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# Prevalence and Clinicopathological Features with Oral Biological Correlates of Potentially Malignant Oral Disorders in Individuals with High-Risk Oral Habits

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## ABSTRACT

Objective: To determine the prevalence, clinicopathological characteristics, and oral biological correlates of potentially malignant oral disorders (PMODs) in individuals with high-risk oral habits.

Materials and Methods: It was an analytical cross-sectional study carried out in a period of one year. Non-probability consecutive sampling was used to enroll 150 participants aged ≥18 years with high-risk oral habits. The oral cavity clinical examination was conducted, and a biopsy of suspected lesions was done to examine them histopathologically. SPSS version 24 was used to analyze the data. The descriptive statistics were provided in frequencies, percentages, and mean ± SD. The Chi-square test was used to assess the associations, and $p \leq 0.05$ was regarded as significant.

Results: The average age of the subjects was 39.8 ± 12.4 years, and the male gender prevailed (68%). Smokeless tobacco use (34.7%) was the most common high-risk habit. PMODs were found in a quarter of the participants. The expression of Ki-67 (69.4%) was more than that of p53 (58.3), and the expression of biomarkers rose greatly as the severity of dysplasia increased ($p = 0.001$). There was a considerable correlation between high-risk oral habits and PMODs ($p = 0.032$).

Conclusions: PMODs are common in patients with high-risk oral habits, and the severity of PMODs is associated with biomarker expression. To avoid malignant transformation, early detection, quitting a habit, and a combination of clinical, pathological, and biological evaluation is needed.

**Keywords**: Potentially malignant oral disorders, Leukoplakia, Oral submucous fibrosis.

## INTRODUCTION

Potentially malignant oral disorders (PMODs) are a category of abnormalities of the mucosa that are at risk of developing into oral squamous cell carcinoma (OSCC).[1] According to the World Health Organization, these disorders encompass leukoplakia, erythroplakia, oral submucous fibrosis (OSMF), and oral lichen planus.[2] PMODs are clinically relevant because their biological activity is variable, unpredictable, and can develop malignant evolution, which can be as low as 0.13% or up to 34% depending on the type of lesion and risk factors.[3] The prompt diagnosis and description of these lesions are essential in minimizing the prevalence of oral cancer in the world..

Oral cancer is one of the ten most frequently occurring cancers in the world, with the highest rates being recorded in South and Southeast Asia.[4] Global Cancer Observatory reports over 377,000 new oral cancer cases and over 177,000 deaths due to oral cancer worldwide in 2020, with a significant percentage of the latter due to previously undiagnosed or untreated PMODs.[5] PMODs have high prevalence in Pakistan and the neighboring areas because of the high-risk oral behaviors, including tobacco smoking, smokeless tobacco (naswar, gutka), chewing gums (betel quid), and alcohol use.[6] Research shows that the incidence of PMODs among high-risk groups is between 4% to 12% and that oral submucous fibrosis and leukoplakia are the most commonly observed lesions.[7] Such practices lead to chronic mucosal inflammation, dysplasia of the epithelial cells, and molecular changes, which predispose people to malignant transformation

The clinical presentation, histopathological grading, and biological behaviour of PMODs vary in a spectrum of clinicopathological patterns.[8] Lesions can be clinically manifested by white patches, red lesions, ulceration, or fibrotic changes in oral functionality.[9] Histopathologically, such lesions exhibit a spectrum of hyperkeratosis to different levels of dysplasia of the epithelial cells, which is deemed to be the best indicator of malignancy potential.[10] Recently, more attention has been paid to finding oral biological correlates, including biomarkers, such as p53, Ki-67, and cyclin D1, which are involved in cell cycle regulation, apoptosis, and proliferation.[11] These molecular markers provide valuable insights into disease progression and may aid in risk stratification and early diagnosis.

Although there is a heavy load of PMODs as well as established correlation with high-risk oral behaviors, a lack of comprehensive data that combines prevalence, clinicopathological features, and biological correlates of high-risk groups in low-resource environments is still evident.[12] The majority of the available research is either clinical or histopathological, and little has been done to examine molecular markers in conjunction with each other to improve early detection and prognostication. Moreover, the differences in lifestyle, cultural beliefs, and access to healthcare services require region-specific data to learn more about the disease trends.

Considering the increasing rates of high-risk oral habits and the resulting growth in PMODs, there is a strong necessity to have a comprehensive assessment that cuts across clinical, pathological, and biological aspects of these disorders. The interaction of habit-related exposure, lesion features, and underlying molecular changes can be a major step towards early diagnosis, risk evaluation, and interventions. Thus, the study aimed to establish the prevalence and clinicopathological characteristics of potentially malignant oral diseases in high-risk oral habit individuals as well as to identify their oral biological counterparts to offer a more comprehensive and clinically pertinent approach to early malignant change detection and prevention.

## MATERIALS AND METHODS

This research was designed as an analytical cross-sectional study. The period of data collection was one year. The sample size was determined with the OpenEpi sample size calculator based on a previously reported prevalence of PMODs of 10% in high-risk populations.[13] The sample size calculated is 138 with a 95% confidence level, a 5% margin of error and an expected population proportion ($p = 0.10$). A total of 150 participants were involved in the study to boost the power of the study and to cover the possible non-response.

A non-probability consecutive sampling method was used. Patients who reported to the outpatient department with a history of high-risk oral habits and met the inclusion criteria in the study period were sequentially recruited until the desired sample size was reached. Individuals older than 18 years who reported having high-risk oral behaviors (tobacco smoking, smokeless tobacco use (naswar, gutka), betel quid chewing, or alcohol use) were included in the investigation. Those individuals who signed the informed consent and offered their willingness to be clinically examined and undergo the biopsy (where necessary) were also involved. Patients that had already been diagnosed with oral cancer, previously undergone treatment due to PMODs, patients with systemic conditions impacting the oral mucosa (e.g., autoimmune diseases), and those who refused to participate were excluded.

A pre-tested and structured proforma was used to collect data. After obtaining informed consent, detailed demographic information and history of high-risk oral habits (type, duration, and frequency) were recorded. An extensive clinical examination of the mouth was conducted with sufficient lighting and with the help of standard diagnostic tools. Clinical characteristics like site, size, color, and texture were used to record suspected lesions. Clinically evident PMOD patients were subjected to biopsy to determine their histopathology. Tissues were subjected to processing and evaluation to reveal the existence and the grade of epithelial dysplasia. Moreover, immunohistochemical analysis of selected cases was conducted to determine biological factors, including p53 and Ki-67, which are biological correlates of the malignant transformation of the mouth.

All the data collected were input and analyzed in SPSS version 24. The descriptive statistics were performed (e.g., frequencies and percentages of categorical variables, e.g., gender, type of habit, presence of PMODs) and the means ± standard deviation of the continuous variables (e.g., age, duration of habit). The percentage of PMODs was computed. The inferential statistics

were used to establish relationships between variables. The Chi-square test was applied to determine the connection between high-risk habits and PMODs, clinicopathological characteristics, and biomarker expression. A p-value ≤0.05 was considered statistically significant.

## RESULTS

A total of 150 participants were included in the study. The average age of the participants was 39.8 ± 12.4 years, with most of them being aged between 31 and 45 years (38.7%), and 18-30 years (28.0%). It was dominated by males with 68.0% men and 32.0% women. In terms of high-risk oral behaviors, most used smokeless tobacco (34.7%), with the next most common being smoking (30.0%), betel quid chewing (20.7%), and combined habits (14.6%) (Table 1).

The general incidence of potentially malignant oral disorders (PMODs) within the study population was 24.0%, and 76.0% of the participants had no lesions. Of the PMODs that were identified, the most common lesion was leukoplakia (38.9%), then oral submucous fibrosis (27.8%), oral lichen planus (19.4%), and erythroplakia (13.9%). The histopathological analysis showed that the most common was mild dysplasia (36.1%), then moderate dysplasia (25.0%), no dysplasia (22.2%), and severe dysplasia (16.7%). (Table 2)

Evaluation of biological markers revealed that Ki-67 expression (69.4%) was more common than p53 expression (58.3%) in PMOD cases. Moreover, a growing tendency towards biomarker positivity with the extent of epithelial dysplasia was observed, with the most intense expression observed in severe cases of dysplasia. The correlation between the grade of dysplasia and the presence of biomarkers has been statistically significant ($p = 0.001$) (Table 3).

High-risk oral habits were found to have a statistically significant relationship with PMODs ($p = 0.032$). The PMODs were the highest among smokeless tobacco users, then the smokers, betel quid users, and combined habits (Table 4).

**Table 1: Demographic Characteristics and Distribution of High-Risk Oral Habits (n = 150)**

| Variable | Frequency (n) | Percentage (%) |
|---|---|---|
| Age (years) | | |
| 18–30 | 42 | 28.0 |
| 31–45 | 58 | 38.7 |
| 46–60 | 34 | 22.7 |
| >60 | 16 | 10.6 |
| Mean Age (years) | 39.8 ± 12.4 | |
| Gender | | |
| Male | 102 | 68.0 |
| Female | 48 | 32.0 |
| High-Risk Habits | | |
| Smoking | 45 | 30.0 |
| Smokeless Tobacco (Naswar/Gutka) | 52 | 34.7 |
| Betel Quid Chewing | 31 | 20.7 |
| Combined Habits | 22 | 14.6 |

**Table 2: Prevalence, Types, and Histopathological Features of PMODs (n = 150)**

| Variable | Frequency (n) | Percentage (%) |
|---|---|---|
| PMOD Status | | |

| | | |
|---|---|---|
| Present | 36 | 24.0 |
| Absent | 114 | 76.0 |
| Types of PMODs (n = 36) | | |
| Leukoplakia | 14 | 38.9 |
| Oral Submucous Fibrosis | 10 | 27.8 |
| Oral Lichen Planus | 7 | 19.4 |
| Erythroplakia | 5 | 13.9 |
| Histopathological Grading (n = 36) | | |
| No Dysplasia | 8 | 22.2 |
| Mild Dysplasia | 13 | 36.1 |
| Moderate Dysplasia | 9 | 25.0 |
| Severe Dysplasia | 6 | 16.7 |

**Table 3: Biological Marker Expression and Its Association with Dysplasia (n = 36)**

| Variable | p53 Positive n (%) | Ki-67 Positive n (%) | p-value |
|---|---|---|---|
| Overall Expression | 21 (58.3) | 25 (69.4) | |
| Dysplasia Grade | | | |
| No Dysplasia | 2 (25.0) | 3 (37.5) | 0.001 |
| Mild Dysplasia | 7 (53.8) | 9 (69.2) | |
| Moderate Dysplasia | 6 (66.7) | 7 (77.8) | |
| Severe Dysplasia | 6 (100) | 6 (100) | |

**Table 4: Association between High-Risk Oral Habits and PMODs (n = 150)**

| Habit Type | PMOD Present n (%) | PMOD Absent n (%) | p-value |
|---|---|---|---|
| Smoking | 10 (22.2) | 35 (77.8) | 0.032 |
| Smokeless Tobacco | 16 (30.8) | 36 (69.2) | |
| Betel Quid | 6 (19.4) | 25 (80.6) | |
| Combined Habits | 4 (18.2) | 18 (81.8) | |

## DISCUSSION

The current research assessed the prevalence, clinicopathological characteristics, and biological correlates of potentially malignant oral disorders (PMODs) in a group of people with high-risk oral practices. The overall prevalence of PMODs in our study was 24%, which is comparatively higher than several recent studies. Arun Dev Sharma et al. (2025) conducted a study in a hospital and found a prevalence of 7.57% among tobacco and areca nut users.[14] This disparity could be explained by the variation in the study population since our research was specifically focused on high-risk groups, and wider screening groups are likely to present lower prevalence rates. Likewise, individual lesions like leukoplakia have much lower estimates globally, with a combined prevalence of 1.36% to 2.23% in general populations, which further supports the greater burden of lesions in high-risk groups in our study.[15]

In terms of demographic distribution, our study showed that it was predominantly male (68%), in line with various recent studies showing a higher prevalence in males because of greater exposure to tobacco and habits related to it. A systematic review conducted in 2024 also reported a higher prevalence of oral submucous fibrosis (OSMF) among males (3.3%) compared to females.[16] Moreover, most of the individuals in our study fell within the middle-aged range (31-45 years), which also coincides with a recent study in India (2023) where the age-specific incidence of oral leukoplakia was highest in the fifth to sixth decade of life.[17]

Smokeless tobacco use was the most prevalent risk factor in our study in terms of habit distribution; this was followed by smoking and betel quid chewing. This is in line with the regional research in South Asia, where the use of areca nuts and smokeless tobacco has been noted to be a significant contributor to PMODs. The 2025 study by Arun Dev Sharma et al. also indicated that more than 70 percent of them were linked to the use of areca nut and smokeless tobacco.[14] This highlights the strong etiological link between these habits and the development of PMODs.

The most common lesions in our study were leukoplakia (38.9%) and OSMF and oral lichen planus. This result is consistent with the world literature, in which leukoplakia is always presented as the most frequent PMOD. In 2023, a systematic review established that leukoplakia contributes to a sizeable percentage of PMOD cases across the globe and has a high risk of malignant progression between 3 and 50% chance.[15] Nevertheless, there are reports of some regional studies, like the 2025 Indian study, which indicate OSMF to be the most common lesion, probably because of increased consumption of areca nut in these groups.[14] These variations emphasize the influence of geographic and cultural factors on disease patterns.

In our study, histopathological analysis showed that mild dysplasia was the most prevalent grade, then moderate and severe dysplasia. These results are similar to those of a 2025 study, which also found moderate dysplasia slightly more common, although a large percentage of cases also showed mild dysplasia.[18] The occurrence of dysplasia in many patients highlights the possibility of malignant change and the significance of early diagnosis and follow-up.

The analysis of biological markers proved that Ki-67 was more expressed than p53 and the severity of dysplasia was associated with the increase of its expression. Recent studies supporting this trend include the emphasis on proliferative and tumor suppressor markers in the measurement of malignant potential. In recent research, Ki-67 has been consistently determined to be a good indicator of cellular proliferation with p53 changes being linked to genetic variations and development towards malignancy.[19] Our study ($p = 0.001$) showed a significant association with these results, which supports the importance of these biomarkers in risk stratification.

Moreover, the statistically significant relationship was detected between high-risk oral habits and the presence of PMODs ($p = 0.032$). This observation is well supported by several studies carried out in the years, which have continually shown that there is a direct association between the frequency and duration of tobacco/areca nut consumption and the onset of PMODs. The 2024 meta-analysis also underscored that prevalence rates of OSMF showed significant increase in more exposed populations to risk factors.[20] These facts further confirm the etiological importance of these habits in oral carcinogenesis.

Altogether, the results of the current research are mostly aligned with the national and international literature, but the increased prevalence could be attributed to specific inclusion of high-risk groups. The combination of clinicopathological characteristics and biological correlates offers a more in-depth insight into PMODs and a congruity with the current research trends that focus on molecular profiling and early detection.

Limitations

There were a number of limitations in this study, which must be taken into account when interpreting the results. As a single-centered, hospital-based study, the findings might not be completely applicable to the general population of the community. Non-probability consecutive sampling could have created selection bias, especially since those with more severe symptoms are more apt to seek medical attention. Moreover, the cross-sectional design did not allow determining the temporal or causal relationships between high-risk habits and the development of potentially malignant oral disorders. Even though some of the most important biomarkers were assessed, the analysis of a broader set of molecular markers would have offered a better insight into the biological dynamics of these lesions. Moreover, the sample size is relatively small and the use of self-reported history of habit could have influenced the strength and accuracy of observed associations.

## CONCLUSION

Finally, this paper provides an account of a significant load of potentially malignant oral conditions in the persons with high-risk oral behaviors, the prevalence of which is significant, and lesions are characterized by different levels of epithelial dysplasia. The significant association between risk habits and PMODs, along with the progressive increase in biomarker expression with dysplasia severity, underscores the critical need for early screening, timely diagnosis, and risk stratification. Clinical, histopathological, and biological parameters integration is a more holistic way to define high-risk individuals and prevent malignant transformation. These results highlight the need to focus on specific public health initiatives, cessation of habits, and integration of biomarker examination into the mainstream clinical practice to diminish oral cancer occurrence

and progression.

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