ORIGINAL RESEARCH PAPER
Volume - 15 | Issue - 07 | July - 2026 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ORAL CANCER: FROM TOBACCO EXPOSURE TO EARLY DETECTION AND PRECISION PREVENTION

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ABSTRACT

Background: Oral cancer remains a significant global health challenge, particularly in low- and middle-income countries where exposure to tobacco, smokeless tobacco, areca nut, and alcohol is highly prevalent. Despite advances in treatment, survival outcomes have improved only modestly because many cases continue to be diagnosed at advanced stages. Oral potentially malignant disorders (OPMDs), including leukoplakia, erythroplakia, oral submucous fibrosis, and oral lichen planus, represent important precursor lesions that offer opportunities for early detection and prevention. Emerging technologies such as salivary biomarkers, liquid biopsy, advanced imaging, and artificial intelligence (AI)-based diagnostics are transforming approaches to oral cancer screening and risk assessment. **Methods:** This review synthesizes current evidence on the epidemiology, risk factors, molecular mechanisms, OPMDs, diagnostic modalities, biomarker research, AI-assisted detection, and precision prevention strategies related to oral cancer. Relevant literature from clinical, molecular, and translational research was examined to provide a comprehensive overview of recent advances in oral oncology.**Results:** Current evidence highlights the critical role of OPMDs in oral cancer prevention and the growing potential of molecular diagnostics for early detection. Salivary biomarkers, liquid biopsy technologies, optical imaging techniques, and AI-driven diagnostic systems have demonstrated promising utility in identifying high-risk individuals and facilitating earlier diagnosis. Advances in genomics, transcriptomics, proteomics, and multi-omics research have improved understanding of oral carcinogenesis and support the development of personalized risk prediction and targeted prevention approaches.**Conclusion:** The integration of molecular diagnostics, risk-based screening, AI-enabled technologies, and precision prevention strategies has the potential to transform oral cancer control. Moving from a reactive treatment-focused model toward a proactive framework emphasizing prediction, prevention, early detection, and personalized care may substantially reduce the burden of oral cancer and improve patient outcomes.

KEYWORDS

Oral Cancer; Oral Squamous Cell Carcinoma; Oral Potentially Malignant Disorders; Early Detection; Salivary Biomarkers; Artificial Intelligence; Precision Medicine; Precision Prevention.

INTRODUCTION

Oral cancer remains a major global health challenge and is among the most common malignancies of the head and neck region. More than 90% of cases are oral squamous cell carcinomas (OSCCs) arising from the oral mucosal epithelium. Despite advances in surgery, radiotherapy, and systemic therapies, improvements in overall survival have been modest because many patients continue to present with advanced-stage disease, when treatment is more complex and outcomes are poorer (1–3).

The burden of oral cancer is particularly high in low- and middle-income countries, especially in South and Southeast Asia, where tobacco use, smokeless tobacco consumption, areca nut chewing, and alcohol intake remain widespread risk factors (1,2). India contributes substantially to the global disease burden, making oral cancer a significant public health concern.

Oral carcinogenesis is a multistep process driven by interactions between environmental exposures, host susceptibility, and molecular alterations. Tobacco remains the most important modifiable risk factor, while alcohol, areca nut, human papillomavirus (HPV) infection, nutritional deficiencies, and genetic predisposition further contribute to malignant transformation (4–8). A distinctive feature of oral cancer is the presence of oral potentially malignant disorders (OPMDs), which provide opportunities for surveillance, early intervention, and prevention before invasive disease develops (9,10).

Early detection remains the most effective strategy for improving outcomes, yet delayed diagnosis continues to be common because early lesions are often asymptomatic and screening practices remain inadequate in many settings (3,11). Recent advances in molecular diagnostics, including salivary biomarkers, liquid biopsy, and genomic technologies, together with the growing application of artificial intelligence, have expanded opportunities for earlier detection and more accurate risk assessment (12–14).

This review examines the continuum of oral carcinogenesis from risk factor exposure and OPMDs to early detection and emerging technologies, highlighting the evolving role of precision prevention in reducing the global burden of oral cancer (14,15).

Epidemiology, Risk Factors and Etiopathogenesis of Oral Cancer

Oral carcinogenesis is a multifactorial and progressive process resulting from interactions between environmental exposures, host susceptibility, and molecular alterations (5,8). Tobacco remains the most important modifiable risk factor and is implicated in a substantial proportion of cases globally. Both smoked and smokeless forms contain carcinogenic compounds capable of inducing DNA damage, oxidative stress, chronic inflammation, and genomic instability. Smokeless tobacco is especially important in South Asian populations because prolonged direct mucosal exposure significantly increases the risk of precursor lesions and malignant transformation (5).

Areca nut chewing, commonly practiced alone or as part of betel quid preparations, is another major etiological factor and a distinctive feature of oral cancer epidemiology in South Asia. Classified as a Group I carcinogen by the International Agency for Research on Cancer, areca nut contributes to chronic mucosal injury and oral submucous fibrosis, a potentially malignant disorder strongly associated with oral cancer development (5,7). Alcohol consumption further increases risk through the carcinogenic effects of acetaldehyde and by enhancing mucosal penetration of tobacco-derived carcinogens. Consequently, combined exposure to tobacco, areca nut, and alcohol produces synergistic effects that substantially increase cancer risk (6,9).

Additional contributors include human papillomavirus (HPV) infection, poor nutrition, chronic inflammation, immunosuppression, and genetic susceptibility (8,10). Variations in genes involved in carcinogen metabolism, DNA repair, and immune regulation may partly explain differences in individual susceptibility. At the molecular level, oral cancer develops through the progressive accumulation of genetic and epigenetic abnormalities involving genes such as *TP53, CDKN2A, NOTCH1,* and *PIK3CA*, together with dysregulation of pathways including EGFR and PI3K/AKT/mTOR (35,36). These alterations gradually transform normal oral epithelium into invasive carcinoma, often through identifiable precursor lesions that provide opportunities for early detection and prevention.

Oral Potentially Malignant Disorders and Malignant Transformation

Oral potentially malignant disorders (OPMDs) represent the critical intermediate stage between exposure to carcinogenic risk factors and the development of invasive oral squamous cell carcinoma (OSCC). Their importance lies in providing a unique opportunity to identify, monitor, and intervene before malignant transformation occurs. Unlike many cancers that lack clinically recognizable precursor stages, oral cancer frequently arises from visible mucosal alterations, making OPMDs central to prevention and early detection strategies (11,12).

The World Health Organization defines OPMDs as clinical presentations associated with an increased risk of future malignant transformation compared with normal oral mucosa (12). However, malignant progression is highly variable. Some lesions remain stable or regress following elimination of risk factors, whereas others progress despite relatively benign clinical appearances. This biological heterogeneity remains a major challenge in oral oncology.

Among recognized OPMDs, oral leukoplakia is the most common and is characterized by a predominantly white plaque that cannot be attributed to another disorder (13). Malignant transformation risk is higher in non-homogeneous lesions, larger lesions, lesions affecting the tongue or floor of the mouth, and those exhibiting epithelial dysplasia. Erythroplakia, although less common, carries the highest malignant potential and frequently demonstrates severe dysplasia, carcinoma in situ, or invasive carcinoma at diagnosis (14). Oral submucous fibrosis (OSMF), strongly associated with areca nut chewing, is particularly important in South Asian populations because of its high prevalence and established risk of malignant transformation (16). Other recognized OPMDs include oral lichen planus and proliferative verrucous leukoplakia (PVL), the latter being one of the most aggressive precursor lesions because of its multifocal nature, frequent recurrence, and high transformation rates (15).

Table 1: Oral Potentially Malignant Disorders and Malignant Transformation Risk

Disorder	Key Clinical Features	Approximate Malignant Transformation Risk
Leukoplakia	White patch	1–20%
Erythroplakia	Red velvety lesion	Highest risk
Oral Submucous Fibrosis	Fibrosis and restricted mouth opening	7–13%
Oral Lichen Planus	Chronic inflammatory lesion	Low–moderate
Proliferative Verrucous Leukoplakia	Multifocal progressive lesion	40–70%

Histopathological assessment remains the cornerstone of risk evaluation, with epithelial dysplasia serving as the most widely accepted predictor of malignant transformation. Nevertheless, histopathology has important limitations because lesions with minimal dysplasia may progress to cancer, while some severely dysplastic lesions remain stable for prolonged periods. Interobserver variability further limits predictive accuracy.

Recent advances in molecular biology have demonstrated that malignant transformation begins long before clinically apparent cancer develops. OPMDs frequently harbor genetic alterations involving *TP53, CDKN2A, NOTCH1,* and EGFR signaling pathways, together with epigenetic abnormalities such as DNA methylation changes and microRNA dysregulation (28,35). These findings support the concept of field cancerization, whereby extensive areas of oral epithelium may contain molecular abnormalities despite appearing clinically normal. This phenomenon helps explain the occurrence of multiple primary tumors, local recurrences, and persistent cancer risk even after treatment of visible lesions.

One of the greatest unmet needs in oral oncology is accurate prediction of malignant transformation. Current risk assessment relies largely on clinical appearance, histopathological findings, and exposure history, all of which possess limited predictive precision. Consequently, growing interest has focused on molecular biomarkers, liquid biopsy technologies, and artificial intelligence-assisted risk assessment as tools for improving risk stratification. Future surveillance strategies are likely to integrate clinical, histopathological, and molecular information to identify high-risk lesions more accurately and facilitate personalized prevention before invasive cancer develops.

Early Detection and Screening of Oral Cancer

Early detection remains the most effective strategy for improving survival and reducing treatment-related morbidity in oral cancer. Prognosis is strongly dependent on stage at diagnosis, with significantly better outcomes observed among patients diagnosed with localized disease compared with those presenting with regional or distant spread (17,18). Despite the accessibility of the oral cavity for examination and the frequent presence of recognizable precursor lesions, a substantial proportion of patients continue to present with advanced-stage disease.

Diagnostic delay is a multifactorial process involving patients, healthcare providers, and health systems. Patient-related factors include limited awareness of early signs such as persistent white or red patches, non-healing ulcers, and mucosal thickening. Because early lesions are often painless, they may be ignored or mistaken for minor trauma or tobacco-related irritation. Socioeconomic barriers, poor health literacy, financial constraints, and fear of diagnosis further contribute to delayed healthcare seeking. Provider-related factors include failure to perform routine oral examinations, misinterpretation of early lesions, and delays in referral to specialist services (19,20). Health system limitations, particularly in resource-constrained settings, may further prolong diagnosis through restricted access to specialist care and histopathological services.

Conventional oral examination (COE) remains the foundation of oral cancer screening worldwide. The procedure involves systematic visual inspection and palpation of the oral cavity and is particularly valuable because it is simple, inexpensive, non-invasive, and suitable for large-scale screening programs. Evidence from community-based screening studies, particularly the Kerala oral cancer screening trials, has demonstrated that visual screening of high-risk populations can facilitate earlier diagnosis and contribute to reductions in oral cancer mortality (23,24). These findings support targeted screening approaches among individuals with significant exposure to tobacco, areca nut, and other established risk factors.

Histopathological examination remains the gold standard for confirming epithelial dysplasia, carcinoma in situ, and invasive oral squamous cell carcinoma. Biopsy provides essential information regarding lesion severity and prognosis but is invasive, subject to sampling error, and may not fully capture lesion heterogeneity. Consequently, several adjunctive diagnostic techniques have been developed to assist lesion detection and biopsy site selection. These include toluidine blue staining, autofluorescence imaging, brush cytology, optical coherence tomography, and other optical imaging technologies (25,26). While such approaches may improve visualization of suspicious lesions, none has demonstrated sufficient accuracy to replace biopsy.

A major limitation of current screening strategies is their inability to reliably predict which oral potentially malignant disorders will progress to invasive cancer. As a result, contemporary approaches increasingly emphasize risk-based screening that incorporates behavioural exposures, OPMD history, clinical characteristics, and emerging molecular markers. Such strategies recognize that oral cancer risk is unevenly distributed across populations and may improve screening efficiency, facilitate earlier intervention, and support the transition toward more personalized prevention models.

Emerging Technologies in Early Detection of Oral Cancer

The limitations of conventional screening methods and the persistent challenge of late-stage diagnosis have stimulated growing interest in molecular and computational approaches capable of detecting oral cancer before clinically evident disease develops. Among emerging technologies, salivary biomarkers, liquid biopsy, and artificial intelligence (AI) have attracted considerable attention because they offer opportunities for earlier diagnosis, improved risk assessment, and more personalized surveillance strategies (27,28).

Saliva has emerged as one of the most promising biological fluids for oral cancer detection because of its close proximity to oral lesions, ease of collection, and non-invasive nature. Compared with blood-based testing, saliva collection is inexpensive, painless, easily repeatable, and highly acceptable to patients, making it particularly suitable for large-scale screening and surveillance programs, especially in resource-limited settings (27). Importantly, saliva contains a wide range of biological molecules derived from host tissues, inflammatory cells, microorganisms, and tumor cells, providing a rich source of diagnostic information.

Numerous salivary biomarkers have been investigated for their potential role in oral cancer detection. These include protein biomarkers such as interleukin-8, interleukin-1β, tumor necrosis factor-alpha, matrix metalloproteinases, and CD44, as well as genetic and epigenetic alterations including *TP53* mutations, DNA methylation abnormalities, and chromosomal changes (29). Particular attention has focused on microRNAs, especially miR-21, miR-31, and miR-184, because of their stability in biological fluids and their involvement in multiple carcinogenic pathways (30). Exosomes and other extracellular vesicles have also emerged as promising biomarkers because they carry DNA, RNA, proteins, and lipids that reflect the molecular characteristics of their parent cells. These advances highlight the potential of saliva-based diagnostics for identifying carcinogenic changes before overt clinical progression occurs.

Table 2: Salivary Biomarkers with Diagnostic Potential

Biomarker	Category	Clinical Utility
IL-8	Cytokine	Early detection
IL-1β	Cytokine	Risk assessment
MMP-9	Protein	Tumor progression
Chemerin	Protein	High sensitivity
miR-21	microRNA	Early diagnosis
miR-31	microRNA	Malignant transformation
Exosomal biomarkers	Extracellular vesicles	Precision surveillance

Liquid biopsy extends this concept by analyzing tumor-derived material present in biological fluids. Unlike conventional tissue biopsy, which provides information from a single site and time point, liquid biopsy offers a dynamic and minimally invasive approach to disease assessment (31). Key targets include circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), cell-free RNA, and exosomal biomarkers. These technologies have potential applications in early cancer detection, surveillance of oral potentially malignant disorders, monitoring treatment response, and detection of recurrence. However, technical challenges remain, particularly in early-stage disease where tumor-derived material is often present in very low concentrations.

Artificial intelligence has emerged as another transformative technology in oral oncology. Machine learning and deep learning algorithms, particularly convolutional neural networks (CNNs), have demonstrated promising performance in analyzing clinical photographs and differentiating benign lesions, oral potentially malignant disorders, and oral squamous cell carcinoma (32,33). AI systems can evaluate objective image characteristics such as color variation, surface texture, border irregularity, and morphological asymmetry, potentially reducing diagnostic variability and improving consistency.

The widespread availability of smartphones has further expanded opportunities for AI-assisted screening and telemedicine. Images of suspicious lesions can be captured by healthcare workers and analyzed using AI-enabled platforms, potentially improving access to specialist expertise in underserved regions. AI is also increasingly being applied to digital pathology, where algorithms can assist in dysplasia detection, histological grading, prognostic assessment, and margin evaluation. Beyond image analysis, AI offers the ability to integrate clinical, histopathological, imaging, genomic, and biomarker data, facilitating more comprehensive risk prediction and clinical decision support.

Despite encouraging advances, significant challenges remain before these technologies can be widely adopted. Lack of standardization, limited external validation, biological heterogeneity, implementation costs, and infrastructure requirements continue to limit clinical translation. Similarly, AI systems face concerns regarding dataset bias, transparency, data privacy, and generalizability across different populations and healthcare settings. Nevertheless, these emerging technologies represent important steps toward more objective, personalized, and data-driven approaches to oral cancer prevention. Their greatest value may ultimately lie in combining molecular diagnostics with computational analysis to identify high-risk individuals and facilitate intervention before invasive disease develops.

Table 3: Emerging Technologies for Early Detection

Technology	Principle	Advantages	Limitations
Conventional Oral Examination	Visual inspection	Simple, inexpensive	Subjective
Toluidine Blue	Vital staining	Easy to perform	False positives
Autofluorescence	Optical imaging	Non-invasive	Variable specificity
Brush Cytology	Cell sampling	Minimally invasive	Requires confirmation
Salivary Biomarkers	Molecular detection	Non-invasive	Standardization needed
Liquid Biopsy	Tumor-derived material	Dynamic monitoring	Cost
Artificial Intelligence	Automated analysis	High scalability	Requires validation

Precision Prevention and Future Directions

Traditional oral cancer prevention strategies have largely focused on population-level interventions such as tobacco control, public awareness campaigns, and opportunistic screening. While these measures remain fundamental to oral cancer control, increasing recognition of the biological heterogeneity of oral carcinogenesis has led to the emergence of precision prevention. This approach seeks to identify individuals at greatest risk and tailor preventive interventions according to their behavioural, clinical, molecular, and genetic profiles rather than applying uniform strategies across entire populations (35,36).

The foundation of precision prevention is risk stratification. Contemporary models increasingly integrate information from multiple domains, including tobacco, areca nut, and alcohol exposure; oral potentially malignant disorders (OPMDs); histopathological findings; and emerging molecular markers such as DNA methylation patterns, microRNA signatures, and salivary biomarker profiles. Such approaches may improve prediction of malignant transformation and enable more efficient surveillance of high-risk individuals.

Future developments are expected to build upon advances in multi-omics technologies, liquid biopsy, artificial intelligence, and digital health. Integration of genomic, epigenomic, transcriptomic, proteomic, and microbiomic data may provide a more comprehensive understanding of oral carcinogenesis and support increasingly accurate risk prediction models (28,38). Similarly, smartphone-based screening, teleconsultation, and AI-assisted decision support may expand access to early detection services, particularly in underserved regions.

Despite considerable promise, important challenges remain, including limited biomarker validation, lack of standardization, implementation costs, data privacy concerns, and healthcare infrastructure requirements. Consequently, precision prevention should be viewed as a complement rather than a replacement for established public health measures. The future of oral cancer control will likely depend on integrating population-based prevention with personalized risk assessment, enabling earlier intervention and more efficient allocation of healthcare resources.

Table 4: Transition from Conventional Prevention to Precision Prevention

Conventional Approach	Precision Prevention Approach
Population-wide screening	Risk-based screening
Visual examination	AI-assisted diagnosis
Single clinical assessment	Dynamic monitoring
Histopathology alone	Multi-omics profiling
Periodic follow-up	Personalized surveillance
General prevention advice	Individualized interventions

CONCLUSION

Oral cancer remains a major global health challenge, particularly in regions where tobacco use, smokeless tobacco products, areca nut consumption, and alcohol exposure remain prevalent. Although advances in treatment have improved outcomes, survival continues to be strongly influenced by stage at diagnosis, emphasizing the critical importance of prevention and early detection.

Current evidence supports a continuum of oral carcinogenesis extending from carcinogenic exposure and molecular alterations to oral potentially malignant disorders and ultimately invasive cancer. This understanding has highlighted opportunities for intervention before malignant transformation occurs. While conventional oral examination and histopathological assessment remain central to diagnosis, emerging technologies including salivary biomarkers, liquid biopsy, artificial intelligence, and multi-omics approaches have expanded the possibilities for earlier detection and more accurate risk assessment.

The growing shift toward precision prevention represents a major advancement in oral oncology. By integrating behavioural, clinical, molecular, and computational information, precision prevention seeks to identify high-risk individuals, personalize surveillance, and facilitate earlier intervention. However, these innovations must complement established public health strategies, particularly tobacco and areca nut control, health education, and improved access to screening services. Continued advances in molecular diagnostics and digital technologies offer an important opportunity to shift oral cancer control from a predominantly treatment-oriented approach toward one focused on prediction, early detection, and prevention.

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