

Molecular and Cytopathological Determinants of Malignant Transformations in Oral Leukoplakia: A Meta-Analytic Synthesis of AgNOR, DNA Ploidy, Cytokeratin, and Podoplanin Evidence

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ABSTRACT

Background: Oral leukoplakia is one of the cancer-causing oral diseases, which often manifest as predecessors of oral cancer. This study summarizes diagnostic characteristics and prognostic predictors of leukoplakia, a known contributor to cancer metamorphosis, by understanding dysplasia categories and lesional properties. **Methodology:** The research adopted a thorough database search in PubMed, Scopus, and Web of Science according to PRISMA protocols, from 2011 till 2024. The inclusion criteria involved studies with retrospective disease measurements coupled with leukoplakia and malignancy evaluation. Non-human research or studies lacking quantitative analysis were excluded. The Newcastle-Ottawa Scale was used for evaluating risk of bias whereas, quality of study was evaluated using GRADE approach. RevMan 5.4 was used for statistical analysis. **Results:** Total 12 studies were included in this study and results showed that the combination of epithelial dysplasia with AgNOR count and DNA ploidy analysis with biomarker expression studies, indicated positive relationships between markers of risk and malignant cell transformation. The risk of bias of most studies was measured as moderate to high through and GRADE rated certainty of evidence as moderate. A pooled odds ratio (OR) of 3.31 (95% CI: 1.69–6.46, $p < 0.05$) with high heterogeneity I^2 value of 98%, were observed. **Conclusion:** An integrated study on the analysis of tissue structure and molecular evidence might help in the better diagnosis of leukoplakia as being a marker of oral malignancy as well as better estimation of risk.

Keywords: Oral Leukoplakia, Oral Neoplasms, Epithelial Dysplasia, Biomarkers, Tumor, Disease Progression

Introduction

Leukoplakia with dysplastic changes often progress into invasive squamous cell carcinoma¹. In diagnostic oral pathology, the assessment of the severity of the dysplasia was made using the structural and cytological criteria to determine the outcomes that might be expected in the future and possible treatments strategies^{2,3}. The exact pathways involved in disease progression during oral leukoplakia remained unclear since the currently used histological grading techniques had limited capacity in predicting cancer transformation^{4,5}. Risk of malignant transformation arises in different ways depending on the exact location, lesion size, how intense the condition appears under a microscope, and patient risks⁶⁻⁸. The diagnostic accuracy of leukoplakia and its prognosis is lacking due to varying interpretation by the technicians as well as limitation of sampling method and dysplasia analysis is by subjective terms⁹.

An in-depth analysis of the association of leukoplakia with the development of oral cancer should be conducted since there was disparate interpretative accuracy of the physicians in decoding diagnostic data and examining clinical manifestations^{10,11}. The systematic assessment with the evidence should state whether or not leukoplakia was an indicator of developing a cancer and its role in risk assessment process.

The current systematic review and meta-analysis was focused on the diagnosis and prediction potential of leukoplakia by analyzing dysplasia stages and lesion characteristics and the influence they might had on malignant outcome. The purpose of the evaluative process was to determine the predictive ability of leukoplakia in the onset of oral malignancy to enhance the clinical decision-making and early diagnosis.

Methodology

The investigation followed the PRISMA 2020 guidelines to assess oral leukoplakia as a potential oral malignancy predictor and its clinical diagnostic and prognostic characteristics ¹².

Inclusion and Exclusion Criteria: The criteria for included studies were human-based studies that had either observational elements or retrospective disease measurements combined with leukoplakia and malignancy evaluation. The evaluation excluded non-human research articles and studies that failed to provide quantitative data regarding the association between oral leukoplakia and malignant transformation.

Database Search: Researchers conducted a detailed literature search in PubMed, Scopus, Web of Science, and the Cochrane Library.

Search String Used: The research employed the terms “oral leukoplakia,” “oral malignancy,” “oral cancer,” “dysplasia,” “malignant transformation,” and “oral pathology,” Boolean operators “AND” and “OR.” were also applied to refine the search.

Study Selection: The title and abstract of were reviewed independently by two researchers until proper inclusion requirement met. The reviewers settled their selection differences either through group agreement or expert consultation.

Data Extraction: Two reviewers extracted data in separate sessions using a pre-developed data extraction form. The investigators extracted information based on study design, sample size, confounders, outcomes measured and key findings. The reviewers used discussion and third-reviewer adjudication to solve discrepancies during the data extraction process.

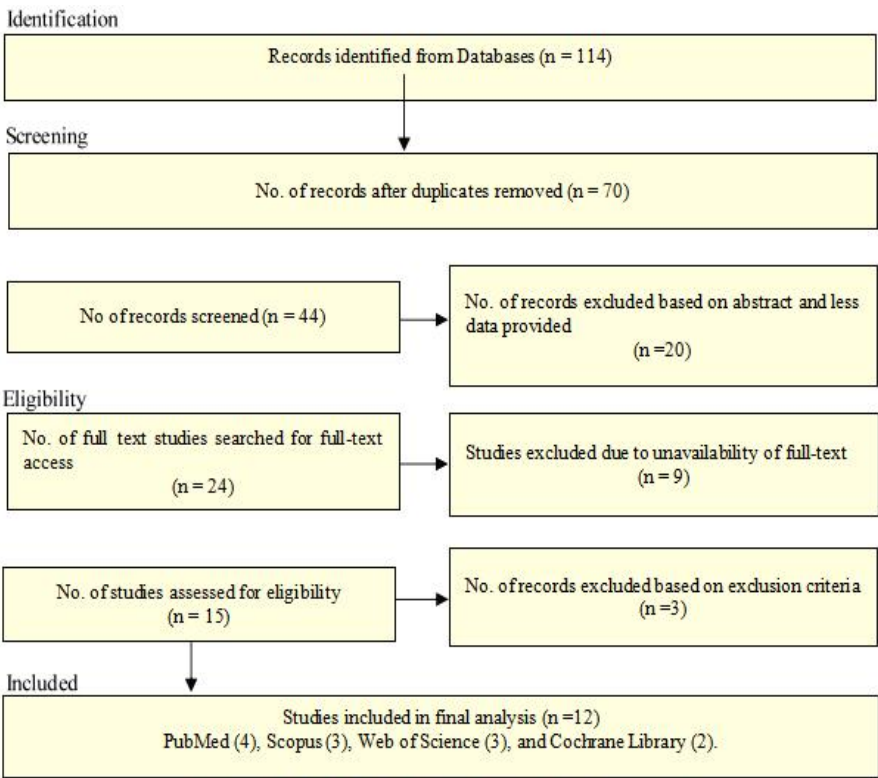


Figure 1: PRISMA Flow Diagram for the Selection of Studies

Primary Outcome: Transformation of oral leukoplakia to oral squamous cell carcinoma (OSCC) had been evaluated based on molecular, cytopathological, and genetic endpoints i.e., number of AgNOR, the state of DNA ploidy, the pattern of cytokeratin expression, podoplanin expression, and select genomic changes.

Quality Assessment: An assessment of selection factors, outcome parameters and comparison of quality in selected observational studies was evaluated using Newcastle-Ottawa Scale (NOS) ¹³. The authors applied the GRADE framework to perform quality assessment on available evidence.

Statistical Assessment: RevMan 5.4 was used for statistical analysis. An inverse variance random effects model was used to derive pooled odds ratios (ORs) together with 95% confidence intervals (CIs) ¹⁴. Heterogeneity was measured through the P statistic, and forest plots were generated to visualize effect sizes. Sensitivity analysis was applied to eliminate studies with a potential high risk of to verify the stability of the obtained data.

Results

The study analyzed the use of leukoplakia and associated dysplastic lesions to predict oral malignancies through retrospective and observational research approaches. A total of 114 records were retrieved after database search and 70 of them were duplicates. Among the 44 screened articles, 20 were removed after the abstract evaluation. Due to unavailability of full text, 9 studies were further removed and remaining 15 studies were assessed for eligibility. After excluding 3 studies on the basis of exclusion criteria, 12 studies were included in this study to establish the synthesis. The 12 included studies ranging from small focused cohort studies up to large population-based studies with a single nationwide observational study of more than 3 million participants. The analysis results involved cross-sectional, retrospective cohort, prospective observational, and observational studies. The main confounders that were usually manipulated in the studies were age, sex, smoking status, alcohol intake, nature of lesions, and histological grade. An overview of the features and key findings of the included works are displayed in Table 1.

Table 1: Summary of Included Studies and their Key Findings

Author & Year	Sample Size (n)	Study Design	Confounders	Outcomes Measured	Key Findings
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Dogenski et al., 2021 ¹⁵	107	Cross-sectional, observational study	Smoking, alcohol use, age, and sex	Mean AgNOR count, lesion characteristics, symptoms, and histopathological traits	AgNOR count significantly linked with lesion characteristics.
Nomura et al., 2018 ¹⁶	114	Retrospective Observational Study	Age, smoking, and drinking habits	Prevalence of oral leukoplakia; association with cumulative PLD dose	High PLD dose is significantly associated with leukoplakia.
Pentenero et al., 2023 ¹⁷	153	Prospective Observational	Clinical presentation, lesion site, DNA ploidy, OED	Malignant transformation (MT)	OED and DNA ploidy predicted malignancy transformation.
Arora, K. S. et al., 2018 ¹⁸	60	Observational study	Age, Gender, Pre-existing conditions	Efficacy of diode laser in managing oral leukoplakia and oral lichen planus	Diode laser is effective in reducing leukoplakia recurrence.
Chiu, S.-F. et al., 2021 ¹⁹	3,362,232	Observational study	Age, Habit, Gender	Malignant transformation rates	Malignant transformation rates are higher for OVH and OSF, with female patients at higher risk.
Wei Cao et al., 2011 ²⁰	76	Observational study	Age, Habit, Gender	EZH2 expression, OSCC development	Higher EZH2 expression levels correlate with dysplasia and OSCC development.
Moreira et al., 2024 ²¹	67	Cross-sectional observational study	Age, Habit (smoking, alcohol consumption), Gender	Sociodemographic and clinicopathological features	Dysplasia is common in proliferative verrucous leukoplakia.
Wils et al., 2023 ²²	176	Retrospective cohort	Presence of classic epithelial dysplasia; cytokeratin 13/17 expression	Malignant transformation to oral squamous cell carcinoma (OSCC) during follow-up	Epithelial dysplasia increases cancer risk, with differentiated dysplasia showing the highest risk.
Wils et al., 2020 ²³	84	Retrospective cohort	Histological grade, CK13/CK17 status	Malignant progression to oral SCC; expression of CK13/17; presence of differentiated vs classic dysplasia	30% of cases developed SCC; differentiated dysplasia and CK13 loss were strongly associated with progression.
Wils et al., 2023 ²⁴	89	Retrospective cohort	Age, Habit, Gender	Genomic copy-number alterations, mutations (TP53, FAT1, NOTCH1), development of OSCC	28% developed OSCC; genetic alterations and dysplasia combined in risk model.
Monteiro et al., 2022 ²⁵	52 OL (41 LG, 11 HG) + 12 NT	Observational	Dysplasia grade, biomarker expression	Malignant transformation (MT), biomarker expression levels	High podoplanin expression increases malignant transformation, combined with dysplasia grade.
Costa et al., 2019 ²⁶	57	Retrospective study	Dysplasia grade, biomarker expression	ALDH1A1 and ALDH2 expression in OLP and OSCC	ALDH1A1 expression decreases in OSCC, while ALDH2 increases.

Abbreviations: AgNOR, Argyrophilic Nucleolar Organizer Regions. ALDH1A1, Aldehyde Dehydrogenase 1 Family Member A1. ALDH2, Aldehyde Dehydrogenase 2. CK13, Cytokeratin 13. CK17, Cytokeratin 17. DNA, Deoxyribonucleic Acid. EZH2, Enhancer of Zeste Homolog 2. HG, High Grade. LG, Low Grade. MT, Malignant Transformation. NT, Normal Tissue. OED, Oral Epithelial Dysplasia. OL, Oral Leukoplakia. OLP, Oral Lichen Planus. OSCC, Oral Squamous Cell Carcinoma. OSF, Oral Submucous Fibrosis. OVH, Oral Verrucous Hyperplasia. PLD, Pegylated Liposomal Doxorubicin. SCC, Squamous Cell Carcinoma. TP53, Tumor Protein p53. FAT1, FAT Atypical Cadherin 1. NOTCH1, Notch Receptor 1.

Malignant transformation OSCC and the expression or change of molecular and cytopathological biomarkers (AgNOR count, DNA ploidy status, cytokeratin (CK13/CK17) expression, podoplanin, EZH2, and ALDH isoenzymes) were the main outcomes that were evaluated. A number of studies proved that the severity of epithelial dysplasia, its aneuploidy, CK13 destruction, CK17 acquisition, and high podoplanin level correlated with the risk of malignant transformation significantly. Newcastle-Ottawa Scale (NOS) was used to determine the risk of bias in observational studies. The overall quality of the studies was moderate to high with the total scores being between 5-9 out of possible 9 points. Four articles had the best score (NOS = 9) of good selection criteria, decent comparability, and good outcome measure. Most of the studies (n=7) had a low or moderately low risk of bias whereas one study had a relatively high risk of bias because of poor comparability and outcome measuring. Table 2 presents the risk of bias scoring in detail.

Table 2: Risk of Bias Assessment of Observational Studies

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)
Dogenski et al., 2021 ¹⁵	★★★	★★	★★	7
Nomura et al., 2018 ¹⁶	★★	★★	★★	6
Pentenero et al., 2023 ¹⁷	★★★★	★★	★★★	9
Arora, K. S. et al., 2018 ¹⁸	★★★★	★★	★★★	8
Chiu, S.-F. et al., 2021 ¹⁹	★★★★	★★	★★★	9
Wei Cao et al., 2011 ²⁰	★★★★	★★	★★★	8
Moreira et al., 2024 ²¹	★★★★	★★	★★★	8

Wils et al., 2023 ²²	★★★	★★	★★★	8
Wils et al., 2020 ²³	★★★	★★	★★★	8
Wils et al., 2023 ²⁴	★★	★★	★★	6
Monteiro et al., 2022 ²⁵	★★★	★★	★★★	8
Costa et al., 2019 ²⁶	★★	★	★★	5

Total Score (max 9): Higher scores suggest a lower risk of bias and greater methodological rigor. 7–9 stars: Low risk of bias, 4–6: Moderate risk of bias, <4: High risk of bias.

The GRADE evidence showed consistent reliability through a combination of studies showing either moderate or high scores, although some studies experienced slight limitations in their comparability and selection methods.

RevMan version 5.4 was used to perform quantitative synthesis, with an inverse variance random-effects model used to explain clinical and methodological heterogeneity by the studies. The pooled analysis showed statistically significant association between the malignant transformation and the molecular/cytopathological abnormalities of the oral leukoplakia with the overall odds ratio (OR) of 3.31 (95% CI: 1.69–6.46, $p < 0.05$), as shown in Figure 2. The result shows that, patients who had high-risk molecular or cytopathological features (compared to the patients who lacked such features) were three times more likely to develop malignant.

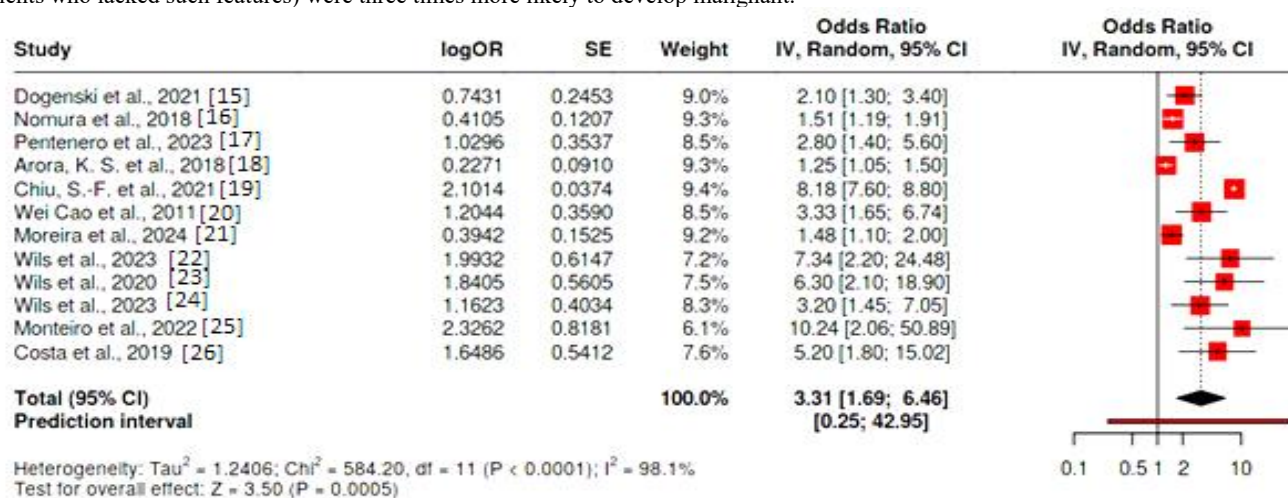


Figure 2: Meta-analytic forest plot of studies examining the association between leukoplakia and oral malignant transformation

There was a significant heterogeneity among the included studies ($I^2 = 98$, $p < 0.01$) that was observed because lesion site, lesion size, histopathological grading, methods used in the assessment of biomarkers and duration of follow-ups varied greatly. Although significant heterogeneity was observed, the direction and magnitude of effect remained constant, confirming the strength of the observed association. The pooled effect estimate was stable and was performed by sensitivity analysis by sequentially dropping out studies until all studies dropped out of the overall conclusions. The results indicated that no single dataset had an overbearing impact in the meta-analytic results.

Discussion

Oral leukoplakia's capability to predict oral malignancies is a hot topic among scientists, since multiple academic investigations analyzed its diagnostic and prognostic value ²⁷. This comprehensive systematic review, together with meta-analysis, demonstrated strong proof regarding the critical predictive value of leukoplakia in oral tissue transformation toward malignancy ²⁸. The analysis revealed that oral cancer development had a higher chance with dysplastic leukoplakia than with other types of leukoplakia. The literature further confirmed that epithelial dysplasia served as a critical element to determine future cancer development risks in patients ²⁹.

The probability of oral cancer development from leukoplakia depended on which location of lesion in the mouth and what stage of dysplasia it displayed, together with AgNOR numbers and DNA ploidy measurements ³⁰. Combining different factors enhanced the accuracy of prediction regarding cancerous potential. The aggressive nature of leukoplakia and its risk of becoming malignant could be better assessed through p53 and Ki-67 biomarker expression levels ^{31,32}. The results showed substantial variation because different procedures had been used for biomarker measurements, as well as limitations of retrospective research designs ³³⁻³⁴. The results showed smoking and alcohol usage as secondary risk factors that created substantial effects on the cancer-forming potential of leukoplakia tissue ^{35,36}. Various research papers indicated that cigarette smoking, along with alcohol consumption, contributed to increase the chances of malignant changes ^{37,38}. Additional research was needed on how environmental risk elements interact with molecular pathways of leukoplakia to cause malignancy because studies show inconsistent findings about how these risk elements influence ^{39,40}.

This study had several limitations. The variable study findings derived from multiple methodological reasons, including sample size differences alongside varied study designs, follow-up protocols, and assessment methods. Research methods that use different protocols for histopathological and molecular analysis contributed to these inconsistent results. Studies with negative or inconclusive results face decreased chances of being published in this field, thus indicating potential biases in overall conclusions. Further research by using standard protocol was needed for better study comparisons. The requirement for extensive multicenter randomized controlled trials (RCTs) was required because they would deliver stronger evidence about oral malignancy prediction linked to leukoplakia.

Conclusion

This meta-analysis based systematic study endorsed oral leukoplakia as a predictive factor in the development of oral tumors. Dysplasia, key molecular pointers and evident clinical signs contribute to the elevation of risk of emergence of malignant development in the future. Across research studies, there was heterogeneity in the research designs and this gap should be bridged by employing the standardized clinical protocols as well as longitudinal studies to ensure the derivation of a conclusive risk assessment model.

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Conflict of Interest: None

Use of Artificial Intelligence: The corresponding author declared that no other artificial intelligence or AI-assisted tools were used anywhere in this manuscript

Authors' Contribution: Study is Meta-Analysis and all Authors Contributed equally as per ICMJE roles.

References

1. Kumari P, Debta P, Dixit A. Oral potentially malignant disorders: Etiology, pathogenesis, and transformation into oral cancer. *Front Pharmacol*. 2022 Mar;13:825266. <https://doi.org/10.3389/fphar.2022.825266>
2. Brouns E, Baart J, Karagozoglu K, Aartman I, Bloemena E, van der Waal I. Malignant transformation of oral leukoplakia in a well-defined cohort of 144 patients. *Oral Dis*. 2014 Mar;20(3):e19-24. <https://doi.org/10.1111/odi.12095>
3. Das NK, Kadir AKMS, Shemanto MU, Akhter E, Sharfaraz A, Tripura S, et al. Genetic revelation of the potentially malignant disorders in the oral and maxillofacial region. In: *Population Genetics—From DNA to Evolutionary Biology*. IntechOpen; 2023. <https://doi.org/10.5772/intechopen.112697>
4. Elimairi I, Sami A, Yousef B. Oral cancer and potentially malignant disorders. In: *Histopathology—An Update*. IntechOpen; 2017. <https://doi.org/10.5772/intechopen.71887>
5. Gómez-Armayones S, Chimenos-Küstner E, Arranz C, Tous S, Marquez S, Penín RM, et al. Risk factors for oral epithelial dysplasias to become malignant: Clinical implications. *Int J Oral Maxillofac Surg*. 2022 Apr;51(4):473-480. <https://doi.org/10.1016/j.ijom.2021.08.012>
6. Gupta I, Badrzadeh F, Tsentalovich Y, Gaykalova DA. Connecting the dots: Investigating the link between environmental, genetic, and epigenetic influences in metabolomic alterations in oral squamous cell carcinoma. *J Exp Clin Cancer Res*. 2024 Jan;43(1):239. <https://doi.org/10.1186/s13046-024-03141-5>
7. Alam SS, Ahmed S, Farook TH, Dudley J. Predicting leukoplakia and oral squamous cell carcinoma using interpretable machine learning: A retrospective analysis. *Oral*. 2024;4(3):32. <https://doi.org/10.3390/oral4030032>
8. He S, Chakraborty R, Ranganathan S. Proliferation and apoptosis pathways and factors in oral squamous cell carcinoma. *Int J Mol Sci*. 2022 Mar;23(3):1562. <https://doi.org/10.3390/ijms23031562>
9. Sundaram E, Pal US, Sowmya MV, Kumar V, Yadav S. Field cancerisation in oral squamous cell carcinoma patients: A systematic review. *J Maxillofac Oral Surg*. 2025 Apr;24(2):416–431. <https://doi.org/10.1007/s12663-024-02287-1>
10. Jing F, Zhang J, Cai X, Zhou X, Bai J, Zhang H, et al. Screening for biomarkers for progression from oral leukoplakia to oral squamous cell carcinoma and evaluation of diagnostic efficacy by multiple machine learning algorithms. *Cancers*. 2022 Dec;14(23):5808. <https://doi.org/10.3390/cancers14235808>
11. Khong B, Ferlito S, Quek S, Conte G, Ingrassia A, Lechien JR, et al. Past, present, and future diagnostic methods for the early noninvasive detection of oral premalignant lesions: A state of the art and systematic review. *Ear Nose Throat J*. 2024 Apr;01455613241245204. <https://doi.org/10.1177/01455613241245204>
12. Parums DV. Review articles, systematic reviews, meta-analysis, and the updated preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guidelines. *Med Sci Monit*. 2021 Aug;27:e934475-1. <https://doi.org/10.12659/MSM.934475>
13. Carra MC, Romandini P, Romandini M. Risk of bias evaluation of cross-sectional studies: Adaptation of the Newcastle–Ottawa Scale. *J Periodontal Res*. 2025 Apr;60(2):e13405. <https://doi.org/10.1111/jre.13405>
14. Jun S, Park H, Kim UJ, Lee HA, Park B, Lee SY, et al. The combined effects of alcohol consumption and smoking on cancer risk by exposure level: A systematic review and meta-analysis. *J Korean Med Sci*. 2024 Jun;39(22):e185. <https://doi.org/10.3346/jkms.2024.39.e185>
15. Dogenski LC, de Figueiredo Ribeiro S, Gambin DJ, Maso PC, Linden MSS, Trentin MS, et al. Oral leukoplakia-epidemiological survey and histochemical analysis of 107 cases in Brazil. *Clin Oral Investig*. 2021 Apr;25(4):1859-1867. <https://doi.org/10.1007/s00784-020-03488-x>
16. Nomura H, Sakamoto K, Sugihara T, Okamoto S, Aoki Y, Tanigawa T, et al. Oral leukoplakia, a precancerous lesion of squamous cell carcinoma, in patients with long-term pegylated liposomal doxorubicin treatment. *Medicine*. 2018 Feb;97(7):e9932. <https://doi.org/10.1097/MD.00000000000009932>
17. Pentenero M, Castagnola P, Castillo FV, Isaevska E, Suter S, Gandolfo S. Predictors of malignant transformation in oral leukoplakia and proliferative verrucous leukoplakia: An observational prospective study including the DNA ploidy status. *Head Neck*. 2023 Oct;45(10):2589-2604. <https://doi.org/10.1002/hed.27483>

18. Arora KS, Bansal R, Mohapatra S, Verma A, Sharma S, Pareek S. Prevention of malignant transformation of oral leukoplakia and oral lichen planus using laser: An observational study. *Asian Pac J Cancer Prev*. 2018 Dec;19(12):3635-3641. <https://doi.org/10.31557/APJCP.2018.19.12.3635>
19. Chiu SF, Ho CH, Chen YC, Wu LW, Chen YL, Wu JH, et al. Malignant transformation of oral potentially malignant disorders in Taiwan: An observational nationwide population database study. *Medicine*. 2021 Sep;100(9):e24934. <https://doi.org/10.1097/MD.00000000000024934>
20. Cao W, Younis RH, Li J, Chen H, Xia R, Mao L, et al. EZH2 promotes malignant phenotypes and is a predictor of oral cancer development in patients with oral leukoplakia. *Cancer Prev Res*. 2011 Nov;4(11):1816-1824. <https://doi.org/10.1158/1940-6207.CAPR-11-0130>
21. Moreira MD, Maia FD, Zimbrão VL, Collodetti E, Grão-Velloso TR, Pimenta-Barros LA, et al. Demographic and clinicopathological comparison among oral lichen planus, lichenoid lesions and proliferative verrucous leukoplakia: A retrospective study. *BMC Oral Health*. 2024 Jan;24(1):1512. <https://doi.org/10.1186/s12903-024-05305-3>
22. Wils LJ, Poell JB, Brink A, Evren I, Brouns ER, de Visscher JGAM, et al. Elucidating the genetic landscape of oral leukoplakia to predict malignant transformation. *Clin Cancer Res*. 2023 Feb;29(3):602-613. <https://doi.org/10.1158/1078-0432.CCR-22-2210>
23. Wils LJ, Poell JB, Evren I, Koopman MS, Brouns EREA, de Visscher JGAM, et al. Incorporation of differentiated dysplasia improves prediction of oral leukoplakia at increased risk of malignant progression. *Mod Pathol*. 2020 Jun;33(6):1033-1040. <https://doi.org/10.1038/s41379-019-0444-0>
24. Wils LJ, Poell JB, Peferoen LAN, Evren I, Brouns ER, de Visscher JGAM, et al. The role of differentiated dysplasia in the prediction of malignant transformation of oral leukoplakia. *J Oral Pathol Med*. 2023 Oct;52(10):930-938. <https://doi.org/10.1111/jop.13483>
25. Monteiro L, do Amaral B, Delgado L, Garcês F, Salazar F, Pacheco JJ, et al. Podoplanin expression independently and jointly with oral epithelial dysplasia grade acts as a potential biomarker of malignant transformation in oral leukoplakia. *Biomolecules*. 2022 May;12(5):606. <https://doi.org/10.3390/biom12050606>
26. Herrera Costa F, Narana Ribeiro El Achkar V, Costa V, Paladini I, Kowalski LP, Rodarte Carvalho Y, et al. Different expression of aldehyde dehydrogenases 1A1 and 2 in oral leukoplakia with epithelial dysplasia and in oral squamous cell carcinoma. *Appl Immunohistochem Mol Morphol*. 2019 Jul;27(7):537-542. <https://doi.org/10.1097/PAI.0000000000000612>
27. Lin HJ, Wang XL, Tian MY, Li XL, Tan HZ. Betel quid chewing and oral potential malignant disorders and the impact of smoking and drinking: A meta-analysis. *World J Clin Cases*. 2022 Mar;10(10):3131-3142. <https://doi.org/10.12998/wjcc.v10.i10.3131>
28. Nasser W, Flechtenmacher C, Holzinger D, Hofele C, Bosch FX. Aberrant expression of p53, p16INK4a and Ki-67 as basic biomarker for malignant progression of oral leukoplakias. *J Oral Pathol Med*. 2011 Aug;40(8):629-635. <https://doi.org/10.1111/j.1600-0714.2011.01026.x>
29. Ranganathan K, Kavitha L. Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders. *J Oral Maxillofac Pathol*. 2019 Jan;23(1):19-27. https://doi.org/10.4103/jomfp.JOMFP_13_19
30. Reibel J. Prognosis of oral pre-malignant lesions: Significance of clinical, histopathological, and molecular biological characteristics. *Crit Rev Oral Biol Med*. 2003 Jan;14(1):47-62. <https://doi.org/10.1177/154411130301400105>
31. Rivero LF, Graudenz MS, Ashton-Prolla P, Delgado AM, Kliemann LM. Accuracy of p53 and ki-67 in the graduation of phyllodes tumor, a model for practical application. *Surg Exp Pathol*. 2020 Mar;3(1):7. <https://doi.org/10.1186/s42047-020-0058-3>
32. Sankaranarayanan R, Ramadas K, Amarasinghe H, Subramanian S, Johnson N. Oral cancer: Prevention, early detection, and treatment. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. *Cancer: Disease Control Priorities*. 3rd ed. The World Bank; 2015. <https://doi.org/10.1596/978-1-4648-0349-9>
33. Sanz-García A, Pérez-Romero M, Pastor J, Sola RG, Vega-Zelaya L, Vega G, et al. Potential EEG biomarkers of sedation doses in intensive care patients unveiled by using a machine learning approach. *J Neural Eng*. 2019 Feb;16(2):026031. <https://doi.org/10.1088/1741-2552/ab039f>
34. Bernard C, Zhang JZ, Klieb H, Blanas N, Xu W, Magalhaes M. Clinical outcomes of oral epithelial dysplasia managed by observation versus excision. *Head Neck*. 2023 Dec;45(12):3096–3106. <https://doi.org/10.1002/hed.27539>
35. Tan Y, Wang Z, Xu M, Li B, Huang Z, Qin S, et al. Oral squamous cell carcinomas: State of the field and emerging directions. *Int J Oral Sci*. 2023 Mar;15(1):1-23. <https://doi.org/10.1038/s41368-023-00249-w>
36. van Zyl AW, van Heerden MB, Langenegger E, van Heerden WFP. Correlation between dysplasia and ploidy status in oral leukoplakia. *Head Neck Pathol*. 2012 Sep;6(3):322-327. <https://doi.org/10.1007/s12105-012-0352-9>
37. Villa A, Woo SB. Leukoplakia—A diagnostic and management algorithm. *J Oral Maxillofac Surg*. 2017 Apr;75(4):723-734. <https://doi.org/10.1016/j.joms.2016.10.012>
38. You JR, Chen YT, Hsieh CY, Chen SY, Lin TY, Shih JS, et al. Exploring possible diagnostic precancerous biomarkers for oral submucous fibrosis: A narrative review. *Cancers*. 2023 Oct;15(19):4812. <https://doi.org/10.3390/cancers15194812>
39. Zygiogianni AG, Kyrgias G, Karakitsos P, Psyrris A, Kouvaris J, Kelekis N, et al. Oral squamous cell cancer: Early detection and the role of alcohol and smoking. *Head Neck Oncol*. 2011 Jan;3:2. <https://doi.org/10.1186/1758-3284-3-2>

