Academia Journal of Medicine
Year 2026, Volume-9, Issue- 1 (January- June)

www.acspublisher.com

Malignant Transformation of Oral Submucous Fibrosis: Risk Factors and Biomarkers – A Comprehensive Review

Arif Awati[1]*, Subho Arpan[2], Rajeev Pareek[3], Prachi Kapade[4], Sulabha A.N[5] and Smriti Choradia[6]

[1]Assistant Professor, Department of Oral Medicine and Radiology, Al-Ameen Dental College and Hospital, Bijapur, Karnataka, India
[2]Consultant Oral and Maxillofacial Surgeon, Rotary Club of Purulia Service Centre - Eye and Multispeciality Hospital, Purulia, West Bengal, India
[3]Consultant Histopathologist, HCG Cancer Centre, Jaipur, Rajasthan, India
[4]Assistant Professor, Department of Oral Pathology and Microbiology, MGV's KBH Dental College and Hospital, Nashik, Maharashtra, India
[5]Professor and Head, Department of Oral Medicine and Radiology, Al-Ameen Dental College and Hospital, Bijapur, Karnataka, India
[6]Additional Professor, Department of Oral and Maxillofacial Surgery, Nair Hospital Dental College, Mumbai, Maharashtra, India

ARTICLE INFO

Keywords: Oral submucous fibrosis; Malignant transformation; Oral squamous cell carcinoma; Areca nut; Biomarkers

doi:10.48165/ajm.2026.9.01.27

ABSTRACT

Oral submucous fibrosis (OSMF) is a chronic, progressive, potentially malignant disorder predominantly associated with areca nut consumption. It is characterized by fibrosis of the oral mucosa, leading to restricted mouth opening and increased risk of malignant transformation into oral squamous cell carcinoma (OSCC). The rate of malignant transformation varies widely, emphasizing the need for early identification of high-risk individuals. This review aims to summarize the key risk factors and emerging biomarkers associated with malignant transformation in OSMF. Major risk factors include prolonged areca nut use, tobacco consumption, genetic susceptibility, nutritional deficiencies, and chronic inflammation. Recent advances have highlighted the role of molecular biomarkers such as p53, Ki-67, cyclin D1, and various salivary and serum markers in predicting malignant potential. Understanding these factors is crucial for early diagnosis, risk stratification, and timely intervention. The integration of clinical assessment with molecular diagnostics may improve patient outcomes and reduce the burden of oral cancer.

Introduction

Oral submucous fibrosis is a well-known potentially malignant disorder affecting the oral cavity, particularly prevalent in South and Southeast Asian populations. The condition is strongly associated with the habitual use of areca nut, often combined with tobacco and other additives. Clinically, OSMF presents with progressive fibrosis of the oral mucosa, resulting in stiffness, burning sensation, and reduced mouth opening.[1]

The significance of OSMF lies in its potential for malignant transformation into oral squamous cell carcinoma (OSCC), with reported transformation rates ranging from approximately 1% to 15%. The pathogenesis involves a complex interplay of chronic irritation, increased collagen synthesis, reduced collagen degradation, oxidative stress, and genetic alterations.[2]

Early identification of individuals at high risk of malignant transformation is essential for improving prognosis and survival rates. In recent years, considerable attention has been directed toward identifying reliable biomarkers that can predict malignant progression. These include molecular markers related to cell proliferation, apoptosis, angiogenesis, and genetic instability.[3]

This review focuses on the major risk factors contributing to malignant transformation in OSMF and highlights the role of emerging biomarkers that may aid in early detection and clinical management.

Corresponding author: Arif Awati
Email id: drarifawati@gmail.com

Overview of Oral Submucous Fibrosis[1,4,5]

Etiology: Oral submucous fibrosis is a chronic, progressive, and potentially malignant disorder primarily associated with the habitual consumption of areca nut, either alone or in combination with tobacco, as seen in products such as gutkha and pan masala. Areca nut contains alkaloids such as arecoline, which stimulate fibroblast proliferation and collagen synthesis, playing a central role in the pathogenesis of the disease. The addition of tobacco further enhances carcinogenic potential by introducing nitrosamines and reactive oxygen species, thereby increasing epithelial dysplasia and the risk of malignant transformation.

In addition to areca nut and tobacco use, several contributing factors have been implicated, including nutritional deficiencies (particularly of iron, vitamins A, B-complex, and C), genetic predisposition, immunological factors, and chronic irritation from spicy food. Socioeconomic status and cultural practices also influence the prevalence of OSMF, especially in South and Southeast Asian populations.

Pathogenesis: The pathogenesis of OSMF is complex and involves a dysregulated balance between collagen synthesis and degradation, leading to excessive deposition of collagen in the subepithelial connective tissue. Arecoline and other constituents of areca nut stimulate fibroblasts to increase collagen production while simultaneously inhibiting collagen degradation by reducing the activity of collagenase enzymes. Increased cross-linking of collagen fibers, mediated by upregulation of lysyl oxidase, results in reduced collagen solubility and increased resistance to enzymatic breakdown. Additionally, the generation of reactive oxygen species and chronic inflammatory responses further contribute to tissue damage and fibrosis. Cytokines such as transforming growth factor-beta (TGF-β) play a crucial role by promoting fibroblast proliferation and extracellular matrix accumulation.

This progressive fibrosis leads to stiffening of the oral mucosa, reduced vascularity, and epithelial atrophy, creating a microenvironment that predisposes to malignant transformation.

Clinical Features: Clinically, OSMF is characterized by a range of symptoms and signs that progress over time. Early symptoms include a burning sensation in the oral cavity, particularly upon consumption of spicy food, along with mucosal blanching and the formation of vesicles or ulcerations.

As the disease advances, fibrous bands develop in the buccal mucosa, labial mucosa, soft palate, and sometimes the floor of the mouth, leading to progressive reduction in mouth opening (trismus). Patients may also experience stiffness of the oral mucosa, difficulty in mastication, speech, and swallowing. Additional features include depapillation of the tongue, xerostomia, and reduced cheek flexibility.

In advanced stages, the mucosa appears pale, stiff, and leathery, with restricted tongue movements and a characteristic "mask-like" facies. The presence of epithelial dysplasia or non-healing ulcers should raise suspicion for malignant transformation into oral squamous cell carcinoma.[1,4-6]

Table 1: Etiological Factors and Underlying Mechanisms in Oral Submucous Fibrosis

Etiological Factor	Key Components	Mechanism of Action	Effect on Oral Tissues
Areca Nut	Arecoline, arecaidine, tannins	Stimulates fibroblast proliferation and ↑ collagen synthesis; inhibits collagenase activity; ↑ lysyl oxidase → collagen cross-linking	Excessive collagen deposition, fibrosis, reduced tissue elasticity
Tobacco (Smoked & Smokeless)	Nitrosamines, reactive oxygen species (ROS)	Induces oxidative stress and DNA damage; promotes epithelial dysplasia; synergistic with areca nut	Increased malignant potential, epithelial atrophy
Slaked Lime (Chuna)	Calcium hydroxide	Enhances alkaloid absorption; increases pH → facilitates arecoline activity	Accelerated fibrosis and mucosal irritation
Nutritional Deficiencies	Iron, Vitamin A, B-complex, Vitamin C	Impaired epithelial repair; increased susceptibility to mucosal injury; reduced antioxidant defense	Epithelial atrophy, increased vulnerability to carcinogens
Genetic Predisposition	Polymorphisms (e.g., collagen-related genes, TGF-β)	Alters collagen metabolism and inflammatory response	Increased individual susceptibility to fibrosis and malignant transformation
Immunological Factors	Cytokines (TGF-β, IL-6, TNF-α)	Promotes chronic inflammation and fibroblast activation; enhances extracellular matrix deposition	Persistent fibrosis and altered tissue homeostasis
Chronic Irritation	Spicy food, mechanical trauma	Sustained mucosal injury and inflammatory response	Aggravates fibrosis and epithelial changes
Oxidative Stress	Free radicals, ROS	Cellular damage, lipid peroxidation, DNA mutations	Contributes to fibrosis and carcinogenesis

Malignant Transformation in Oral Submucous Fibrosis

Transformation Rates: Oral submucous fibrosis is recognized as a potentially malignant disorder with a well-documented risk of progression to oral squamous cell carcinoma. The reported rate of malignant transformation varies widely across studies, ranging from approximately 1% to 15%, depending on factors such as geographic location, duration of habit, study design, and follow-up period.

Higher transformation rates have been observed in populations with prolonged areca nut and tobacco use, particularly in South and Southeast Asia. Long-term cohort studies suggest that the risk increases with disease severity, especially in patients exhibiting epithelial dysplasia. The presence of additional risk factors such as nutritional deficiencies, genetic susceptibility, and coexisting habits like smoking and alcohol consumption further elevates the likelihood of malignant transformation.

Despite variability in reported rates, OSMF remains one of the most significant oral potentially malignant disorders due to its chronicity, high prevalence, and irreversible nature.

Mechanisms of Malignant Transformation[7,8]

Chronic Inflammation: Persistent exposure to areca nut and related irritants leads to a state of chronic inflammation within the oral mucosa. This results in continuous release of inflammatory mediators such as cytokines (e.g., transforming growth factor-beta, interleukins, and tumor necrosis factor-alpha), which contribute to tissue remodeling and fibrosis.

Chronic inflammation also promotes the generation of reactive oxygen species (ROS), leading to oxidative stress, lipid peroxidation, and DNA damage. This creates a microenvironment conducive to carcinogenesis by inducing genetic mutations and altering normal cellular regulatory pathways.

Epithelial Atrophy and Dysplasia Progression: As fibrosis progresses, there is a reduction in vascularity of the underlying connective tissue, leading to epithelial atrophy. The atrophic epithelium becomes more susceptible to carcinogenic insults, particularly from tobacco-related chemicals.

Over time, these changes may result in epithelial dysplasia, characterized by cellular atypia, increased nuclear-cytoplasmic ratio, and disordered maturation. Dysplastic changes represent a critical step in the multistep process of carcinogenesis, eventually progressing to invasive oral squamous cell carcinoma.

Molecular and Genetic Alterations: Malignant transformation in OSMF is associated with multiple molecular changes, including mutations in tumor suppressor genes (such as p53), overexpression of oncogenes, and alterations in cell cycle regulatory proteins like cyclin D1. Increased expression of proliferation markers such as Ki-67 reflects enhanced cellular turnover and dysregulated growth. Epigenetic modifications, including DNA methylation and histone alterations, further contribute to gene silencing and activation of oncogenic pathways. These molecular events collectively drive the transition from a fibrotic, premalignant state to malignancy.

Tumor Microenvironment Changes: The fibrotic stroma in OSMF alters the tumor microenvironment by reducing oxygenation and nutrient supply, promoting hypoxia. Hypoxic conditions activate pathways such as hypoxia-inducible factor (HIF), which facilitate angiogenesis, tumor survival, and invasion.

Additionally, increased extracellular matrix deposition and altered cell–matrix interactions support tumor progression and metastasis.

Risk Factors for Malignant Transformation in Oral Submucous Fibrosis[9]

Habit-Related Factors (Areca Nut and Tobacco): The most significant risk factor for the development and malignant transformation of oral submucous fibrosis is the habitual consumption of areca nut, either alone or in combination with tobacco. Areca nut contains alkaloids such as arecoline, which stimulate fibroblast proliferation and excessive collagen synthesis, contributing to fibrosis. In addition, areca nut-specific nitrosamines exhibit carcinogenic potential and are implicated in DNA damage.

The concurrent use of tobacco, particularly in smokeless forms such as gutkha and pan masala, further enhances the risk of malignant transformation. Tobacco contains numerous carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons, which induce genetic mutations and promote epithelial dysplasia. The synergistic effect of areca nut and tobacco significantly increases oxidative stress and accelerates the progression toward oral squamous cell carcinoma (OSCC).

The frequency, duration, and method of consumption (chewing vs. smoking) play a crucial role in determining disease severity and transformation risk.

Genetic Predisposition: Genetic susceptibility plays an important role in determining an individual's risk of malignant transformation in OSMF. Variations in genes related to collagen metabolism, inflammatory pathways, and carcinogen detoxification can influence disease progression.

Polymorphisms in genes such as transforming growth factor-beta (TGF-β), matrix metalloproteinases (MMPs), and tumor suppressor genes like p53 have been associated with increased fibrosis and carcinogenic potential. Individuals

with altered genetic profiles may exhibit enhanced fibroblast activity, impaired DNA repair mechanisms, and increased vulnerability to environmental carcinogens.
These genetic factors may explain why only a subset of individuals with similar habits develop severe OSMF or progress to malignancy.

Nutritional Deficiencies: Nutritional deficiencies, particularly of iron, vitamins A, B-complex, and C, have been implicated in the pathogenesis and malignant transformation of OSMF. Deficiencies in these micronutrients can impair epithelial integrity, reduce antioxidant defense mechanisms, and hinder tissue repair.
Iron deficiency, in particular, may lead to epithelial atrophy and increased susceptibility to carcinogens. Similarly, deficiencies in antioxidant vitamins contribute to increased oxidative stress and free radical–mediated cellular damage, thereby promoting genetic mutations and dysplastic changes. Poor nutritional status, often associated with low socioeconomic conditions, may further exacerbate disease progression and transformation risk.

Environmental and Lifestyle Factors: Environmental and lifestyle factors also contribute to the malignant transformation of OSMF. Chronic irritation from the consumption of spicy foods, alcohol use, and poor oral hygiene can lead to persistent mucosal injury and inflammation.
Exposure to environmental carcinogens and toxins may further enhance oxidative stress and DNA damage. Additionally, socioeconomic factors, lack of awareness, and delayed diagnosis contribute to disease progression and increase the likelihood of malignant transformation. The combined effect of these environmental influences with existing habits and biological susceptibility creates a multifactorial risk profile for malignancy in OSMF patients.

Biomarkers in Malignant Transformation of Oral Submucous Fibrosis: Early identification of malignant transformation in oral submucous fibrosis remains a clinical challenge. Biomarkers play a crucial role in detecting early cellular and molecular alterations, enabling risk stratification and timely intervention. These biomarkers can be broadly classified into tissue, salivary, serum, and molecular/genetic markers.[10-12]

Tissue Biomarkers: Tissue biomarkers are among the most extensively studied indicators of malignant transformation, as they directly reflect histopathological and cellular changes within the lesion.
Tumor suppressor protein p53 is commonly altered in OSMF and oral squamous cell carcinoma (OSCC). Overexpression or mutation of p53 leads to impaired DNA repair and uncontrolled cell proliferation, making it a key marker for dysplastic progression.
The proliferation marker Ki-67 is used to assess cellular growth activity. Increased Ki-67 expression correlates with higher epithelial turnover and is often associated with dysplasia and malignant transformation.
Cyclin D1, a cell cycle regulatory protein, plays a critical role in the transition from the G1 to S phase. Its overexpression results in uncontrolled cell cycle progression and has been linked to increased risk of carcinogenesis in OSMF.
Other tissue markers, such as PCNA (proliferating cell nuclear antigen) and Bcl-2, have also been studied for their role in apoptosis and cell survival, further contributing to malignant potential.

Salivary Biomarkers: Saliva has emerged as a non-invasive diagnostic medium with significant potential in the early detection of malignant transformation.
Salivary biomarkers include proteins, enzymes, cytokines, and nucleic acids that reflect pathological changes in the oral cavity. Elevated levels of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have been associated with chronic inflammation and disease progression.
Markers of oxidative stress, such as malondialdehyde (MDA), and antioxidant enzymes like superoxide dismutase (SOD), are also altered in OSMF, indicating ongoing cellular damage.
Additionally, salivary microRNAs (miRNAs) have gained attention as potential early indicators of malignant transformation due to their role in gene regulation and tumor progression.

Serum Biomarkers: Serum biomarkers provide systemic insights into disease progression and malignant potential. Increased levels of serum cytokines, growth factors, and oxidative stress markers have been observed in patients with OSMF and OSCC.
Elevated serum levels of lactate dehydrogenase (LDH) may indicate increased cellular turnover and tissue breakdown. Similarly, increased levels of ceruloplasmin and other acute-phase proteins reflect inflammatory status.
Serum markers related to oxidative stress and antioxidant capacity, such as glutathione and lipid peroxidation products, also play a role in assessing disease severity and transformation risk.
Although serum biomarkers are useful, their specificity for oral lesions may be limited, necessitating their use in combination with other diagnostic tools.

Molecular and Genetic Markers: Molecular and genetic alterations are central to the malignant transformation process in OSMF. These include mutations in tumor

suppressor genes, activation of oncogenes, and epigenetic modifications.

Alterations in genes such as p53, p16, and RAS contribute to dysregulation of cell cycle control and apoptosis. Epigenetic changes, including DNA methylation and histone modification, can lead to silencing of tumor suppressor genes and activation of oncogenic pathways.

MicroRNAs (miRNAs) play a significant role in post-transcriptional gene regulation and have been implicated in tumor initiation and progression. Specific miRNA expression profiles may serve as early diagnostic and prognostic markers.

Advancements in genomics and proteomics have facilitated the identification of novel biomarkers, offering promising avenues for personalized medicine and targeted therapy in OSMF.

Clinical Implications of Malignant Transformation in Oral Submucous Fibrosis: Understanding the risk factors and biomarkers associated with malignant transformation in oral submucous fibrosis has significant clinical implications. It enables clinicians to identify high-risk individuals, implement early interventions, and improve overall patient outcomes.[13-15]

Early Diagnosis: Early diagnosis of OSMF and its potential for malignant transformation is critical in reducing morbidity and mortality. Clinical recognition of initial symptoms—such as burning sensation, mucosal blanching, and reduced mouth opening—should prompt thorough examination and habit history assessment.

Adjunctive diagnostic aids, including toluidine blue staining, brush biopsy, and autofluorescence-based devices, can assist in identifying suspicious lesions. However, definitive diagnosis relies on histopathological evaluation. Incorporating biomarkers such as p53 and Ki-67 into routine assessment may enhance the detection of early dysplastic changes before the onset of overt malignancy.

Early diagnosis allows timely cessation of etiological habits and initiation of appropriate management strategies, thereby reducing the risk of progression to oral squamous cell carcinoma (OSCC).

Screening: Screening plays a vital role, particularly in high-risk populations with prevalent areca nut and tobacco use. Community-based screening programs can facilitate early identification of OSMF and other potentially malignant disorders.

Non-invasive and cost-effective methods, such as visual oral examination and salivary biomarker analysis, are particularly suitable for large-scale screening in resource-limited settings. Integration of mobile health technologies and awareness programs can further improve screening coverage and patient compliance.

Regular follow-up and monitoring of diagnosed cases are essential for early detection of malignant changes, especially in individuals with long-standing habits or advanced fibrosis.

Prognostic Value: Biomarkers hold significant prognostic value in predicting disease progression and malignant transformation. Increased expression of proliferation markers (e.g., Ki-67) and mutations in tumor suppressor genes (e.g., p53) are associated with higher risk of dysplasia and carcinoma.

Assessment of biomarker profiles may help in stratifying patients into low-, moderate-, and high-risk categories, enabling personalized management approaches. Patients identified as high-risk can be subjected to more frequent monitoring and early therapeutic interventions.

Furthermore, combining clinical findings with molecular markers enhances the accuracy of prognosis and aids in decision-making regarding treatment and surveillance.

Future Diagnostic Tools: Advances in molecular biology and diagnostic technologies are paving the way for more precise and non-invasive tools for early detection of malignant transformation in OSMF. Salivary diagnostics, including the analysis of microRNAs, proteins, and metabolites, offer a promising, patient-friendly approach. Liquid biopsy techniques, which detect circulating tumor DNA and other biomarkers in blood or saliva, are emerging as potential tools for real-time monitoring of disease progression.

Artificial intelligence (AI)-based diagnostic systems and imaging technologies may further enhance early detection by analyzing clinical images and identifying subtle changes indicative of malignancy. The integration of these advanced tools into routine clinical practice could significantly improve early diagnosis, prognostic assessment, and overall management of patients with OSMF.

Future Directions in Oral Submucous Fibrosis Research: Despite significant advances in understanding oral submucous fibrosis (OSMF), several gaps remain in predicting and preventing malignant transformation. Future research should focus on integrating molecular insights, advanced diagnostic technologies, and robust clinical study designs to improve early detection and patient outcomes.

Need for Advanced Molecular Research: There is a pressing need for deeper exploration of the molecular mechanisms underlying malignant transformation in OSMF. While several biomarkers have been identified, their clinical applicability remains limited due to variability in results and lack of standardization.

Future studies should focus on:

· Identifying highly specific and sensitive biomarker panels rather than single markers

· Exploring genomic, proteomic, and metabolomic profiles

· Understanding epigenetic modifications such as DNA methylation and microRNA regulation

Such approaches may help in developing targeted therapies and improving risk prediction models for malignant transformation.

Role of Artificial Intelligence and Salivary Diagnostics: Emerging technologies such as artificial intelligence (AI) and salivary diagnostics hold great promise in revolutionizing the early detection of OSMF and its progression to malignancy.

· AI-based tools can assist in:
· Automated analysis of clinical images
· Detection of subtle mucosal changes

Risk prediction using integrated clinical and molecular data

Salivary diagnostics offer a non-invasive, cost-effective, and patient-friendly approach for screening and monitoring. Future research should aim to validate salivary biomarkers, including proteins, cytokines, and microRNAs, for routine clinical use.

The combination of AI and salivary diagnostics could enable real-time, chairside detection and improve accessibility in resource-limited settings. [16-18]

Need for Large-Scale Longitudinal Studies: Most existing studies on OSMF are cross-sectional or limited by small sample sizes, restricting the ability to establish causal relationships and long-term outcomes.

There is a need for:

· Large-scale, multicenter longitudinal studies
· Standardized diagnostic criteria and biomarker assessment protocols
· Long-term follow-up to evaluate malignant transformation rates

Such studies would provide stronger evidence regarding disease progression, validate potential biomarkers, and guide clinical decision-making.

Conclusion

Oral submucous fibrosis is a significant potentially malignant disorder with a risk of progression to oral squamous cell carcinoma. Its malignant transformation is influenced by habit-related, genetic, and nutritional factors, along with complex molecular alterations. Early diagnosis, regular screening, and the use of reliable biomarkers are essential for timely intervention. Advancements in molecular research and non-invasive diagnostic tools may further improve early detection and patient outcomes.

References

Shih, Y. H., Wang, T. H., Shieh, T. M., & Tseng, Y. H. (2019). Oral submucous fibrosis: A review on etiopathogenesis, diagnosis, and therapy. *International Journal of Molecular Sciences, 20*(12), 2940. https://doi.org/10.3390/ijms20122940

Xu, H., Lyu, F. Y., Song, J. Y., Xu, Y. M., Jiang, E. H., Shang, Z. J., Chen, L. L., & Xu, Z. (2021). Research achievements of oral submucous fibrosis: Progress and prospect. *BioMed Research International, 2021*, Article 6631856. https://doi.org/10.1155/2021/6631856

Rao, N. R., Villa, A., More, C. B., Jayasinghe, R. D., Kerr, A. R., & Johnson, N. W. (2020). Oral submucous fibrosis: A contemporary narrative review with a proposed inter-professional approach for early diagnosis and clinical management. *Journal of Otolaryngology - Head & Neck Surgery, 49*(1), 3. https://doi.org/10.1186/s40463-019-0398-5

Arakeri, G., & Brennan, P. A. (2013). Oral submucous fibrosis: An overview of the aetiology, pathogenesis, classification, and principles of management. *British Journal of Oral and Maxillofacial Surgery, 51*(7), 587–593. https://doi.org/10.1016/j.bjoms.2012.08.014

Hazare, V. K., Goel, R. R., & Gupta, P. C. (1998). Oral submucous fibrosis, areca nut and pan masala use: A case-control study. *National Medical Journal of India, 11*(6), 299–300.

Lin, F., Xiao, T., Wang, B., Wang, L., Liu, G., Wang, R., Xie, C., & Tang, Z. (2024). Mechanisms and markers of malignant transformation of oral submucous fibrosis. *Heliyon, 10*(1), e23314. https://doi.org/10.1016/j.heliyon.2023.e23314

Warnakulasuriya, S., et al. (2021). Oral potentially malignant disorders: A consensus report from an international seminar on nomenclature and classification. *Oral Diseases, 27*(8), 1862–1880. https://doi.org/10.1111/odi.13704

Warnakulasuriya, S., et al. (2022). Areca nut and oral cancer: Evidence from studies conducted in humans. *Journal of Dental Research, 101*(10), 1139–1146. https://doi.org/10.1177/00220345221091568

Kujan, O., Mello, F. W., & Warnakulasuriya, S. (2021). Malignant transformation of oral submucous fibrosis: A systematic review and meta-analysis. *Oral Diseases, 27*(8), 1936–1946. https://doi.org/10.1111/odi.13727

You, J. R., Chen, Y. T., Hsieh, C. Y., Chen, S. Y., Lin, T. Y., Shih, J. S., Chen, G. T., Feng, S. W., Peng, T. Y., & Lee, I. T. (2023). Exploring possible diagnostic precancerous biomarkers for oral submucous fibrosis: A narrative review. *Cancers, 15*(19), 4812. https://doi.org/10.3390/cancers15194812

Zhou, S., Zhu, Y., Mashrah, M., Zhang, X., He, Z., Yao, Z., Zhang, C., Guo, F., Hu, Y., & Zhang, C. (2017). Expression pattern of DKK3 in the malignant progression of oral submucous fibrosis. *Oncology Reports, 37*(2), 979–985. https://doi.org/10.3892/or.2016.5317

Surboyo, M. D. C., Merdietio Boedi, R., Mahdani, F. Y., Ayuningtyas, N. F., Shalgm, B., Paramananda, D. B., & Indriyani, I. (2024). Alteration of salivary biomarkers in oral submucous fibrosis: A three-level meta-analysis study. *Clinical Biochemistry, 130*,

110790. https://doi.org/10.1016/j.clinbiochem.2024.110790

Naik, V., Kumar, M., Solomon, M. C., Chandrashekhar, C., & Guddattu, V. (2025). Clinical and histological indicators for malignant transformation of oral submucous fibrosis. *BMC Oral Health, 25*(1), 1053. https://doi.org/10.1186/s12903-025-04606-1

Hazarey, V. K., Erlewad, D. M., Mundhe, K. A., & Ughade, S. N. (2007). Oral submucous fibrosis: Study of 1000 cases from central India. *Journal of Oral Pathology & Medicine, 36*(1), 12–17. https://doi.org/10.1111/j.1600-0714.2006.00462.x

Jian, X. C., Peng, J. Y., Tang, Z. G., Shen, Q., & Su, T. (2000). Three cases of oral cancer associated with oral submucous fibrosis. *Journal of Clinical Stomatology, 18*, 130–131.

Bohra, A., Maheswari, T. N. U., & Harsh, A. (2025). Artificial intelligence innovations in understanding oral submucous fibrosis: A systematic review. *Asian Pacific Journal of Cancer Prevention, 26*(11), 3925–3930.

Dinesh, Y., Ramalingam, K., Ramani, P., & Mohan Deepak, R. (2023). Machine learning in the detection of oral lesions with clinical intraoral images. *Cureus, 15*(8), e44018. https://doi.org/10.7759/cureus.44018

Chaudhary, N., Rai, A., Rao, A. M., Faizan, M. I., Augustine, J., Chaurasia, A., et al. (2024). High-resolution AI image dataset for diagnosing oral submucous fibrosis and squamous cell carcinoma. *Scientific Data, 11*(1), 1050. https://doi.org/10.1038/s41597-024-03659-4