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ORIGINAL ARTICLE

# Evaluation of Risk Factors for Oral Premalignant Lesions

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**OBJECTIVE**

Oral cancer is a serious global problem. Oral cancers sometimes arise on the premise of clinically visible lesions that are not initially cancerous and are therefore called premalignant. This study was conducted to contribute to the determination of the patient profile with oral premalignant lesions and the risk factors of the disease.

**METHODS**

This prospective cross-sectional study included 180 patients. The research was conducted using a questionnaire comprised of closed-ended questions directed at the patients. Statistical analysis of the data was conducted using the IBM SPSS Statistics software. The Pearson chi-square test was employed to analyze potential differences between groups, while the Mann-Whitney U test was utilized to evaluate lesion locations, with $p<0.05$ being significant.

**RESULTS**

Upon evaluating the areas of premalignant lesions in the case group, the predominant location was the cheek mucosa at 37.8% (n=68), followed by the tongue and lip mucosa at 12.2% (n=22). Our study identified a significant correlation between the presence of premalignant lesions and various factors, including paraphunctional habits, smoking, tobacco use, systemic diseases, amalgam fillings, aspirin consumption, and educational status ($p<0.001$ for all except $p=0.004$ for educational status). No statistically significant difference was seen between gender and premalignant lesions ($p=0.297$).

**CONCLUSION**

The early identification of clinically observable oral premalignant lesions is essential for the prevention of oral cancer. This study enhances the literature by assessing the risk variables associated with oral premalignant lesions.

**Keywords:** Oral cavity; premalignant lesion; risk factor.



## INTRODUCTION

Premalignant lesions of the oral mucosa encompass a category of disorders that necessitate early identification. During the World Health Organization meeting on the "histological definition of premalignant lesion," two distinct definitions were established: "premalignant lesion" and "premalignant condition." A premalignant lesion is characterized as "morphologically differentiated tissue exhibiting a heightened propensity to progress to cancer relative to its normal state," while a premalignant condition is described as "a generalized phenomenon associated with a markedly elevated risk of cancer".[1] Based on these definitions, localized cases such as leukoplakia and erythroplakia, palatal lesions resulting from reverse smoking, and actinic chei-

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litis are classified as "premalignant lesions," whereas generalized cases like sideropenic dysphagia (a potential premalignant condition) are cited as examples of "premalignant condition".[2]

The origin of premalignant lesions in the oral mucosa remains poorly understood, and research on this topic is ongoing.[3] Certain studies in the literature indicate that oral premalignant lesions correlate with various nutritional factors, including smoking, betel (areca quid) chewing, excessive alcohol consumption, diabetes, body mass index, and low vegetable intake; however, not all risk factors have been elucidated.[4–7]

Timely identification of oral premalignant lesions is crucial for survival, as they may evolve into lethal diseases like carcinoma in situ or severe dysplasia in later stages.[8] The principal strategy against these lesions should focus on diminishing disease incidence and decreasing the occurrence of oral premalignant lesions by preventing risk factors.

Given that premalignant instances are localized lesions with an elevated risk of malignant transformation relative to normal tissues, the early identification of these lesions is crucial for preventing progression to more severe cancer in the future. Moreover, despite several advancements in the diagnosis and treatment of cancer and premalignant lesions, mortality and morbidity are escalating globally, and there remains a lack of consensus among experts regarding their causation.[9,10] This study was conducted with a cohort of patients diagnosed with oral premalignant lesions and a control group without such lesions. It was designed as a cross-sectional prospective research study aimed at identifying the risk factors influencing premalignant lesions in human life.

## MATERIALS AND METHODS

This study adhered to the principles of the Declaration of Helsinki, and ethical approval was secured by the Clinical Research Ethics Committee of the Faculty of Medicine (no: KAEK: 2955, Date: 20/04/2022). This prospective cross-sectional study included 180 patients who presented to the Department of Oral and Maxillofacial Radiology at the Faculty of Dentistry from January 2023 to November 2023. The case group comprised 90 patients diagnosed clinically with oral premalignant lesions, while the control group included 90 healthy individuals devoid of such lesions. All patients having a history of trauma, surgery, cysts, tumors, malignant disorders, and prior malignancy in the orofacial region were excluded from the study. Patients unable to independently respond to the questionnaire were excluded from this study.

The research was conducted using a questionnaire comprised of closed-ended questions directed at the patients. The questionnaire of 14 items, including 4 aimed at assessing the demographic characteristics of the participants and 10 focused on evaluating the correlation between oral premalignant lesions and various causes. All surveys were administered in person to the patients, and the initial four questions inquired about age, gender, educational attainment, and occupation. The remaining 10 questions inquired about the presence and quantity of amalgam fillings, systemic diseases, frequent medications, parafunctional habits, the duration of these habits (in years), as well as smoking and alcohol consumption and their respective durations, with responses duly documented.

### Statistical Analysis

Based on the participants' responses, storage analyses were conducted using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corporation ) to assess the outcomes.

To ascertain the appropriate statistical analysis method for evaluating hypotheses regarding the comparison of continuous variables based on lesion locations, the Kolmogorov-Smirnov and Shapiro-Wilk tests were employed to assess data normality, while the Levene Test was utilized to examine variance homogeneity. Due to the absence of parametric distribution assumption qualities in the data set, the Mann-Whitney U Test, a nonparametric hypothesis test, was employed for analyses involving two groups. The Pearson chi-square test was employed to analyze potential differences between groups, while the Mann-Whitney U test was utilized to compare lesion locations, with a level of significance set at $p<0.05$.

## RESULTS

Among the 180 patients involved in the study, 89 (49.4%) were female and 91 (50.6%) were male. The patients' ages varied from 16 to 72 years, with a mean age of 43.8 years. An equal number of patients was included in both the case and control groups of the study. The predominant location of premalignant lesions in the case group was the cheek mucosa at 37.8% (n=68), succeeded by the tongue and lip mucosa at 12.2% (n=22). Table 1 presents the socio-demographic and cultural distribution of the patients. Among the patients, 37.2% (n=67) were secondary school graduates, 30.6% (n=55) were high school graduates, and 32.2% (n=58) were university graduates. Regarding occupational distribution, housewives constituted the predominant occupa-

**Table 1** Demographic and cultural characteristics of the patients

| Variable | n | % | Variable | n | % |
|---|---|---|---|---|---|
| Presence of Lesion | | | Parafunctional habit | | |
| None | 90 | 50 | None | 122 | 67.8 |
| There is | 90 | 50 | Teeth clenching and grinding | 45 | 25 |
| Lesion Location (n=90) | | | Other | 13 | 7.2 |
| Cheek Mucosa | 68 | 37.8 | Cigarette tobacco | | |
| Tongue/Lip Mucosa | 22 | 12.2 | None | 103 | 57.2 |
| Gender | | | There is | 77 | 42.8 |
| Male | 91 | 50.6 | Alcohol use | | |
| Woman | 89 | 49.4 | None | 179 | 99.4 |
| Education level | | | There is | 1 | 0.6 |
| Secondary Education | 67 | 37.2 | Clinical prediagnosis (n=90) | | |
| High School | 55 | 30.6 | Leukoplakia | 34 | 18.9 |
| Undergraduate and above | 58 | 32.2 | Lichen Planus | 34 | 18.9 |
| Profession | | | Other (Erythroplakia, Submucous Fibrosis) | 22 | 12.2 |
| Housewife | 68 | 37.8 | Systemic disease status | | |
| Tourism | 28 | 15.6 | None | 109 | 60.6 |
| Production | 28 | 15.6 | There is | 71 | 39.4 |
| Other | 56 | 31.1 | Systematic disease* | | |
| Employment Status | | | Cardiac | 22 | 31.0 |
| Not working | 68 | 37.8 | Respiration | 6 | 8.5 |
| Working | 112 | 62.2 | Haematological | 7 | 9.9 |
| Presence of amalgam filling | | | Endocrine | 30 | 42.3 |
| None | 88 | 48.9 | Kidney | 0 | 0.0 |
| There is | 92 | 51.1 | Autoimmune | 11 | 15.5 |
| Medication used | | | Malignant Diseases | 1 | 1.4 |
| None | 138 | 76.7 | Allergic | 0 | 0.0 |
| There is | 42 | 23.3 | Gastro | 9 | 12.7 |
| | | | Other | 1 | 1.4 |

*: Multiple answer. n: Number; %: Percent.

**Table 2** Descriptive statistics of patients characteristics and habits

| | n | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|
| Age | 180 | 43.8 | 12.9 | 45.0 | 16.0 | 72.0 |
| Number of amalgam fillings | 93 | 2.6 | 1.7 | 2.0 | 1.0 | 9.0 |
| Duration of parafunctional habit (year) | 58 | 6.2 | 5.9 | 4.0 | 1.0 | 20.0 |
| Number of cigarettes per day | 77 | 12.9 | 8.3 | 10.0 | 3.0 | 60.0 |
| Duration of smoking (year) | 141 | 9.9 | 13.1 | 2.0 | 0.0 | 40.0 |

n: number; SD: Standard deviation; Min: Minimum Max: Maximum

tion at 37.8% (n=68), followed by other occupational sectors (education, finance, health) at 31.1% (n=56). Of the participants, 42.8% (n=77) engaged in smoking and tobacco usage, but only 0.6% (n=1) were habitual alcohol consumers. Parafunctional habits were identified in 32.2% (n=58) of patients, with teeth grinding being the most prevalent habit at 25% (n=45). Systemic disease was identified in 39.4% (n=71) of patients, with endocrine diseases being the most prevalent, accounting for 42.3% (n=30). Amalgam fillings were identified in 51.1% (n=92) of patients.

Table 2 presents the average age, quantity of amalgam fillings, length of parafunctional habits (in years), daily cigarette use, and average smoking duration (in years) of patients in both groups. The average number of amalgam fillings was 2.6±1.7, the average duration

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**Table 3** Association of the presence of lesions with other factors

| | Presence of lesion | | | | Chi-square | p |
|---|---|---|---|---|---|---|
| | None | | There is | | | |
| | n | % | n | % | | |
| Gender | | | | | | |
| Male | 42 | 46.7 | 49 | 54.4 | 1.089 | 0.297 |
| Female | 48 | 53.3 | 41 | 45.6 | | |
| Education level | | | | | | |
| Secondary education | 23 | 25.6 | 44 | 48.9 | 10.852 | 0.004* |
| High School | 31 | 34.4 | 24 | 26.7 | | |
| Undergraduate and above | 36 | 40.0 | 22 | 24.4 | | |
| Profession | | | | | | |
| Housewife | 42 | 46.7 | 26 | 28.9 | 30.836 | <0.001* |
| Tourism | 4 | 4.4 | 24 | 26.7 | | |
| Production | 7 | 7.8 | 21 | 23.3 | | |
| Other | 37 | 41.1 | 19 | 21.1 | | |
| Employment status | | | | | | |
| Not working | 42 | 46.7 | 26 | 28.9 | 6.050 | 0.014* |
| Working | 48 | 53.3 | 64 | 71.1 | | |
| Presence of amalgam filling | | | | | | |
| None | 66 | 73.3 | 22 | 24.4 | 43.043 | <0.001* |
| There is | 24 | 26.7 | 68 | 75.6 | | |
| Medication Used | | | | | | |
| None | 82 | 91.1 | 56 | 62.2 | 20.994 | <0.001* |
| There is | 8 | 8.9 | 34 | 37.8 | | |
| Parafunctional habit | | | | | | |
| None | 81 | 90.0 | 41 | 45.6 | 41.084 | <0.001* |
| Teeth clenching and grinding | 6 | 6.7 | 39 | 43.3 | | |
| Other | 3 | 3.3 | 10 | 11.1 | | |
| Cigarette Tobacco | | | | | | |
| None | 64 | 71.1 | 39 | 43.3 | 14.185 | <0.001* |
| There is | 26 | 28.9 | 51 | 56.7 | | |
| Systemic disease status | | | | | | |
| None | 68 | 75.6 | 41 | 45.6 | 16.956 | <0.001* |
| There is | 22 | 24.4 | 49 | 54.4 | | |

*: <0.05; Chi-square test statistic, n: number

of parafunctional habits was 6.2±5.9 years, the average number of daily smokes was 12.9±8.3, and the average duration of smoking was 9.9±13.1 years.

Our cross-sectional survey investigation revealed a statistically significant association between the presence of premalignant lesions and educational status (p=0.004). The incidence of lesions diminishes with an increase in educational attainment.

Our investigation identified a statistically significant correlation between the existence of premalignant lesions and the presence of amalgam fillings (p<0.001). It can be concluded that an increase in the number of amalgam fillings correlates with a rise in the incidence of lesions.

Aspirin was the pharmaceutical utilized in our study, and an statistically significant correlation was identified with the occurrence of premalignant lesions (p<0.001). Aspirin consumption elevates the occurrence of oral premalignant lesions.

Our investigation identified a significant connection between the existence of premalignant lesions and paraphunctional habits, tobacco smoking, and systemic disorders (p<0.001 for all).

The existence of parafunctional behaviors, smoking, tobacco use, and systemic disorders elevates the frequency of oral premalignant lesions. Table 3 presents data assessing the correlation between the existence of premalignant lesions and other parameters.

**Table 4** Comparison of patients characteristics according to presence of lesion

| Presence of lesion | None | | | There is | | | z | p |
|---|---|---|---|---|---|---|---|---|
| | n | Mean±SD | Median (Q1–Q3) | n | Mean±SD | Median (Q1–Q3) | | |
| Age | 90 | 42.0±14.8 | 42.0 (29.8–53.0) | 90 | 45.6±10.4 | 45.0 (40.0–52.0) | 1.665 | 0.096 |
| Number of amalgam fillings | 25 | 2.1±2.1 | 1.0 (1.0–2.5) | 68 | 2.8±1.5 | 3.0 (1.0–4.0) | 2.752 | 0.006* |
| Duration of parafunctional habit (year) | 9 | 2.8±2.1 | 2.0 (1.0–4.0) | 49 | 6.9±6.2 | 4.0 (2.0–10.0) | 1.948 | 0.051 |
| Duration of smoking (year) | 90 | 3.9±8.5 | 0.0 (0.0–2.0) | 51 | 20.3±13.4 | 20.0 (10.0–35.0) | 8.019 | <0.001* |

*: <0.05. n: number; SD: standard deviation

There was no statistically significant difference between premalignant lesions for gender (p=0.297).

Table 4 presents the statistical analysis of the factors assessing the existence of lesions. No statistically significant difference was observed between age and duration of parafunctional habits and the existence of lesions (p=0.096, p=0.051, respectively). The quantity of amalgam fillings and the length of smoking shown a statistically significant correlation with the existence of lesions (p=0.006, p<0.001, respectively).

## DISCUSSION

The oral mucosa is a region where a considerable percentage of premalignant lesions, exceeding 5%, progress to malignancy.[2] Consequently, the diagnosis of premalignant lesions is crucial for the early identification of potential cancerous developments. The examination of risk factors, including tobacco use, betel quid chewing, alcohol consumption, HPV, mucosal inflammation, and oral mucosal trauma from teeth and prosthetic devices, believed to contribute to the development of premalignant lesions, has garnered heightened interest in numerous clinical and scientific investigations.[11] Given that the majority of risk factors can be mitigated, the development of premalignant lesions and oral cancer can be regarded as predominantly avoidable conditions. Nonetheless, its manifestation in patients outside of risk categories remains feasible.[12] Our research will aid in diminishing the progression of premalignant lesions to potential oral malignancies by investigating the risk factors associated with the development of these lesions and implementing preventive measures.

Although our survey investigation revealed no statistically significant difference in the prevalence of premalignant lesions by gender, Nair et al.[13] identified a greater prevalence of oral potentially malignant illnesses and oral cancer in men. A comparable discovery was documented by Chung et al.[4] A study conducted in Taiwan indicated a statistically significant difference between numerous oral potential malignant illnesses and gender. This disparity in our study may stem from the smaller population size and the almost equal distribution of male and female participants while examining the risk variables for premalignant lesions. Furthermore, the disparities shown in our study may also stem from racial composition, variations in social customs, and variances in average age.

A study indicated that a high socioeconomic index and elevated education level serve as preventive factors against oral premalignant lesions.[6] Our questionnaire investigation revealed a statistically significant correlation between the existence of premalignant lesions and educational attainment, leading to the conclusion that the incidence of lesions diminishes with higher educational levels. We also determined that occupational status was statistically significant as a pertinent risk factor in the development of premalignant lesions. A separate study proposed the socioeconomic index as a potential factor in the development of oral malignancies.[14] The prevalence of oral premalignant lesions is likely elevated among individuals with lower educational attainment and socioeconomic status, as they have reduced access to medical care, are less inclined to seek treatment for oral premalignant lesions, and place diminished emphasis on oral health information due to their limited knowledge.

Dental amalgams are often utilized posterior restorative materials in dentistry. The research has demonstrated a correlation between mercury contact allergy and the development of oral lichen planus.[15] A case report on oral leukoplakia indicated that the lesions fully resolved within three weeks following the replacement of amalgam restorations, with no recurrence seen during a five-year follow-up period.[16] In our investigation, a statistically significant correlation was identified between the existence of oral premalignant lesions and the presence of amalgam fillings. The

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incidence of lesions may rise with an increase in the number of amalgam fillings. These instances, aligned with our findings, indicate that addressing clinically identifiable premalignant lesions is crucial for preventing oral cancer, with an emphasis on eliminating risk factors. Should premalignant lesions in patients with amalgam restorations exhibit resistance to standard treatment modalities, it is advisable to conduct a patch test; if a reactivity to mercury or amalgam constituents is observed, such restorations should be substituted.

Our investigation identified aspirin as the utilized medication, revealing a statistically significant correlation between the occurrence of premalignant lesions and aspirin usage. Consequently, we conclude that aspirin consumption elevates the incidence of oral premalignant lesions. with a separate study, distinct from our findings, Jayaprakash et al.[17] examined 529 head and neck squamous cell carcinoma cases and 529 healthy individuals from 1992 to 1998, revealing that aspirin use resulted with a 25% reduction in the incidence of oral squamous cell carcinomas among non-smokers and a 33% reduction among smokers. A previous investigation revealed that the risk of oral cancer escalated in young individuals who used low-dose aspirin, corroborating our finding.[18] While certain studies have identified beneficial outcomes associated with prolonged (>5 years) aspirin consumption, the underlying mechanisms of aspirin's antineoplastic properties remain contentious.[19] The inability to distinctly identify other risk factors among the individuals may have impacted our results. A substantial cohort with a diverse age range is required to assess the overall impact of aspirin on oral premalignant lesions.

Our investigation identified a statistically significant correlation between the prevalence of premalignant lesions and parafunctional habits, with teeth clenching and grinding being the most prevalent parafunctional habit. Parafunctional habits may induce chronic trauma, which we believe could contribute to cancer. Experimental investigations into chemically induced carcinogenesis via mechanical irritation of the oral mucosa have demonstrated that chronic trauma may serve as a promoter and risk factor for oral neoplasms.[20,21] A further study corroborating this notion determined that parafunctional habits elevate the probability of premalignant lesion development following persistent trauma.[22] Chronic inflammation can trigger the carcinogenic process by inducing the release of cytokines, which may lead to oxidative stress and subsequent DNA damage.[23] Epidemiological studies typically investigate the correlation between chronic trauma generated by prostheses and malignancy. Most studies exclude additional traumatic factors, such as faulty dentition or parafunctional habits, and fail to examine the correlation between oral premalignant conditions.[24,25]

Tobacco is recognized to have over 60 carcinogenic substances. These compounds expedite the inflammatory process upon contact with the oral mucosa, and prolonged use may result in pathological alterations in the oral mucosa.[26] A separate investigation indicated that smokers have a greater risk of developing oral premalignant lesions compared to nonsmokers, aligning with our findings.[27] In instances of oral premalignant lesions attributable to smoking, quitting of smoking may lead to partial or total regression of the lesion.[28] A meta-analysis indicated that smokers have a threefold increased chance of acquiring oral cancer compared to non-smokers.[29] Furthermore, it has been reported that smoking prevalence and the occurrence of smoking-related malignancies have markedly declined due to anti-smoking initiatives implemented in numerous affluent nations in recent years.[30] This study identified a statistically significant link between smoking and tobacco use and the development of oral premalignant lesions, indicating that these factors contribute to the production of such lesions and are critical risk factors.

Numerous studies in the literature have identified a positive relationship between diabetes and the onset of oral possibly malignant illnesses.[31,32] The diabetic individual exhibits inadequate oral hygiene, diminished salivation, and xerostomia, which may heighten vulnerability to oral mucosal illnesses and infections.[33] This study indicated that systemic diseases, including respiratory, cardiovascular, hematological, endocrinological, renal, autoimmune, allergic, and gastrointestinal disorders, may elevate the incidence of oral premalignant lesions.

This research possesses certain limitations. This is a cross-sectional study. The study comprised adult patients, and risk factors for the establishment of premalignant lesions in the juvenile population could not be assessed. Ultimately, it is advisable to assess the risk variables associated with premalignant lesions and do research involving a broader population to obtain more definitive conclusions.

## CONCLUSION

The current study enhances the literature by assessing the risk variables associated with oral premalignant lesions. It is crucial to identify risk factors to avoid the progression of clinically detectable oral premalignant lesions into oral carcinomas and to mitigate exposure to these risk factors among affected persons.

**Ethics Committee Approval:** The study was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (no: 2955, date: 20/04/2022).

**Informed Consent:** Informed consent was obtained from all participants.

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