with history of smoking tobacco (OR=1.32; 95%CI: 1.05–1.68, p-value=0.02), consuming smokeless tobacco (OR=318.60; 95%CI: 101.68–998.30, p-value<0.0001), and alcohol (OR=1.15; 95%CI: 9.0–1.49, p-value=0.269). Females had lower odds of developing OL (OR=0.77; 95%CI: 0.60–0.99, p-value=0.042).

Conclusion We observed high prevalence of OL (5.6%). OL was significantly associated with older age, male sex, and tobacco-related adverse habits. While, alcohol consumption may possibly be a risk factor, no statistically significant relation was observed.

Introduction

Globally, cancer is the predominant cause of mortality [1]. Of all the cancers, oral cavity squamous cell carcinoma (OSCC) is the sixth most frequently observed cancer, and its incidence is high, especially in South Asia [2]. OSCC is ushered by clinically visible but usually asymptomatic whitish patchy lesion of the oral mucosa termed as oral leukoplakia (OL). OL is considered as the most frequently observed premalignant lesion involving the oral cavity [3]. Additionally, at the time of OSCC diagnosis, up to 60% patients have co-incidence of OL [4].

OL has a global prevalence of 2.6% with a malignant transformation (MT) rate of 0.13-34% [5]. In India, OL has a higher prevalence (0.2-5.2%) but with a lower MT rate (0.13-10%) [6]. It has multifactorial origin, but tobacco smoking is most frequently implicated. Alcohol is considered as an independent risk factor; however, it acts synergistically with tobacco smoking [7].
Globally, India is the third largest producer and second largest consumer of tobacco [8]. In India, Madhya Pradesh (MP) tops the chart in the consumption of areca nut-based tobacco products among males. Around 50% males and 17% females residing in MP use either smoked and/or smokeless tobacco. It is further proposed that Gutkha (13.7%) and Khaini (11.7%) are the two most prevalent forms of smokeless tobacco products used in MP [9]. Alcohol consumption is a rising socio-economic issue in India and country liquor is consumed by a significant number of individuals residing in MP. Additionally, females (53.2%) residing in Alirajpur district of MP have the highest prevalence of alcohol consumption among Indian women [10].

Though several studies have reported variable prevalence of OL in global population, similar studies with respect to individuals residing in MP are lacking. Considering high tobacco and alcohol consumption, we proposed this study to assess the prevalence of OL among individuals residing in MP (Central India) and evaluate its association with age, gender, and history of adverse habits.

**Methods**

This prospective, observational, cross-sectional study was performed over a period of 15 months (January 2019 to March 2020). The study involved 10,012 patients of either sex, aged 18-90 years, and attending the out-patient Department of Oral Medicine and Radiology of a tertiary care center located in Madhya Pradesh. Of 10,012 patients, 9954 consented to participate and were enrolled in the study. While patients with underlying systemic diseases (including malignancy), history of skin graft in oral cavity, and those unwilling to share their habit history were excluded. The approval of Institutional Ethical Committee was obtained before initiating the study.

Demographic data of participants and detailed habit history was recorded, subsequently the examination of oral mucosa was carried out using artificial light and mouth mirrors. All cases with white patchy lesions of the oral mucosa were subjected to detailed clinical examination. As a part of extensive clinical examination, the presence of OL was recorded by the observer. The clinical diagnosis of OL was arrived by exclusion of all the lesions mimicking OL. Variables including age, sex, history of adverse habits (such as smoking, smokeless tobacco and alcohol), and sites of oral cavity involved were recorded.

**Statistical analysis**

The data was analyzed with SPSS (IBM, Armonk, NY, USA) version 17.0 for Windows. The categorical and continuous variables were represented in terms of frequency (percentages) and mean ± standard deviation (SD), respectively. Independent sample test was used to identify the significance of mean difference between ages of male and female patients with OL. OL was categorized into dichotomous outcome: “Present” or “Absent”. Pearson’s Chi-Square test was used to assess the associations of age, sex, and history of adverse habits with status of OL. Bivariate logistic regression was used to predict the OL (dependent variable) among patients by employing selected predictors including age, sex, and history of smoking tobacco and consumption of smokeless tobacco and alcohol (independent variables).
Results were represented as odds ratio (OR), 95% confidence interval (95%CI) with a two-tailed significant p-value<0.05.

Results

Of 9954 patients, OL was observed in 557 patients, thus resulting in a prevalence of 5.6%. Distribution of patients according to age groups revealed increase in prevalence of OL with increase in age, with maximum prevalence observed in those aged >78 years (21.3%). OL was predominantly prevalent among males (7.8%) and the male to female ratio was 3.9:1. Almost all sites of oral cavity were found to be affected by OL; however, buccal mucosa (1.8%, right and left) followed by labial mucosa (1.4% right and left) were most commonly affected. Additionally, involvement of multiple sites of oral cavity was documented in 0.8% patients (Table 1).
| Characteristics            | Total Examined (N = 9954) | Presence of OL (n = 557) | Prevalence of OL (%) |
|---------------------------|---------------------------|--------------------------|----------------------|
| Age groups                |                           |                          |                      |
| 18-38 year                | 5301                      | 35                       | 0.7%                 |
| 39-58 year                | 3785                      | 348                      | 9.2%                 |
| 59-78 year                | 821                       | 164                      | 20.0%                |
| > 78 year                 | 47                        | 10                       | 21.3%                |
| Sex                       |                           |                          |                      |
| Female                    | 4290                      | 113                      | 2.6%                 |
| Male                      | 5664                      | 444                      | 7.8%                 |
| Site of oral cavity       |                           |                          |                      |
| Buccal mucosa at right/left| -                         | 175                      | 1.8%                 |
| Labial mucosa at right/left| -                         | 138                      | 1.4%                 |
| Vestibule at right/left   | -                         | 69                       | 0.7%                 |
| Tongue                    | -                         | 35                       | 0.4%                 |
| Floor of mouth            | -                         | 21                       | 0.2%                 |
| Hard palate               | -                         | 14                       | 0.1%                 |
| Gingiva & alveolar ridges | -                         | 22                       | 0.2%                 |
| Multiple                  | -                         | 83                       | 0.8%                 |
| OL type                   |                           |                          |                      |
| Homogeneous               | -                         | 517                      | 5.2%                 |
| Non-Homogeneous           | -                         | 40                       | 0.4%                 |
| H/o adverse habits        |                           |                          |                      |
| Smoking                   | 1638                      | 132                      | 8.1%                 |
| Smokeless Tobacco         | 4046                      | 554                      | 13.7%                |
| Alcohol                   | 1135                      | 101                      | 8.9%                 |

OL: Oral leukoplakia
The presence and absence of OL was found to be highest among patients age 39-58 years (3.5%) and 18-38 years (52.9%), respectively. Adult age group (39-58 year) had significantly higher presence of OL (p-value<0.0001). OL was present in significantly higher number of males than females (4.5 vs 1.1%, p-value=0.008). Evaluation of smoking history suggested that OL was significantly higher among patients who did not smoke (4.3% vs 1.3%, p-value<0.0001). Likewise, OL was significantly higher among patients who did not consume alcohol (4.6% vs 1.0%, p-value<0.0001). However, consumption of smokeless tobacco was associated with significantly higher chances of developing OL (5.6% vs 0.0%, p-value<0.0001) (Table 2).

| Characteristics                     | Oral leukoplakia | p-value |
|-------------------------------------|------------------|---------|
|                                     | Absent (n=9397)  | Present (n=557) | Total (N=9954) |
| Age groups                          |                 |          |               |
| 18-38 year                          | 5266 (52.9%)    | 35 (0.4%) | 5301 (53.3%)  | <0.0001 |
| 39-58 year                          | 3437 (34.5%)    | 348 (3.5%) | 3785 (38.0%)  |         |
| 59-78 year                          | 657 (6.6%)      | 164 (1.6%) | 821 (8.2%)    |         |
| > 78 year                           | 37 (0.4%)       | 10 (0.1%)  | 47 (0.5%)     |         |
| Sex                                 |                 |          |               |
| Female                              | 4177 (42.0%)    | 113 (1.1%) | 4290 (43.1%)  | 0.008   |
| Male                                | 5220 (52.4%)    | 444 (4.5%) | 5664 (56.9%)  |         |
| H/o smoking                         |                 |          |               |
| Absent                              | 7891 (79.3%)    | 425 (4.3%) | 8316 (83.5%)  | <0.0001 |
| Present                             | 1506 (15.1%)    | 132 (1.3%) | 1638 (16.5%)  |         |
| H/o smokeless tobacco consumption   |                 |          |               |
| Absent                              | 5905 (59.3%)    | 3 (0.0%)  | 5908 (59.4%)  | <0.0001 |
| Present                             | 3492 (35.1%)    | 554 (5.6%) | 4046 (40.6%)  |         |
| H/o alcohol consumption             |                 |          |               |
| Absent                              | 8363 (84.0%)    | 456 (4.6%) | 8819 (88.6%)  | <0.0001 |
| Present                             | 1034 (10.4%)    | 101 (1.0%) | 1135 (11.4%)  |         |
Following multivariate binary logistic regression analysis, age, sex, and history of tobacco consumption (both smoked and smokeless) were found to be significantly associated with the presence of OL. The odds of developing OL among patients aged \( \geq 50 \) years were found to be 1.08 times (OR=1.08; 95%CI: 1.07–1.08, p-value<0.0001) higher than those aged <50 years. Females had 0.77 times lower chance of developing OL than males (OR=0.77; 95%CI: 0.60–0.99, p-value=0.042). Patients with history of smoking tobacco and consuming smokeless tobacco had 1.32 (OR=1.32; 95%CI: 1.05–1.68, p-value=0.02) and 318.6 times (OR=318.60; 95%CI: 101.68–998.30, p-value<0.0001) higher chance of developing OL, respectively. Though patients consuming alcohol had 1.15 times (OR=1.15; 95%CI: 0.90–1.49) higher chances of developing OL, this did not reach statistically significant level (p-value=0.269) (Table 3).

### Table 3
Multivariate analysis of association between OL statuses with various patient characteristics

| Predictors       | \( \beta \) | Std. Error | p-value | Odds Ratio | 95% CI     |
|------------------|-------------|------------|---------|------------|------------|
| Age (\( \geq 50 \) year) | 0.074       | 0.004      | 0.000   | 1.08       | 1.07–1.08  |
| Sex (Female)     | -0.261      | 0.128      | 0.042   | 0.77       | 0.60–0.99  |
| Smoking (Yes)    | 0.281       | 0.121      | 0.02    | 1.32       | 1.05–1.68  |
| Smokeless Tobacco (Yes) | 5.764     | 0.583      | 0.000   | 318.60     | 101.68–998.30 |
| Alcohol (Yes)    | 0.143       | 0.130      | 0.269   | 1.15       | 0.90–1.49  |

**Discussion**

Because of its ability to undergo MT, OL poses challenges for both diagnosis and management [11]. It is associated with a high risk of developing cancer either in an area near the lesion, in some other parts of the oral cavity, or head and neck region [12]. In etiological terms, OL is classified as idiopathic OL (with absence of causal factors), and tobacco-associated OL [13, 14]. There is a significant association between tobacco consumption and development of OL. The ingestion of tobacco is thought to expose the oral epithelium to free oxygen and nitrogen radicals which can impair antioxidant mechanisms. Elevated level of these free radicals presents as oral pre-cancerous and cancerous lesions. Additionally, alcohol has been shown to have a synergistic effect on growth of OL, but definitive evidence is still lacking [15].

In India, 4.5% adults consume betel quid with tobacco daily [8]. Recent report highlights that around 24% Indian adults consume areca nuts and a majority (14.2%) of them combine areca nut with tobacco [16]. These findings suggest a reason for high prevalence of OL in India. Individuals residing in MP (Central India) have high prevalence of tobacco and alcohol consumption [9, 10], but the prevalence of OL has not been assessed in large population. A previous study from MP assessed 1241 patients and reported an OL prevalence of 4.02% [17]. We assessed 9954 patients and observed a prevalence of 5.6%. Other studies
from Northern (7.1%) and Southern (8.2%) parts of India have reported higher prevalence of OL [18, 19]. However, studies from other parts of India have reported lower prevalence (0.63–2.60%) [20, 21]. This variation in prevalence of OL could be attributed to differences in demographic patterns, cultural beliefs, and patterns of tobacco consumption among different people and different geographic areas.

Tobacco consumption in any form is the principal risk factor of OL. Various studies have reported a clear and significant association between tobacco consumption and OL [5, 22–24]. We observed that the history of smoking tobacco was significantly associated with the presence of OL and those having history of smoking were found be at 1.32 times higher risk of developing OL. Likewise, history of consumption of smokeless tobacco was significantly associated with the risk of developing OL and this risk was 318.6-times higher than those who did not consume smokeless tobacco. The risk of developing OL is related to the age of adverse habit initiation, and the type and amount consumed. While, Western countries report a significant association between OL and consumption of tobacco (both smoked and smokeless) and alcohol [24], Southeast Asian nations associate OL with betel quid consumption [25]. The action of various carcinogens, including tobacco depends on the duration of exposure. This fact highlights the higher prevalence of OL in older populations [23].

Alcohol consumption leads to accumulation of toxic ethanol metabolites, altered DNA repair mechanism, and raised cellular permeability, which results in increased cell entry of various carcinogens including tobacco (smoked/smokeless), thus highlighting the synergistic effect of alcohol and tobacco consumption [26]. An early study from Southern India reported that alcohol consumption was an independent risk factor and history of ever alcohol consumption was significantly associated with the risk of developing OL in non-smokers (2.1-times) and non-chewers (1.8-times) [27]. In another study, alcohol consumption resulted in significantly higher OL risk in both never-users and current users of tobacco. Compared to non-drinkers, drinkers of 0.1 to 14.9 g/d, 15 to 29.9 g/d, and ≥30 g/d had a relative risk of 1.7, 2.9, and 2.5, respectively [28]. While, a study concluded that alcohol is a promoter rather than an initiator, as it was not associated with the development of OL [29]. In our study, though history of alcohol consumption was associated with 1.15-times higher risk of developing OL, it did not achieve significance level. Likewise, a meta-analysis reported that alcohol consumption was associated with 1.54-times higher risk of developing OL; however, this was not significantly associated [5]. These contradictory findings need to be confirmed in prospective studies with large sample size.

The prevalence of OL is higher among males than females and increases with advancing age. It usually affects individuals over 40 years of age [30]. We observed a significant association between the presence of OL and adult age group. Additionally, patients aged ≥ 50 years had 1.08-times higher risk of developing OL than those aged <50 years. Other studies have reported similar findings [5, 22]. The median age of smokers with OL is reported to be significantly less than in non-smokers [31]. Likewise, we observed that the prevalence of OL increased with increase in age, from 0.7% (in patients aged 18-38 year) to 21.3% (in patients aged >70 year). This could be attributed to the fact that early and chronic exposure to adverse habits (consumption of tobacco and/or alcohol) results in higher prevalence in elderly age group.
Male sex is a risk factor for developing OL [5]. We observed that male sex was significantly associated with the presence of OL and female sex was found to be a protective factor, with 0.77-times less risk of developing OL. This could be attributed to the cultural differences, as males are more commonly involved in practicing adverse habits than females [9]. OL and other potentially oral malignant lesions are predominant among males, particularly in chronic smokers [22]. Additionally, in our study, enrolled patients were predominantly males (1.3:1) and the prevalence of OL was also more in males than females (3.9:1). Thus, higher proportion of males than females could have affected the prevalence of OL.

This was a prospective study involving a large population. However, our study had certain limitations. First, we relied on the presence and absence of adverse habits and thus, could not comment on the effect of type, amount, and duration of adverse habits (both tobacco and alcohol). Second, we confirmed the diagnosis clinically, and histopathological examination of lesion was not performed. Third, we did not follow-up the patients, thus we could not check for MT of OL. Finally, we excluded the patients with known history of oral cancer, so we did not evaluate the effect of adverse habits on development of oral cancer.

Conclusion

We report a high prevalence of OL (5.6%) in Central Indian population. It was most prevalent in elderly population and male sex. The most common adverse habit resulting in OL was consumption of smokeless tobacco. OL was significantly associated with older age, male sex, and tobacco-related adverse habits. Alcohol consumption may possibly be a risk factor, but no statistically significant relation was observed. There is a need of further studies to clarify the relationship of alcohol intake in OL and other multiple oral premalignant lesions.

Declarations

Ethics approval

All procedures performed in studies involving human participants were in accordance with the standards of the Institutional Ethics Committee of the Sri Aurobindo College of Dentistry, Indore, Madhya Pradesh, India and with the Helsinki declaration.

Consent to participate

Due to retrospective nature of study, participant consent was waived off.

Consent for publication

Due to retrospective nature of study, consent for publication could not be obtained.

Conflict of interest
The authors declare that they have no competing interests.

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Author contributions

Conceptualization: Trushna Rahangdale, Tushar Phulambrikar, Tanvi Dosi. Methodology: Trushna Rahangdale, Tushar Phulambrikar, Vihang Naphade. Formal analysis and investigation: Trushna Rahangdale, Gauri Barkalle, Anushree Somani. Writing-original draft preparation: Trushna Rahangdale, Gauri Barkalle, Anushree Somani. Writing-review and editing: Tushar Phulambrikar, Tanvi Dosi, Vihang Naphade. Data collection: Trushna Rahangdale, Gauri Barkalle, Anushree Somani. Resources: Tushar Phulambrikar, Tanvi Dosi, Vihang Naphade. Supervision: Tushar Phulambrikar, Tanvi Dosi, Vihang Naphade. All authors read and approved the final manuscript.

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Data Availability

All data generated or analyzed during this study are included in this published article.

Code availability

Not applicable.

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