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Role Of Salivary Biomarkers In Oral Cancer Screening: A Review

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Abstract:

Oral cancer remains a significant global health challenge, with late-stage diagnosis contributing to poor prognosis. Salivary biomarkers have emerged as a promising non-invasive alternative for early detection, diagnosis, and prognostic assessment. Saliva directly reflects the tumor microenvironment and contains a diverse array of molecules, including proteins, enzymes, cytokines, growth factors, DNA, RNA, and microRNAs. Studies have consistently reported elevated levels of IL-6, IL-8, TNF-α, MMP-9, VEGF, and miRNA-21 in oral squamous cell carcinoma, with combinations of multiple biomarkers enhancing diagnostic accuracy. Despite promising evidence, clinical adoption is limited by variability, lack of standardized protocols, and the need for multicenter validation. Integration of salivary biomarker panels could facilitate non-invasive screening, personalized management, and improved outcomes in oral cancer care.

Keywords: Oral cancer; Salivary biomarkers; Cytokines; MicroRNAs; Salivaomics

Introduction

Oral cancer remains a major global health concern, exhibiting high incidence and mortality rates, particularly in South and Southeast Asia. In India, oral cancer is the most common cancer in men and the third most common in women, comprising 13–16% of all malignancies. Notably, 95% of cases are linked to tobacco use.[1] Traditional methods like biopsy and imaging are invasive, uncomfortable, and often lead to delayed detection of cancers like oral cancer, which is compounded by resource limitations and low patient compliance. These factors result in poor prognosis, especially in low-resource settings. Salivary biomarkers have emerged as a promising non-invasive, rapid, and cost-effective approach for the early detection, diagnosis, and prognostic assessment of oral cancer, providing an attractive alternative to conventional diagnostic methods such as biopsy and imaging.[2] Saliva is an ideal diagnostic medium for oral cancer screening because its proximity to lesions efficiently captures tumor-derived biomolecules. Its non-invasive, painless collection method ensures high patient acceptance and ease of repeated sampling for screening and monitoring. Furthermore, its rich molecular content (proteins, DNA, RNA, etc.) reflects disease processes, making it suitable for biomarker-based diagnostics. Since saliva directly bathes oral lesions, it reflects the tumor microenvironment and allows for painless, repeatable sampling, making it an ideal medium for biomarker analysis.[3] A wide spectrum of molecules including proteins, peptides, cytokines, growth factors, enzymes, DNA, RNA, and microRNAs can be detected in saliva, many of which are strongly associated with oral squamous cell carcinoma (OSCC) and its progression. Elevated levels of cytokines like IL-6, IL-8, and TNF-α, enzymes such as LDH and MMPs, and proteins including albumin and survivin have consistently been reported, while growth factors like VEGF and proteases such as MMP-9 correlate with tumor invasiveness.[4]

Similarly, genomic and epigenetic alterations, notably salivary microRNAs like miRNA-21, along with other potential molecules including tetranectin, cyclin D1, Ki-67, defensin-1, and profiling-1, offer valuable insights into malignant transformation. Studies and systematic reviews demonstrate that individual markers, particularly IL-8, can achieve high diagnostic accuracy with sensitivity up to 91% and specificity of 89%, while panels combining multiple biomarkers further enhance precision in early detection, risk prediction, and monitoring therapeutic response.[5] Beyond diagnosis, salivary biomarkers hold significant value in prognostication, recurrence surveillance, and treatment evaluation, although challenges such as variability due to oral hygiene, diet, or coexisting oral diseases, and the lack of standardized protocols, still limit routine clinical adoption. [6] This article gives an overview on role of salivary biomarkers in oral cancer screening.

Protein and Cytokine Biomarkers (Proteomics)

Key salivary protein and cytokine biomarkers have gained considerable attention in oral cancer research due to their altered expression patterns in oral squamous cell carcinoma (OSCC) and their potential diagnostic and prognostic significance. Interleukin-6 (IL-6) is consistently elevated in OSCC, promoting carcinogenesis through JAK/STAT and MAPK signaling pathways while contributing to angiogenesis, immune evasion, and suppression of tumor suppressor genes such as p53.[7] Similarly, interleukin-8 (IL-8), a pro-inflammatory chemokine, is overexpressed in oral cancer, enhancing angiogenesis and tumor proliferation via CXCR1/CXCR2 signaling, with studies showing high sensitivity for OSCC detection. Tumor necrosis factor-alpha (TNF-α) supports tumor survival and progression by activating NF-κB, inhibiting apoptosis, and enhancing proliferative signals, while matrix metalloproteinase-9 (MMP-9) facilitates extracellular matrix degradation, invasion, and metastasis, correlating with tumor aggressiveness.[8] Elevated lactate dehydrogenase (LDH) activity in saliva reflects the metabolic reprogramming characteristic of cancer cells, whereas cytokeratin fragment CYFRA 21-1 is often three times higher in OSCC patients and linked to invasion and recurrence. Cancer antigen 125 (CA 125) and soluble CD44 are also elevated, with CD44 supporting cell adhesion and migration, and defensin-1, an antimicrobial peptide, reflecting inflammatory and tumor-driven microenvironmental changes.[9] Furthermore, vascular endothelial growth factor (VEGF) indicates active angiogenesis and tumor progression, particularly in advanced cases. Collectively, these biomarkers especially IL-6, IL-8, TNF-α, MMP-9, LDH, and CYFRA 21-1 demonstrate high sensitivity and specificity for OSCC diagnosis, and

when combined into biomarker panels, significantly enhance early detection, prognostic assessment, and recurrence monitoring. The non-invasive, reproducible nature of salivary sampling further underscores the promise of proteomic biomarkers for routine, community-based, and longitudinal screening of oral cancer.[10]

Nucleic Acid Biomarkers (Transcriptomics)

Salivary nucleic acid biomarkers, particularly messenger RNA (mRNA) panels and microRNAs (miRNAs), are gaining recognition as reliable, non-invasive diagnostic tools for oral cancer, reflecting molecular alterations associated with tumor initiation, progression, and malignant transformation.[11] Panels of mRNAs such as NAB2, CYP27A1, NPIPB4, MAOB, SIAE, and COL3A1 have shown significantly altered levels in oral squamous cell carcinoma (OSCC) patients compared to healthy controls, with multivariate combinations like CYP27A1 + SIAE achieving an AUC of up to 0.84, thereby enabling good discrimination, particularly in individuals under 60 years of age.[12] These mRNA signatures are highly sensitive in detecting early-stage OSCC and in differentiating premalignant lesions from invasive carcinoma. Similarly, salivary miRNAs provide critical insights into oncogenesis: miRNA-21 is consistently upregulated in OSCC and oral potentially malignant disorders (OPMD), promoting proliferation, inhibiting apoptosis, and correlating with tumor aggressiveness; miRNA-184, though variably expressed, is implicated in cell growth and apoptosis regulation, serving as a potential discriminator between premalignant and malignant mucosal conditions; and miRNA-31 is strongly associated with recurrence and malignant transformation, making it a valuable marker for early detection and risk stratification.[13,14] Additional miRNAs such as miRNA-146a, miRNA-199a, and miRNA-155 demonstrate altered expression in OSCC and tobacco users, reflecting both cancer biology and exposure-related risk. Collectively, these nucleic acid biomarkers exhibit strong diagnostic accuracy, distinguishing normal, OPMD, and malignant states, including early disease, with reproducible results using platforms like real-time PCR, microarray, and next-generation sequencing.[15] Their non-invasive, easily repeatable nature makes saliva-based nucleic acid analysis particularly suitable for population-level screening and surveillance of high-risk groups, with miRNA-21, miRNA-184, and miRNA-31 standing out as the most promising candidates for integration into clinical and public health strategies for oral cancer.[16]

DNA & Epigenetic Biomarkers (Genomics)

Salivary DNA and epigenetic biomarkers represent an effective non-invasive approach for oral cancer detection and monitoring, as they capture key genetic and epigenetic alterations associated with oral squamous cell carcinoma (OSCC). Circulating tumor DNA (ctDNA) detected in saliva functions as a liquid biopsy, reflecting tumor-specific mutations and burden with high sensitivity, and has been successfully identified in nearly all OSCC cases, including early stages, with strong applicability for recurrence monitoring after surgery.[17] Mutations in the tumor suppressor gene p53, frequently observed in oral cancer, can be reliably identified in saliva through detection of both loss of heterozygosity (LOH) and p53 mutations, correlating closely with tissue biopsy results and serving as a surrogate for tumor genotyping. Similarly, salivary detection of human papillomavirus (HPV) DNA, particularly high-risk subtypes HPV-16 and HPV-18, provides valuable screening for virus-driven oral and oropharyngeal cancers, which display unique clinical and prognostic patterns, especially in younger and non-smoking patients.[18] Epigenetic alterations, notably promoter hypermethylation of tumor suppressor genes and methylated microRNA loci (such as mgmiR-9, mgmiR-124, MGMT, and p16), silence regulatory pathways and have demonstrated strong potential for OSCC diagnosis and risk stratification. Additionally, allelic loss (LOH) at chromosomal regions like 3p, 9p21, and 17p13 is commonly reported in oral cancer and serves as a marker of genetic instability and malignant transformation, with salivary-based detection offering a feasible means to track these alterations.[19] Collectively, salivary genomics encompassing ctDNA, p53 mutations, HPV DNA, promoter methylation, and LOH provides high sensitivity and specificity for early diagnosis, prognosis, and post-treatment surveillance, while bypassing the invasiveness of tissue biopsies. As this field rapidly evolves, DNA and epigenetic biomarkers in saliva are expected to further enhance early detection, individualized risk management, and therapeutic monitoring, supporting a shift toward precision medicine in oral oncology.[20]

Diagnostic Performance of Salivary Biomarkers

Salivary biomarkers have demonstrated strong diagnostic performance for oral cancer, with varying sensitivity, specificity, and predictive values across individual studies and meta-analyses, highlighting their potential for reliable, non-invasive screening. Messenger RNA (mRNA) panels show remarkable accuracy with sensitivity and specificity values around 90% and an AUC of 0.96, while microRNA (miRNA) biomarkers, particularly miRNA-21, exhibit comparable performance with pooled sensitivity and specificity near 91% and an AUC of 0.95, making them excellent diagnostic tools.[21] Protein-based markers such as interleukin-8 (IL-8) consistently achieve sensitivities and specificities above 80%, outperforming other cytokines like IL-1β, whereas angiogenic markers like vascular endothelial growth factor (VEGF) and structural markers such as CYFRA 21-1 display high diagnostic power, with sensitivities and specificities often exceeding 85% and up to 96% in some studies. Genomic biomarkers, including circulating tumor DNA (ctDNA) and salivary HPV DNA, also demonstrate promising accuracy but still require large-scale validation to confirm their clinical utility. In terms of predictive values, miRNAs yield positive likelihood ratios as high as 9.77, indicating a nearly tenfold higher chance of oral cancer in test-positive individuals, while negative likelihood ratios for mRNA and miRNA remain low (~0.10), offering strong rule-out capability.[22] Diagnostic odds ratios (DORs) for salivary biomarkers range from moderate to high, with values around 13.4, further supporting their clinical relevance. Importantly, multi-marker panels combining cytokines, miRNAs, and mRNAs consistently outperform single biomarkers by capturing diverse biological pathways such as inflammation, angiogenesis, and genetic instability thereby increasing accuracy and reducing false results. Overall, the collective evidence highlights the high diagnostic potential of salivary biomarkers, with mRNA and miRNA profiles, alongside IL-8, VEGF, CYFRA 21-1, and ctDNA, representing the most robust candidates, and multi-biomarker panels offering superior performance for early detection, prognostic stratification, and monitoring in oral cancer care.[23]

Clinical Applications of Salivary Biomarkers in Oral Cancer

Salivary biomarkers have emerged as valuable tools for clinical applications in oral oncology, supporting early detection, prognosis, recurrence monitoring, and personalized care. In the context of early screening and risk prediction, biomarkers such as IL-6, LDH, ferritin, and specific microRNAs are significantly elevated in oral potentially malignant disorders (OPMDs), allowing non-invasive distinction of high-risk lesions from healthy oral mucosa. Screening in high-risk groups, particularly tobacco and betel quid users, has shown strong diagnostic potential, with biomarker panels including MMP1, KNG1, ANXA2, and HSPA5 achieving sensitivities near 88% and specificities around 80%, making saliva-based assays a practical tool for community-level surveillance in regions with high oral cancer prevalence.[24] Beyond early detection, salivary biomarkers hold important prognostic and predictive value by tracking disease progression and recurrence, as fluctuations in IL-8, MMPs, microRNAs, and circulating tumor DNA (ctDNA) correlate with tumor burden, treatment response, and recurrence risk. Elevated ferritin and total protein levels, in particular, have been linked with malignant transformation of OPMDs, while biomarker-based risk scoring systems can guide follow-up intensity and inform early intervention strategies. In addition, salivary biomarkers play a key role in personalized and precision medicine, enabling tailored surveillance and treatment approaches based on individual molecular profiles.[25] Multi-marker panels that integrate proteomic, genomic, and epigenetic signatures capture tumor heterogeneity more effectively, thereby improving diagnostic accuracy and prognostic prediction. Furthermore, saliva-based liquid biopsy provides real-time, non-invasive monitoring of tumor evolution, allowing clinicians to adapt treatment plans dynamically and avoid unnecessary invasive procedures. Collectively, these applications highlight the transformative role of salivary biomarkers in oral cancer care, where they not only facilitate early detection and risk stratification but also support ongoing disease monitoring and personalized management strategies, ultimately improving outcomes in both general and high-risk populations.[26]

Technological Platforms and Limitations in Salivary Biomarker Detection

The detection of salivary biomarkers in oral cancer relies on a range of conventional, high-throughput, and emerging technologies, each offering unique strengths and limitations for clinical translation. Among conventional assays, ELISA remains widely used for quantifying salivary cytokines and proteins such as IL-6, IL-8, and TNF-α with good sensitivity and specificity, while quantitative PCR (qPCR) serves as the gold standard for nucleic acid detection, enabling accurate measurement of miRNAs, mRNAs, and methylated DNA associated with OSCC.[27] High-throughput approaches like microarray profiling facilitate simultaneous analysis of hundreds of genes or miRNAs to uncover novel biomarker signatures, whereas next-generation sequencing (NGS) provides detailed genomic and transcriptomic insights, including mutation profiling and methylation analysis at high resolution. More recently, advanced platforms such as digital PCR have enabled ultra-sensitive detection of low-abundance targets like circulating tumor DNA (ctDNA), proving useful for early detection and recurrence monitoring.[28] Similarly, nanotechnology-based biosensors incorporating gold nanoparticles and graphene offer label-free, rapid, and highly sensitive biomarker detection suitable for point-of-care testing, while CRISPR-based assays (e.g., SHERLOCK, DETECTR) show promise for rapid, highly specific nucleic acid detection in saliva. Lab-on-a-chip microfluidic devices further integrate multiplexed biomarker detection into portable, automated systems, paving the way for cost-effective, scalable oral cancer screening in community and low-resource settings. Despite this progress, several challenges limit clinical adoption. Pre-analytical variability arising from differences in saliva collection (stimulated vs. unstimulated), storage, and patient-related factors such as diet, oral hygiene, circadian rhythm, and comorbidities affects biomarker consistency.[29] Technical barriers include assay reproducibility, cross-reactivity, and the absence of standardized operating protocols or normalization controls, which hinder inter-laboratory comparability. Clinical barriers are equally important, as advanced technologies like NGS and nanobiosensors remain expensive, limiting accessibility in low-resource regions, while the absence of validated diagnostic cut-off values and lack of regulatory approval for standardized test kits further impede translation into practice. [30]

Future Perspectives and Conclusion

Salivary biomarkers represent a transformative, non-invasive approach for oral cancer detection, prognosis, and monitoring, with future progress relying on advanced strategies such as multi-omics integration ("salivaomics") and artificial intelligence-driven analysis to enhance accuracy and personalize care. While individual biomarkers like IL-8, miRNA-21, CYFRA 21-1, and ctDNA show strong diagnostic value, multi-marker panels are likely to provide superior sensitivity and specificity by capturing diverse biological pathways. To achieve clinical translation, however, large-scale multicenter validation trials, standardized saliva collection protocols, and regulatory approval are essential. The development of cost-effective, point-of-care diagnostic devices and integration into public health screening programs will be particularly valuable in high-risk regions with limited resources. In summary, with continued innovation, validation, and standardization, salivary biomarkers hold the potential to revolutionize oral oncology by enabling earlier detection, personalized surveillance, and improved patient outcomes.

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