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Salivary Biomarkers for Oral Cancer Detection - A Review Article

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Abstract: ***Globally, oral cancer is the sixth most common type of cancer with a high mortality rate. More than 90% of oral cancers are squamous cell carcinomas (SCC). The standard methods used to detect oral cancers include clinical examination, biochemical investigations, and invasive biopsies. The identification of biomarkers from biological fluids (blood, urine and saliva) helps in early diagnosis. Although advancements have been made, not all patients respond to these therapies in the same way. To overcome this, several studies have identified biomarkers that can identify the patient who may benefit from a particular treatment or are at risk of poor prognosis. Saliva is the safest and most easily accessible biofluid, it requires non - invasive sampling techniques. Saliva is composed of secretions from both major and minor salivary glands. Biomarkers play a vital role in the diagnosis, treatment, and prevention of various diseases. Oral cancer lesions have direct contact with saliva, making it a more specific and potentially sensitive screening tool. Saliva has a broad spectrum of biomarkers that can be classified into Proteome, genome, epigenome, transcriptome, microbiome, and metabolome. However, further research is required for the reliability and validation of salivary biomarkers for clinical applications.***

Keywords: saliva, Biomarker, tobacco, squamous cell carcinoma, microarray

1. Introduction

Globally oral cancer is the sixth most common type of cancer with a high mortality rate [1], with India contributing to almost one - third of the total burden.2According to WHO oral cancer is a major public health challenge in India.3Global incidence of oral cancer is estimated at 529500 annually, [4] Particularly in India 77 thousand new cases and 52 thousand deaths are reported annually.[5] At the time of diagnosis, more than 60% of oral cancers are late - stage widespread malignancies. This suggests the need to educate people about the risk factors, signs, symptoms, and prevention of oral cancer.6 Oral cancer is a multifactorial disease. More than 90 % of oral cancers are squamous cell carcinomas, which arise from the epithelial lining of the oral cavity.[6, 7] several risk factors are implicated in the development of oral cancer, of which the most common are tobacco smoking and betel quid chewing. However, many patients are diagnosed with oral cancer despite missing known lifestyle or environmental risk factors that are thought to be associated factors like genetic susceptibility, which are believed to play a causative role.[8, 9] According to the National Cancer Institute, biomarker is defined as "A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.[10] Tumor biomarkers are essential for early detection, a better outcome of survival and preventing extensive treatment.[11] Several body fluids, such as blood, serum, plasma, pleural fluid, urine, and saliva, are useful for biomarker evaluations.[12, 13]

Diagnostic body fluid in oral cancer: SALIVA

Saliva is the safest, non - invasive, cost - effective, non - coagulative, body fluid for the identification of biomarkers (Figure1).[14] Oral cancer lesions have direct contact with saliva as cancerous cells shed directly into the oral cavity that makes it a more specific and potentially sensitive screening tool.[15, 16] Saliva is composed of secretion from three major salivary glands (Parotid Gland, Submandibular Gland, Sublingual Gland) and minor salivary glands present in the oral mucosa and palate, and, the Gingival Crevicular fluid, oral mucosal transudate, desquamated oral epithelial cells, debris, blood cells, nonadherent bacteria, and food residuals are present.[17]

Whole saliva is a complex balance among local and systemic sources that allow saliva the diagnosis of not only salivary gland disorders but also oral diseases and systemic conditions. Several studies have shown that salivary biomarkers are used for the diagnosis of cancers other than the oral cavities, such as breast cancer, lung cancer, and ovarian cancer. Saliva plays a crucial role in speech, taste, mastication, digestion, and defense mechanism.[18] Blood has a gold standard for most examinations but the collection of saliva has several advantages compared to blood as saliva is stable over time, it does not clot and it is less complex in terms of having a low background of inhibitory substances and normal material.[19] Saliva contains various circulatory molecules, such as proteins, nucleotides (DNA, mRNA, microRNA), and several metabolites that can be used as potential biomarkers for screening and diagnostic purposes.[20] The diagnostic test is a simple and easily repeatable process that does not require specific storage conditions or skilled clinicians. Moreover, the use of salivary fluids could be more advantageous than exfoliated cells, as several tumor locations in the head and neck regions cannot be easily accessed by performing a swab test. Especially in oral cancer, therefore saliva is considered. It has been observed that in the last two decades, saliva has attracted increasing interest from the specific community thus, leading to many recent studies. Many fields, including pharmacotherapy, medicine and dentistry have focused on the use of saliva as a diagnostic tool.[21] In this context, the term "Salivaomics" aims to include those studies regarding the genome (genomic) [22] RNA (Transcriptomics) [23,

metabolites (metabolomics) [24], proteins (proteomic) [25] and microbial population (microbiomics).[26]

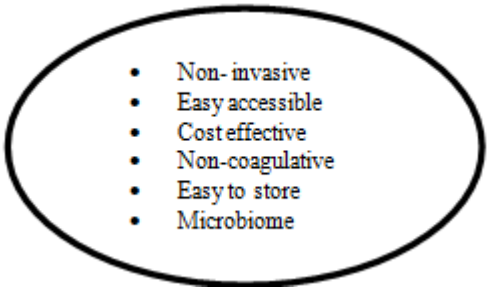

Figure 1: Saliva an ideal diagnostic bio-fluid

Salivary Biomarkers for Oral Cancer

Saliva is a unique and complex biofluid that is used to detect the circulating cancer biomarkers that provide better specificity and sensitivity in terms of diagnosis, prognosis, and treatment of disease. In 1986, Jenzano et al. used saliva for the first time to screen distant tumors.2[7] Cell - free DNA, micro RNA, and circulating tumor cells are among the potential biomarkers. They are released into the blood directly from the tumor and most can be found in saliva. Thus, can be easily sampled. Other potential candidates fall into categories of proteins and mRNAs that do not originate from tumor cells themselves but are instead secreted into the blood as a response to the surrounding tumor environment.

Classification of Salivary Biomarkers

Saliva contains a wide spectrum of biomarkers which can be broadly divided into genome, epigenome, transcriptome, Proteome, metabolome and microbiome as shown in figure 2 and a non - noninvasive diagnostic test can be performed to identify biomarkers with diagnostic and prognostic values by monitoring changes in the salivary biomarkers [18, 28]

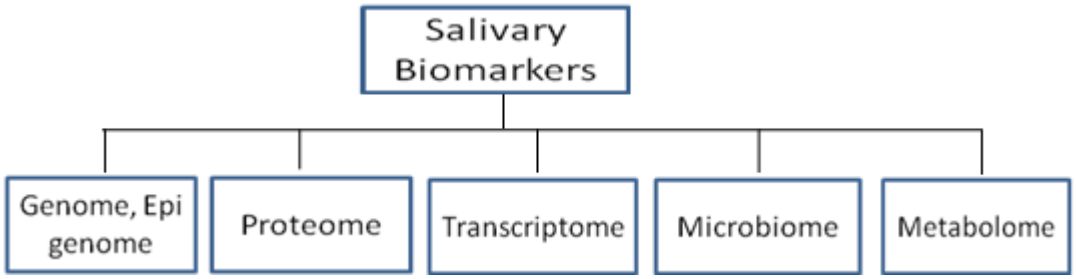

Figure 2: Classification of Salivary Biomarkers.

Proteome Biomarkers

Proteomics is a branch of Salivaomics that deals with the study of proteins in saliva. The number of proteins present in the whole saliva ranges between 0.5 to 3 mg/ml.2[9] The methods used for analyzing the salivary Proteome are top - down and bottom - up.3[0] In the "top - down" approach, whole proteins and peptides are examined with minimum or no alteration of samples without chemical or proteolytic digestion. In the "bottom - up" approach, a complete analysis of samples is performed on a peptide mixture from digestive proteins before mass spectrometry (MS) analysis.1[5] Recently, saliva has been analyzed for protein biomarker detection using either gel - based or gel - free approaches.3[1] Studies have shown that if patient - based salivary proteomes are used, then the informative protein biomarkers will be present in oral cancer patients' saliva for detection of the disease.2[8] Some potential proteome biomarkers use for oral cancer detection are mentioned in table1.

Table 1: Proteome biomarkers

Biomarker	Reference
EGFR [A8K2T7]	32
Albumin	33
P02774	34
CD44	35
Alpha - 1 antitrypsin (AAT)	36, 37
Hemopexin (HPX)	37
Insulin growth factor - 1 (IGF - 1)	38
CD59	39, 40
Profilin	39
Transferrin	41

Genome and Epigenome Biomarkers

Genetic alterations are responsible for the initiation and progression of cancerous cells and various Tumor - specific genomic biomarkers have been reported and identified[15] as shown in Table2. The Salivary genome consists of DNAs representing the genome of an individual, oral microbiota and infecting DNA viruses. compared to blood and urine, the quality and yield of DNA obtained from saliva are good and can be used for genotyping, amplification, and sequencing DNA can show tumor - specific features such as p53 and tumor suppressor genes.4[0] Detection of tumor - derived DNA in saliva seems to be site dependent, and efficient for oral cancers.4[1] Many studies have shown that genomic material is absent in one of the chromosomal pairs in case of loss of heterogeneity. Hence, the presence of loss of heterogeneity in areas that hold a specific human suppressor gene is an early indicator of precancerous lesions. Moreover, some studies have concluded that chromosomes 9p, 3q, 13q, and 17p have frequent LOH in them which indicates an early stage of oral carcinogenesis.4[2, 43, 44]

Table 2: Genome and Epigenome biomarkers

Biomarker	Reference
DNA	45
Histone family 3 (HAS)	46
S100 Calcium binding protein P (S100P)	47
Ornithin decarboxylase antizyme 1 (OAZ)	48
P53 gene codon 63	49

Microbiome Biomarkers

The oral cavity is colonized by several microorganisms, which include bacteria, viruses, and microbes.5[0]Oral cavity

has the second largest and most diverse microbiota. oral microbiome provides an ideal source for evaluating biomarkers due to its low biological variations compared to other tumor biomarkers.5[1]Many studies have shown the relationship between microbiome variation and cancer. Alteration in resident oral bacterial flora into non - resident pathogenic microbes in the presence of etiological factors, such as smoking, tobacco chewing, and alcohol consumption contributes to oral carcinogenesis [52] Lee et al. studied the differences in microbiota between oral cancer patients, patients with epithelial precursor lesions and healthy controls. Researchers found significant abundance of 5 genera in the salivary microbiome (Bacillus, Enterococcus, Parvimonas, Slakia & Peptostreptococcus) 99 in cancer patients.5[3] Recently, many studies have focused on the oral microbiome, which is used in oral cancer detection, particularly oral squamous cell carcinoma (OSCC) studies have shown that high salivary counts of P. gingivalis, F nucleatum are used as biomarkers for oral cancers and C. gingivalis, P. melaninogenica and S. mitis used as diagnostic indicators of OSCC.5[2, 54] some potential microbial biomarkers for the oral cancer detection are shown in table 3.

Table 3: Microbiome Biomarkers

Biomarker	Reference
Bacillus, Enterococcus, Parvimonas, Slakia, Peptostreptococcus	53
Lactobacillus and Streptococcus	55
Bacteroides, Pseudomonas, Ruminiclostridium, Aggregatibacter	56
C. Gingivalis, P. melaninogenica, S. mitis	54

Transcriptome Biomarkers

The transcriptome is a new clinical advancement in oral cancer for the non - invasive detection of a large group of individual RNAs.1[8] The total RNA level in cell - free whole saliva ranges from 0.108 ± 0.023 ug/ml [57] to 6.6 ± 3.6 ug/ml [58] An assumption to it is the salivary mRNA is enclosed in the apoptotic bodies and is actively released out in exosomes and macrovesicles.1[5] Initially, microarray and qRT–PCR validation studies were conducted by prof. David Wong and colleagues identified an enormous transcriptome load in saliva.5[9]

Both microarray and qRT–PCR are preliminary methods in saliva - based biomarkers discovery and identification. Li et al. reported the role of salivary mRNA in oral cancer detection and their utility as circulating biomarkers in 2004.6[0, 61] Although much variability was seen for mRNA in different patients, also seven transcripts have shown significance in OSCC in several reports [60, 62, 63, 64] which include interleukin - 8 (IL - 8), interleukin - 1B (IL - 1B), dual specificity phosphatase1 (DUSP1) ornithine decarboxylase antizyme 1 (OAZ1), S100 calcium - binding protein P (S100P), spermidine/spermine N1 - acetyltransferase 1 (SAT) and H3 histone family 3A (H3F3A) as shown in table 4. Among the seven mRNAs, IL - 8 and SAT were identified as top performers, in multiple OSCC cohorts, and in a large sample.6[2] Some potential Transcriptome biomarkers for oral cancer detection are mentioned in table 4.

Table 4: Transcriptome Biomarkers

Biomarker	Reference
IL - 8 and Il - 1B	65
DUSP - 1	65, 66
OAZ1	66
S100p	67, 68
SAT - 1	69, 70
H3F3A	62, 69, 71

2. Conclusion

Human saliva is truly a unique biofluid with huge clinical and diagnostic potential. Saliva has benefits such as being non - invasive, painless, simple, and easier to administer. In line with the current status and clinical perspectives of liquid biopsy and saliva analysis, saliva has promising implications in OSCC management; it is easy to believe that future studies on the employment of ctDNAs, EVs, S100P, miRNAs, CD44, CTCs, etc as salivary biomarkers in OSCC clinical routine, will certainly help establish consistent strategies for early diagnosis of cancer lesions, facilitate advance prevention and support the development of targeted therapies, this will improve treatment outcomes of OSCC patients, also reducing chemotherapy/radiotherapy side effects. The emergence of new technologies with higher sensitivity for detection can be expected in the near future. The accessibility of these highly sensitive techniques (next - generation sequencing, mass spectrometry, microarray technologies) will enable even smaller quantities of salivary analytes for accurate diagnosis.

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Author Profile

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