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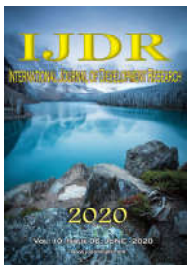

RESEARCH ARTICLE OPEN ACCESS

SALIVARY BIOMARKER: A NONINVASIVE DIAGNOSTIC MARKERS FOR EARLY DETECTION OF ORAL CANCER; A REVIEW

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ABSTRACT

Oral cancer is among the most common cancers worldwide. More than 90% of oral cancers are oral squamous cell carcinoma (OSCC). Diagnosis of such malignant oral tumor are often at late state with poor prognosis and the survival rate is generally very low; So considering this fact, early detection of oral cancer is urgently needed. Many recent studies have been conducted to the search for early salivary biomarkers of oral cancers. Investigation of Salivary biomarkers are simple, non-invasive and inexpensive test. Altered and abnormal DNA, RNA, and protein molecules released by malignant cells can be easily obtained from saliva. The use of saliva as a diagnostic marker may avoid unnecessary painful and expensive investigations. Salivary biomarkers could be useful tool for early detection of oral cancer.

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INTRODUCTION

Saliva is an easily accessible biofluid with immense diagnostic potential in oral cancer. The identification of potential saliva signatures for early, noninvasive detection of oral squamous cell carcinoma (OSCC) lead to early detection, better outcome, and survival.[1] Most cases are detected at advanced stages, resulting in poor prognosis. Therefore, improved detection of early oral health disorders is indispensable.[2] Oral cancer is one of the major global public health problems and is the sixth most common human malignancy with a five year mortality[3]. Early Detection of potentially malignant diseases can significantly affect patient discomfort, prognosis, therapeutic intervention, survival rates, and recurrence[4]. The invasive procedures such as Biopsies and repeated blood Diagnosis are invasive and painful. The discovery of saliva-based microbial, immunologic, and molecular biomarkers provides unique opportunities to avoid these measures Salivary diagnostics is emerging as an important tool for human cancer detection. Saliva has been long proposed and used as a diagnostic medium[5]. It is easily accessible and its collection is non-invasive, not time-consuming, inexpensive, requires minimal training and can be used for the mass screening of large population samples[6]. Here we discuss saliva as a biomarker in early detection of oral cancer.

Definition: Lehto and Pontén have defined tumor markers as "specific, novel, or structurally altered cellular macromolecules or temporarily, spatially, or quantitatively altered normal molecules that are associated with malignant (and in some cases benign) neoplastic cells."[7]

The Diagnostic Salivary Tumor Markers In Oral Cancer: Neoplastic process produces several abnormal cellular products which can be detected in various body fluids and on the surface of cancer cells either by biochemical methods or by immunohistochemistry; such products that are detected and measured are known as "tumor markers"[8]. Molecular diagnostics feeds into a wide range of disciplines including drug development, personalized medicine (pharmacogenomics) and plays a major role in discovery of biomarkers for the diagnosis of oral cancers[9]. The salivary tumor markers in oral cancer include genomic markers, transcriptome markers, protein markers and microbiota Biomarkers exist in a variety of different forms, including antibodies, microbes, DNA, RNA, lipids, metabolites, and proteins. More than 90% in weight of the about 3,000 protein components detected in saliva are derived from the secretion of three couples of "major" glands, proline-rich proteins (PRP), α-amylases, mucins, salivary ("S-type") cystatins, histatins and statherin. All these components and derivatives

account for about 200 proteins/ peptides[10]. All the other components detected in saliva represent the remaining 10% in weight. Some of these, i.e. lipocalin, are secreted by minor salivary. Others, such as α-defensins and b-thymosins, derive mainly from gingival crevicular fluid[11]

Advantages of Uses of Saliva As A Biomarker: Saliva is a most attractive body fluid for diagnosis of disease for many reasons: The collection of saliva is usually economical, safe, easy and can be performed without the help of healthcare workers[12], There are various advantages of use of salivary biomarkers. Saliva contains a wide range of compounds, which is easily accessible ,. low cost and available. It is a noninvasive method for early detection of oral cancer and represents a very helpful source of diagnostic and prognostic biomarker detection. In comparison to blood samples, saliva samples are easy to store, as saliva does not clot[13].

plays role in metastasis and recurrence of oral cancer[15]. Defensins are peptides which possess antimicrobial and cytotoxic properties, shows Elevated levels of salivary defensin-1and have proved indication for the detection of OSCC. Salivary CEA tumor marker, which is a glycoprotien occurring during fetal development shows higher expression in OSCC patients. CEA level of saliva could be as a prognostic factor for oral cancer[16]. In normal cell biology p53 acts as a regulator of DNA synthesis. P53 gene is located on chromosome 17p .When genomic DNA is damaged p53 is produced to block the cell division at the Gl-S boundary and stimulate DNA repair. P53 also activates pathways leading to apoptosis. The mutation of p53 in the DNA shows predictability as a salivary biomarker of the OSCC patients and can be used for the oral cancer detection. Candida albicans**,** a diploid asexual fungus, is an opportunistic pathogen which is the predominant genus among the yeasts of the oral

List of the Tumor Markers in the Diagnosis of Oral Cancer

Salivary genomic markers	Salivary transcriptome markers	Salivary protein markers	Salivary microbiota
Somatic mutations in tumor suppressor genes (p53)	IL-8	Elevated levels of defensin-1	Significant increase in the levels of *Porphyromonas gingivalis, Tannerella Forsythia* and *Candida albicans*
Loss of heterozygosity in chromosome 3p, 9q, 13q and 17p	H3F3A	Elevated CD44	Significantly elevated levels of *Bacteroides melaninogenica* and *Streptococcus mitis*
Promoter hypermethylation of genes (p16, MGMT, or DAP-K)	IL1β	Elevated IL-8	Presence of HPV and EBV
Cyclin D1 gene amplification	S100P	SCC-Ag	
Decrease in 8-oxoguanine DNA glycosylase, phosphorylated-Src and mammary serine protease inhibitor (Maspin)	DUSP1	Calcyclin, Rho GDP dissociation inhibitor	
Microsatellite alterations of DNA	OAZ1	CEA, carcinoantigen (CA19-9), CA128	
	SAT (spermidine/ spermine N1-acetyltransferase)	Intermediate filament protein (Cyfra 21-1)	
		RNS	
		8-OHdG DNA damage marker	
		LDH)	

H3F3A: H3 histone, family 3A, DUSP1: Dual specificity phosphatase 1, SCC-Ag: Squamous cell carcinoma antigen 2, IL: Interleukin, OAZ1: Ornithine decarboxylase antizyme 1, CEA: Carcino-embryonic antigen, RNS: Reactive nitrogen species, LDH: Lactate dehydrogenase, HPV: Human papilloma virus, EBV: Epstein–Barr Virus, CA: Cancer antigen

The Salivary Tumor Markers: These markers consisting of DNA and RNA for the detection of oral cancer from saliva, which shows genetic alterations. DNA shows tumor-specific characteristics such as somatic mutations in tumor suppressor genes and p53, microsatellite alteration, abnormal promoter methylation, mitochondrial DNA mutations. The most abundant proteins are α-amylase, albumin, cystatins, hystatins, secretory-IgA, lactoferrin, mucins, lysozymes, proline rich proteins, statherin and transferrin--which together account for more than 98% of the total salivary protein[14]. Inflammatory cytokines have also been investigated as potential biomarkers of oral cancer. Many studies proved that IL8 and IL1β were significantly more expressed in saliva of OSCC patients than in healthy controls. Overexpression of IL8 can induce tumor cell prolliferation, angiogenesis and allows cells to migrate. Elevated level salivary of IL8 is observed in oral cancer patients. Similarly IL6 is also associated with angiogenesis and

cavity. Candida was isolated from 88.6% of patients with oral cancer and 45.7% in oral precancerous group. C. albicans was the predominant species found in 100% of oral precancerous and 71% in oral cancerous patients. Other Candida species found were C. tropicalis (9.7%) and C. krusei (19.6%)[17], Various authors have documented the prevalence of Candida in oral cancerous lesions ranging from 68% to 86%[18]. Some researchers found significantly elevated levels of P. gingivalis, P. melaninogenica, and Streptococcus mitis in the saliva of OSCC patients, thereby suggesting the role of salivary microbiota as a diagnostic indicator in OSCC[19]. Head and neck squamous cell carcinoma (HNSCC) encompasses a heterogeneous group of malignancies that arise in the oral cavity, larynx and pharynx There is an increasing incidence of oropharyngeal SCC involving the palatine and lingual tonsils, commanly in younger males. HPV is often associated oropharyngeal cancers (HPV-OSCCs)[20]. Significant

association was reported in OSCC with HPV-16 and to a lesser extent with HPV-18. In the salivary samples HPV-16was the most detectable virus reported in the literature.

DISCUSSION

This diagnostic modality in the field of molecular biology has led to the discovery and potential of salivary biomarkers for the detection of oral cancers. Salivary diagnostics has evolved into a sophisticated science, and serves as a subset of the larger field of molecular diagnostics. Molecular studies serve as the basis by which we will eventually be able not only to augment clinical assessment and classification of oral lesions but also predict malignant potential of oral lesions, thus reducing the incidence and increasing the scope for early diagnosis and treatment of oral cancers[21]. The biomarkers present in blood and urine can mostly be detected in a sample of saliva. Discovering, validating, and understanding saliva-based biomarkers could have a considerable role in establishing oral fluids as a credible diagnostic biofluid.[22]. Biomarkers are the molecular signatures and indicators of normal biological, pathological process, and pharmacological response to treatment hence may provide useful information for detection, diagnosis, and prognosis of the disease[23,24].

Conclusion

Several biomarkers have emerged, but salivary biomarker could show a promising results in diagnosis, early detection and prognosis of OSCC However, further research is still required for the reliability and validation of salivary biomarkers for clinical applications.

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