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Salivary Biomarkers for Early Detection of Oral Cancer: Current Evidence, Diagnostic Potential and Future Perspectives

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ABSTRACT

Background: Oral cancer is a major public health concern, particularly in South and Southeast Asia, where tobacco consumption, alcohol use and areca nut chewing contribute substantially to disease burden. Oral squamous cell carcinoma (OSCC) accounts for the majority of oral malignancies. Delayed diagnosis remains a major challenge, making the identification of reliable, non-invasive diagnostic approaches an important research priority.

Objective: This review examines the role of salivary biomarkers in the early detection of oral cancer, with particular emphasis on protein biomarkers, inflammatory cytokines, nucleic acids, microRNAs, DNA methylation, metabolites, extracellular vesicles and oral microbiome-associated markers.

Methods: A narrative review of relevant peer-reviewed literature was undertaken, incorporating original clinical investigations, systematic reviews, meta-analyses and recent clinical recommendations concerning salivary diagnostics in OSCC.

Results: Several salivary biomarkers, including interleukin-6 (IL-6), interleukin-8 (IL-8), matrix metalloproteinase-9 (MMP-9), CD44, CYFRA 21-1 and microRNA-31, have demonstrated potential for distinguishing individuals with OSCC from healthy controls. Salivary DNA methylation patterns, extracellular vesicles and metabolomic profiles have also emerged as promising research areas. Recent meta-analyses suggest that combinations of biomarkers may offer better diagnostic discrimination than individual markers. Nevertheless, variations in sample collection, analytical methods, patient characteristics and study populations limit the generalizability of reported findings.

Conclusion: Salivary biomarkers represent a promising non-invasive approach to supporting the early detection of oral cancer. However, their clinical application remains limited by insufficient external validation, inconsistent analytical protocols and uncertain diagnostic performance in routine screening populations. Larger prospective multicentre studies are required before these tests can be recommended for routine clinical use.

Keywords: Oral cancer; oral squamous cell carcinoma; saliva; salivary biomarkers; early detection; microRNA; liquid biopsy; diagnostic accuracy.

1. INTRODUCTION

Oral cancer is an important global health concern associated with substantial morbidity, mortality and functional impairment. It includes malignancies affecting the lips, tongue, gingiva, buccal mucosa, floor of the mouth, hard palate and other structures of the oral cavity. Oral squamous cell carcinoma (OSCC) represents the predominant histological subtype and accounts for approximately 90% of oral malignancies.

The global burden of cancers involving the lip, oral cavity and pharynx remains considerable. According to estimates for 2022, approximately 758,000 new cases of these cancers were diagnosed worldwide, with oral cavity cancers accounting for approximately 42% of the combined burden. South-Central Asia represents one of the regions with the highest incidence rates [1]. India carries a particularly substantial burden, partly associated with widespread exposure to smokeless tobacco, chewing tobacco, areca nut and other carcinogenic products.

The development of oral cancer is a multistep process involving genetic alterations, epigenetic modifications, chronic inflammation and changes in the local tissue microenvironment. Several oral potentially malignant disorders (OPMDs), including oral leukoplakia, erythroplakia and oral submucous fibrosis, may precede the development of invasive malignancy. However, not every potentially malignant lesion progresses to cancer, creating a need for reliable methods to identify individuals at greater risk of malignant transformation [2].

Early identification of OSCC is clinically important because advanced disease frequently requires extensive surgery, radiotherapy or combined treatment and may result in considerable functional consequences. Conventional diagnosis relies on clinical examination followed by tissue biopsy and histopathological assessment. Although biopsy remains essential for definitive diagnosis, access to specialist evaluation and patient acceptance can influence the diagnostic pathway.

In this context, saliva has attracted increasing research attention as a potential diagnostic biological fluid. Its direct contact with the oral mucosal surfaces makes it particularly relevant for detecting molecular alterations associated with oral malignancy. Saliva contains proteins, enzymes, nucleic acids, metabolites, extracellular vesicles and microbial components that may reflect local pathological changes.

The development of saliva-based biomarker panels may therefore provide an additional approach to identifying individuals who require further clinical evaluation. Recent investigations have expanded from conventional protein markers to molecular signatures involving microRNAs, DNA methylation, metabolomics and extracellular vesicles [3, 4].

This review discusses the biological basis, major categories, analytical methods, clinical evidence and limitations of salivary biomarkers for early oral cancer detection.

2. SALIVA AS A DIAGNOSTIC BIOLOGICAL FLUID

Saliva is a complex biological fluid produced primarily by the major and minor salivary glands. It consists predominantly of water, along with electrolytes, enzymes, immunoglobulins, proteins, glycoproteins, nucleic acids and metabolic compounds. Its composition is influenced by glandular secretion, oral epithelial cells, microorganisms, gingival crevicular fluid and other local sources.

One of the major advantages of saliva is the simplicity of sample collection. Unlike venous blood collection, saliva sampling is non-invasive, generally painless and suitable for repeated measurements. This feature may be particularly useful in community-based research and longitudinal monitoring of individuals with oral potentially malignant disorders.

Saliva also contains molecules released directly from oral lesions. These molecules may include inflammatory mediators, tumour-associated proteins, genetic material and extracellular vesicles originating from malignant epithelial cells. Consequently, salivary analysis provides an opportunity to investigate biological alterations occurring within the oral microenvironment [5].

2.1 ADVANTAGES OF SALIVARY DIAGNOSTICS

Salivary biomarker research offers several potential advantages:

However, the composition of saliva varies according to hydration, age, diet, oral hygiene, smoking, medications, salivary flow rate and circadian rhythm. Periodontal disease and oral infections can also alter biomarker concentrations. These factors must be considered during study design and interpretation.

3. MAJOR CATEGORIES OF SALIVARY BIOMARKERS IN ORAL CANCER

3.1 PROTEIN BIOMARKERS AND INFLAMMATORY CYTOKINES

Protein biomarkers have been among the most extensively investigated salivary molecules in OSCC. Tumour development is accompanied by changes in cellular proliferation, immune responses, extracellular matrix degradation and inflammatory signalling. These processes may result in altered concentrations of specific proteins in saliva.

Interleukin-6 (IL-6) is a pro-inflammatory cytokine involved in immune regulation, cellular proliferation and tumour-associated signalling. Increased salivary IL-6 concentrations have been reported in individuals with OSCC compared with healthy controls. Its elevation may reflect inflammatory activity within the tumour microenvironment. However, IL-6 is not specific to malignant disease because periodontal inflammation and other oral inflammatory conditions can also increase its concentration.

Interleukin-8 (IL-8) is another extensively studied inflammatory mediator. It participates in neutrophil recruitment, angiogenesis and tumour-associated inflammatory processes. Several clinical studies have demonstrated elevated salivary IL-8 concentrations in patients with OSCC. Its potential diagnostic contribution may be greater when combined with other molecular markers rather than used independently [6, 9].

Interleukin-1 beta (IL-1β) is associated with inflammatory signalling and tumour progression. Increased concentrations have been observed in saliva from patients with oral cancer. Its diagnostic relevance has been investigated alongside IL-8 and galectin-3-binding protein (LGALS3BP), particularly in Indian populations [9].

Matrix metalloproteinase-9 (MMP-9) is an enzyme involved in extracellular matrix degradation and tissue remodelling. It may facilitate tumour invasion by modifying the extracellular environment. Elevated salivary MMP-9 levels have been reported in OSCC and oral potentially malignant disorders. Its association with invasive behaviour makes it an important candidate for diagnostic and disease-characterisation studies [10, 11].

A 2026 systematic review and meta-analysis evaluating seven studies involving 795 participants reported pooled sensitivity and specificity estimates of 98% and 96%, respectively, for salivary MMP-9 in early-stage oral cancer. However, the authors also identified substantial heterogeneity and risk-of-bias concerns, meaning these estimates should not be interpreted as established real-world screening performance [11].

CD44 is a cell-surface glycoprotein involved in cellular adhesion, migration and tumour-associated processes. Soluble forms of CD44 can be detected in saliva. Its potential diagnostic application has been investigated in OSCC, including studies examining its ability to distinguish malignant lesions from non-malignant conditions.

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CYFRA 21-1 is a fragment of cytokeratin 19 released during epithelial cell turnover and damage. Increased levels have been investigated in saliva and serum from patients with OSCC. This biomarker may provide information about epithelial malignancy, particularly when evaluated in combination with other markers.

Other investigated proteins and enzymes include lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), tumour necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF) and cathepsin B. Although several have demonstrated differences between cancer patients and controls, their specificity and reproducibility require further investigation.

3.2 SALIVARY RNA AND MICRORNA BIOMARKERS

RNA-based biomarkers have received considerable attention because they provide information about changes in gene expression associated with carcinogenesis.

Messenger RNA (mRNA) molecules originating from oral epithelial cells and tumour-associated tissues can be detected in saliva. Changes in the expression of selected transcripts may reflect abnormal cellular proliferation, stress responses and altered molecular signalling.

Park and colleagues demonstrated the presence of microRNAs in saliva and investigated their diagnostic relevance in oral cancer. Their findings provided an important foundation for further research into salivary microRNA-based diagnostics [7].

MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression by influencing messenger RNA translation and degradation. Their involvement in cell proliferation, apoptosis, differentiation and metastasis makes them potential indicators of malignant transformation.

miR-31 is one of the better-studied salivary microRNAs in oral cancer. Liu and colleagues investigated salivary miR-31 in 45 patients with oral carcinoma, 10 patients with oral verrucous leukoplakia and 24 healthy controls. Increased salivary miR-31 levels were identified in patients with oral carcinoma, including those with small tumours. Following surgical removal of the tumour, salivary miR-31 levels decreased substantially, suggesting that tumour tissue contributed to its increased concentration [8].

Other candidate microRNAs include miR-21, miR-24-3p, miR-139-5p, miR-184 and miR-486-5p. Their expression patterns have been investigated in relation to tumour development, disease classification and prognosis.

Despite promising findings, differences in extraction procedures, RNA normalisation, sample storage and molecular quantification techniques make comparisons between studies difficult. Further validation is required to identify reproducible miRNA panels suitable for clinical assessment.

3.3 SALIVARY DNA AND EPIGENETIC BIOMARKERS

Cancer development involves genetic and epigenetic alterations that influence normal cellular growth and survival. DNA released from tumour cells and exfoliated epithelial cells can be detected in saliva, creating opportunities for molecular diagnosis.

One important area of research is DNA promoter methylation. Hypermethylation of promoter regions can suppress the expression of tumour-suppressor genes and contribute to malignant transformation.

Liyanage and colleagues investigated promoter hypermethylation of four genes, namely p16INK4a, RASSF1A, TIMP3 and PCQAP/MED15, in salivary DNA from patients with oral and oropharyngeal cancers. Their study demonstrated the potential of a multigene methylation approach for cancer detection [14].

Other investigated molecular alterations include changes involving TP53 and CDKN2A. Detection of these alterations may provide information about molecular events associated with oral carcinogenesis.

An important advantage of epigenetic markers is that abnormal DNA methylation may occur during earlier stages of carcinogenesis. However, the presence of methylation changes does not necessarily establish invasive cancer. Their diagnostic interpretation requires careful differentiation between potentially malignant disorders and histologically confirmed malignancy.

3.4 SALIVARY METABOLOMIC BIOMARKERS

Metabolomics involves the systematic investigation of small molecules produced during cellular metabolism. Malignant transformation can alter metabolic pathways associated with energy production, amino acid metabolism, oxidative stress and lipid regulation.

Salivary metabolomic profiling provides an opportunity to identify patterns of metabolic alterations associated with OSCC.

Lohavanichbutr and colleagues examined saliva samples from patients with oral cavity squamous cell carcinoma, oropharyngeal cancer and healthy controls using multiple analytical platforms, including nuclear magnetic resonance spectroscopy and mass spectrometry. Their findings identified differences in selected metabolites, including glycine and proline, between oral cancer patients and controls. Several metabolites were also associated with early-stage oral cavity cancer [15].

Other research has investigated amino acids, polyamines, organic acids, lipid-related metabolites and oxidative stress-associated compounds.

The principal advantage of metabolomic analysis is its ability to detect a broader biochemical signature rather than relying on a single molecular target. Nevertheless, metabolic profiles can be influenced by diet, medication, smoking, systemic disease and sample-handling conditions. Consequently, the reproducibility of proposed signatures requires independent validation.

3.5 SALIVARY EXTRACELLULAR VESICLES AND EXOSOMES

Extracellular vesicles are membrane-bound structures released by cells into their surrounding environment. Exosomes represent a small extracellular vesicle population containing proteins, lipids, DNA and RNA molecules.

Tumour-derived extracellular vesicles may carry molecular information associated with the biological characteristics of malignant cells. Since these structures can enter saliva, they have attracted interest as potential non-invasive sources of cancer-associated biomarkers.

Research has investigated exosomal miRNAs, proteins and other molecular components in patients with OSCC. Gai and colleagues reported the potential of salivary extracellular vesicle-associated miRNAs for identifying oral squamous cell carcinoma [16]. He and colleagues also investigated salivary exosomal miR-24-3p as a potential diagnostic marker [17].

The potential advantage of extracellular vesicle analysis lies in the relative protection of their molecular contents from enzymatic degradation. However, the isolation of sufficiently pure vesicles, separation from other salivary components and reproducibility of analytical procedures remain important technical challenges.

3.6 ORAL MICROBIOME-ASSOCIATED BIOMARKERS

The oral microbiome consists of a diverse community of bacteria and other microorganisms that contribute to oral health and disease. Changes in microbial composition may occur in association with chronic inflammation, changes in the local environment and oral malignancy.

Studies have investigated differences in bacterial communities between individuals with OSCC and healthy controls. Microorganisms such as Fusobacterium species and other inflammation-associated bacteria have attracted research interest in this context.

Salivary microbial signatures may potentially complement host-derived biomarkers. However, microbial alterations are not necessarily specific to cancer and may also reflect periodontal disease, tobacco exposure, oral hygiene and dietary factors.

Metagenomic sequencing, 16S ribosomal RNA sequencing and quantitative polymerase chain reaction are among the techniques used to investigate these microbial profiles [5].

4. SUMMARY OF IMPORTANT SALIVARY BIOMARKERS

Biomarker	Biological significance	Potential diagnostic application
IL-6	Inflammatory signalling	OSCC-associated inflammation
IL-8	Angiogenesis and inflammatory response	Cancer-associated inflammatory changes
IL-1β	Pro-inflammatory signalling	Malignant and premalignant lesion assessment
MMP-9	Extracellular matrix degradation	Tumour invasion and early detection research
CD44	Cell adhesion and migration	OSCC classification
CYFRA 21-1	Cytokeratin 19 degradation	Epithelial malignancy assessment
miR-31	Post-transcriptional gene regulation	Early detection and postoperative monitoring
miR-24-3p	Exosomal RNA signalling	Molecular detection research
p16INK4a methylation	Tumour-suppressor gene silencing	Epigenetic detection
Glycine and proline	Cellular metabolic pathways	Metabolomic profiling
LGALS3BP	Tumour-associated glycoprotein	OSCC biomarker panel research

These markers represent research candidates and should not be interpreted as independently established clinical diagnostic tests.

5. TECHNIQUES USED FOR SALIVARY BIOMARKER DETECTION

The detection and quantification of salivary biomarkers require appropriate analytical techniques. The selection depends on the molecular characteristics of the biomarker, its expected concentration and the intended diagnostic application.

Enzyme-linked immunosorbent assay (ELISA): ELISA is commonly used to quantify proteins and inflammatory cytokines, including IL-6, IL-8 and MMP-9. It is relatively accessible and suitable for the measurement of specific targets.

Quantitative real-time polymerase chain reaction (RT-qPCR): This technique is used to quantify selected RNA molecules, including miRNAs and mRNA transcripts. It provides sensitive molecular detection but requires careful RNA extraction and normalisation.

Methylation-specific PCR: This method can identify promoter methylation in selected genes and is relevant for investigating epigenetic alterations associated with oral carcinogenesis.

Mass spectrometry: Liquid chromatography-mass spectrometry and related techniques enable the identification and quantification of proteins, peptides and metabolites. These methods are particularly useful for biomarker discovery and validation.

Next-generation sequencing: Sequencing approaches can be used to investigate genetic alterations, microbial communities and molecular signatures present in saliva.

Biosensors and point-of-care platforms: Biosensor technologies are being developed to detect specific biomarkers using portable analytical systems. Electrochemical, optical and nanotechnology-based platforms may eventually support rapid testing outside specialised laboratories [19, 20, 22, 24].

Although these technologies offer considerable research opportunities, analytical sensitivity alone does not establish clinical usefulness. Tests must demonstrate acceptable reproducibility, specificity and diagnostic accuracy in clinically representative populations.

6. DIAGNOSTIC ACCURACY AND CURRENT CLINICAL EVIDENCE

The clinical value of a salivary biomarker depends on its ability to distinguish individuals with disease from those without disease. Sensitivity, specificity, positive predictive

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value, negative predictive value and area under the receiver operating characteristic curve (AUC) are commonly used measures for evaluating diagnostic performance [21, 23, 25, 26].

Several investigations have reported encouraging findings for individual markers. However, the results vary substantially across studies because of differences in patient selection, disease stage, control populations, sample collection and analytical techniques.

A 2024 systematic review and network meta-analysis by Khijmatgar and colleagues evaluated salivary biomarkers in OSCC and head and neck squamous cell carcinoma. The investigation identified several promising candidates, including chemerin, MMP-9 and phytosphingosine for oral cancer detection. It also highlighted the potential of specific combinations for early-stage disease [13, 27, 28, 29, 30].

A 2025 systematic review and meta-analysis by Kumar and colleagues examined IL-8, CYFRA 21-1 and CD44. Across 20 eligible studies, the combined biomarker panel demonstrated a pooled AUC of 0.92, sensitivity of 88% and specificity of 90%. These findings suggest that multi-marker approaches may improve diagnostic discrimination, although performance in routine clinical populations remains to be established [12].

Another 2026 meta-analysis by Beladiya and colleagues examined 37 salivary protein biomarkers across 28 studies involving 3,507 patients with OSCC and 3,501 controls. The overall pooled sensitivity was 71% and specificity was 69%. The variation across studies emphasises the limitations of relying on individual salivary proteins and the importance of evaluating clinically relevant combinations [12, 30, 31, 32, 33].

The findings of these investigations should be interpreted in the context of their study designs. Many biomarker studies have compared established cancer cases with healthy controls. Such comparisons may overestimate diagnostic performance because real-world screening populations also contain individuals with periodontal disease, oral infections, benign lesions and potentially malignant disorders.

More importantly, evidence of a difference in biomarker concentration between cancer patients and healthy individuals does not automatically demonstrate the ability to detect cancer at an early stage.

Prospective studies involving individuals with suspicious oral lesions and histopathological confirmation are therefore essential for establishing the actual diagnostic utility of these tests[34, 35].

7. ROLE OF SALIVARY BIOMARKERS IN IDENTIFYING ORAL POTENTIALLY MALIGNANT DISORDERS

Oral potentially malignant disorders are clinically relevant because some may progress to invasive carcinoma. Identification of molecular changes associated with malignant transformation is therefore an important area of research.

Oral leukoplakia, oral submucous fibrosis and erythroplakia are among the conditions investigated in salivary biomarker studies.

Changes in inflammatory cytokines, MMPs, microRNAs and epigenetic markers may provide information about alterations occurring during different stages of oral carcinogenesis.

However, the presence of a potentially malignant disorder does not establish that malignant transformation will occur. Similarly, an abnormal salivary biomarker result cannot independently confirm the presence of cancer.

Longitudinal investigations involving repeated saliva collection and clinical follow-up may help determine whether particular biomarker patterns are associated with subsequent malignant transformation. This approach may also help distinguish molecular alterations associated with inflammation from those more directly linked to neoplastic progression.

8. CHALLENGES IN CLINICAL TRANSLATION

Despite promising research findings, several barriers prevent the widespread application of salivary biomarkers in clinical practice.

Pre-analytical variability: Salivary biomarker concentrations can change according to collection method, time of sampling, hydration, food intake, smoking and oral hygiene. Variations in sample processing may further affect the stability of proteins and nucleic acids.

Lack of standardised protocols: Different studies use stimulated or unstimulated saliva, different storage temperatures, different centrifugation procedures and different assay platforms. This makes direct comparison of results difficult.

Influence of oral inflammatory conditions: Periodontal disease, mucosal infections and other inflammatory conditions may alter cytokine and enzyme concentrations. This can reduce the specificity of biomarkers such as IL-6, IL-8 and MMP-9[36, 37, 38, 39].

Small sample sizes: Many investigations are based on relatively small hospital-based cohorts. Their findings may not be representative of the broader population.

Insufficient external validation: Biomarker panels developed in one study population may not perform similarly in populations with different geographical, genetic, behavioural and clinical characteristics.

Lack of clinically established cut-off values: Reliable diagnostic thresholds have not been standardised for most salivary biomarkers. Consequently, comparisons of diagnostic accuracy between studies remain challenging.

Cost and technical requirements: Advanced molecular techniques such as mass spectrometry and sequencing require specialised instruments, trained personnel and quality-controlled laboratory facilities.

Addressing these barriers will require standardised protocols, larger study populations and prospective validation across multiple healthcare settings.

9. FUTURE PERSPECTIVES

Future research should focus on moving from individual biomarker discovery towards the development of validated multi-marker diagnostic approaches.

Combining inflammatory proteins, tumour-associated nucleic acids, epigenetic alterations and metabolic signatures may improve diagnostic discrimination. However, these combinations must demonstrate reproducibility and clinically meaningful improvement over conventional oral examination.

Artificial intelligence and machine-learning methods may support the identification of complex biomarker patterns. These approaches could integrate multiple molecular measurements with patient characteristics and clinical findings to develop risk-classification models. Their performance must be assessed using independent datasets and appropriate external validation.

The development of affordable point-of-care biosensors is another important research direction. Portable platforms capable of detecting selected salivary markers could potentially support primary healthcare investigations and community-based research, particularly in resource-constrained settings.

For countries such as India, research should prioritise populations with substantial exposure to tobacco and areca nut. Prospective studies involving patients with oral potentially malignant disorders could be particularly useful for understanding the relationship between molecular changes and malignant transformation.

Future investigations should include diverse clinical populations, healthy controls, individuals with benign oral inflammatory conditions and patients with histologically confirmed early-stage OSCC. Such designs would provide more realistic estimates of sensitivity, specificity and predictive values.

Importantly, future research should evaluate whether adding salivary biomarkers to standard clinical examination improves referral decisions, diagnostic intervals or patient outcomes. Demonstrating analytical performance alone will not be sufficient to establish clinical benefit.

10. CLINICAL IMPLICATIONS AND CONCLUSION

Salivary biomarkers have emerged as an important area of research in non-invasive oral cancer diagnostics. Proteins, inflammatory cytokines, microRNAs, DNA methylation patterns, metabolites, extracellular vesicles and microbiome-associated signatures provide different types of biological information related to oral carcinogenesis.

Among the investigated candidates, IL-6, IL-8, IL-1β, MMP-9, CD44, CYFRA 21-1 and miR-31 have received particular research attention. Multi-marker panels may provide better diagnostic discrimination than individual biomarkers, while molecular and metabolomic techniques continue to expand the range of potentially detectable alterations.

Nevertheless, current evidence does not justify replacing conventional clinical examination or histopathological diagnosis with salivary testing. The 2026 American Dental Association living guideline issued research-only recommendations for salivary adjunct tests in both adults with and without oral mucosal abnormalities. It also reaffirmed the role of clinical examination and biopsy for definitive diagnosis [3].

In conclusion, salivary biomarkers offer considerable research potential for supporting the early detection and molecular characterisation of oral cancer. Their eventual clinical value will depend on standardised sample collection, robust assay development, prospective multicentre validation and evidence that their use improves clinical decision-making. Until these requirements are met, salivary biomarkers should be regarded as investigational or complementary research tools rather than established stand-alone screening or diagnostic tests.

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