ORIGINAL ARTICLE

Intisari Sains Medis 2020, Volume 11, Number 1: 112-117
P-ISSN: 2503-3638, E-ISSN: 2089-9084

The role of salivary biomarker as a diagnostic tool in oral cancer: A literature review

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ABSTRACT

Background: Saliva is an informative biological fluid that has gained a lot of interest because of its physiologic diagnostic medium. The recent findings suggest that saliva could be used as a biomarker in diagnosing oral cancer. This study aims to elaborate further on the role of salivary biomarker as a diagnostic tool in oral cancer through literature review.

Methods: A total of 44 relevant kinds of literature were studied regarding saliva and oral cancer. The data collection for eligible articles were conducted from 1997 to 2019. Different database and manual search methods were used to find the topic-related articles.

Results: The study of saliva as a biological matrix has been identified as a new landmark initiative in search of a useful biomarker to diagnose oral cancer through proteomics and transcriptomics. Most oral cancers are oral squamous cell carcinoma. Using saliva for early oral cancer detection in the search for new clinical markers is a promising approach because of its noninvasive sampling and easy collection method. Identification of this salivary biomarker could help to screen patients at risk, predict disease outcome and effectively contribute to planning treatment strategies.

Conclusion: proteomics and transcriptomics molecules on the saliva could be used as a biomarker in diagnosing oral cancer.

Keyword: salivary biomarker, diagnostic tool, oral squamous cell carcinoma

Cite this Article: Prestiyanti, N.M.I. 2020. The role of salivary biomarker as a diagnostic tool in oral cancer: A literature review. *Intisari Sains Medis* 11(1): 112-6. DOI: 10.15562/ism.v11i1.622

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INTRODUCTION

Oral cancer is one of the most common malignancies.[1] According to GLOBOCAN 2018, there are approximately 149.102 new cases and 89.377 deaths due to oral cancer both in all ages and sexes, and the fifth most common cancer that occurs in the Southeast Asian countries.[2] In the United States, the 5-year Oral Squamous Cell Carcinoma (OSCC) survival rate is 60%, but a higher incidence and lower survival rates have been reported in some South Asian countries.[3]

Oral cancer can occur anywhere in the mouth, lowers lip, mouth floor and the most affected sites are the tongues. Most oral cancers are squamous cell carcinomas. It is estimated that more of 90% of all oral neoplasms are OSCC.[4] Tobacco consumption, alcohol, and human papillomavirus infections are major risk factors for oral cancer. Prevention of oral cancer is critically important and can be accomplished by understanding the cause, effect and modifying associated risks, recognizing and controlling precancerous lesions, establishing the earliest possible diagnosis and administering timely and appropriate therapy and effectively managing the complications of treatment.[5,6]

The key challenge to reduce the mortality and morbidity of oral cancer is to develop strategies to identify and detect oral cancer. A critical factor in the lack of prognostic improvement is the fact that a significant proportion of cancers initially are asymptomatic lesions and are not diagnosed or treated until they reach an advanced stage. Detection of the OSCC is currently based on the expert clinical examination and histological analysis of suspicious areas, but it may be undetectable in hidden sites. Therefore, sensitive and specific biomarkers for OSCC may be helpful in screening high-risk patients.[7,8]

During the past decades, salivary diagnostics have received increasing attention. The saliva-based analysis is a noninvasive alternative compare to serum analysis. The development of salivary diagnostic tools is essential, especially in the identification of a high-risk group, patients with premalignant lesions and patients with a previous history of cancer.[9,10] Among all the malignancies, oral cancer is one such malignancy, where the saliva examination for detection shows the most significant benefit because of its direct contact with oral cancer lesions. The most critical point for selecting saliva as a diagnostic tool is that it also contains the fallen cells in the oral cavity which allow saliva to be the first choice of screening and identification of potential biomarkers in the OSCC.[9,10]

These biomarkers are going to be important indicators of physiological or pathological conditions and provide information for the detection of early

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Received: 2019-09-17
Accepted: 2020-01-04
Published: 2020-03-03

and differential markers for disease.[6,9] Based on the mentioned above, this literature study mainly highlights the role of saliva as a diagnostic tool in OSCC and its uses for the early diagnosis of OSCC.

Saliva Composition and Methods of Collection

Human saliva is a clear, slightly acidic (pH 6.0 to 7.0) mostly made of water (99.5%.), proteins (0.3%), and inorganic substances (0.2%). On average, individual salivation can range from 0.3 to 0.7 ml of saliva per minute, producing a range of 1 to 1.5 litres daily. This complex fluid has several important functions such as lubricates the oral mucosa, protects and maintains the health of both soft and hard tissues in the oral cavity, oral digestion and buffering capacity.[11]

Saliva is generated within the salivary glands by acinus cells, collected in small ducts, and subsequently released into the oral cavity. There are three important glands, the parotid, submandibular, and sublingual glands, contribute >90% of total saliva, while the minor gland a the labial, buccal, lingual, and palatal glands. Besides, capillaries passing through the salivary glands facilitate the entry of analytes from the systemic circulation into saliva.[12,13]

At present, various techniques can be used to collect saliva. Saliva can be obtained in two ways; it can be unstimulated or stimulated. Unstimulated whole saliva is collected by draining or drool, spitting, suction or swab. This method can be designated as unstimulated since it uses saliva that has naturally pooled in the mouth. Unstimulated whole saliva also called resting saliva is composed mainly of submandibular gland saliva together with saliva from the sublingual gland and minor salivary glands. The characteristics of unstimulated saliva are more viscous and mucin-rich.[11,14]

Stimulated saliva is collected by providing the patients with a stimulant agent, such as citric acid, paraffin or a gum base. Stimulated saliva is collected where samples of saliva are attained through methods such as absorbent pads or chewing on paraffin. Stimulated whole saliva is mainly composed of parotid gland saliva and to some extent saliva from the submandibular gland that is produced upon stimulation. Characteristics of stimulated saliva reveal that it is thin, watery and amylase-rich.[15,16]

Although saliva collection is non-invasive, simple, and rapid, saliva collection can manifest unique issues within specific populations. These may include salivary flow rate, circadian rhythm, type of salivary gland, salivary kind of stimulus, diet, age, physiological status, and method of collection. The method of collecting and processing phase is the next critical phase that must be well-regulated.[15,17] In the traditional collection of blood samples for testing of biomarkers, trained personnel must perform venipuncture, collect blood samples in vacuum tubes, and then process the samples to remove red blood cells. Saliva collection can be done more conveniently and efficiently. Furthermore, type of saliva; stimulated or unstimulated will have a significant effect on salivary biomarker composition and analysis and this needs to be taken into consideration when using saliva for diagnostic or screening purposes.[15,17]

Current State of Oral Squamous Cell Carcinoma Specific Salivary Biomarkers

Saliva contains biomarkers, which can be used as indicators of disease. According to the World Health Organization (WHO), the definition of a biomarker is following "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease".[18,19] A biomarker must be verified and validated before it can be used in a clinical assay and have any impact or application in health risk assessment. Scientists are working on salivary biomarkers around the world, in order to indicate, prognosis and diagnose various conditions. They would serve as a non-invasive, painless, rapidly collected method, easily and economically performed by minimally trained personnel.[18,19]

Over the last decade, human saliva has attracted attention as a liquid biopsy for the detection of oral diseases like dental caries, gingivitis, periodontitis, Bechet disease, oral squamous cell carcinoma, cleft palate and lips, salivary gland diseases, oral leukoplakia and systematic diseases such as breast cancer, diabetes, human immune deficiency virus (HIV). The clinical realization of any biomarker used for health risk assessment or prognosis.[20,21]

Analysis of these markers in oral secretions and other accessible specimens may allow for early detection and screening of individuals at high risk for cancer. Depending on the location of the tumour, one may not be able to access and swab the tumor bed easily. Thus, the use of saliva may show unique advantages over the use of exfoliated cells. Although the use of salivary biomarkers did not identify the site from which the tumour originated, they were able to identify patients at risk.[22,23]

In conventional clinical procedures, the diagnosis of OSCC, especially at an early stage, relies on the experience of the dentist and pathologist. It is essential to recognize that early diagnosis is a prerequisite for improving the cure rate and promoting the quality of life of OSCC patients. Patients at an early stage have a better survival rate with single surgical therapy.

In contrast, patients at an advanced stage have to undergo multidisciplinary synthetic and sequential treatment, which gives rise to longstanding pain and mental trauma. Moreover, less than half of them survive and they have a poor quality of life.[24,25] Existing therapy for OSCC patients is based on traditional stage-predicting guides mostly used are the TNM criteria [tumour, node, metastasis] and histological grading. A significant advancement in salivary diagnostics is the development of omics-based biomarkers.[5] Salivaomics integrates the study of saliva and its constituents, functions, and related techniques. Salivaomics technologies are derived from scientific advances in genomics, transcriptomics, and proteomics, and these high-throughput technologies have prompted interest in the use of saliva as a source of disease biomarkers. The development of particular saliva biomarkers and their associated could facilitate point of care diagnostics.[20,21,26]

Proteomic and transcriptomic indicators have yielded the most promising results to date. At the mRNA level of gene expression, the transcriptomic represents all genes transcribed at any one moment, and the proteome represents both genetic information and helps to understand the translational regulation of the host body and the oral microbiota. This explains the increasing interest on this subject in several fields including dentistry, medicine and microbiology. Oral fluids may represent a significant source of discriminatory biomarkers for local, systemic, and infectious disorders.[27-29] This review will continue further in the identification of salivary biomarker in oral cancer via proteomics and transcriptomics approaches.

PROTEOMICS

The proteome refers to all the individual proteins that may make up a biological system. They directly perform biological functions and are indispensable for orchestrating a cell's activities and act as dynamic indicators of a cell's state. Primary aims in the proteomic analysis are the discovery of key modified proteins, the determination of affected pathways, and the development of biomarkers for association with and eventual prediction of disease.[14,30] Other studies have further shown, the salivary proteome can be used to draw connections between saliva and cystic fibrosis, diabetes, periodontitis, dental caries, and acquired immune deficiency syndrome (AIDS). The salivary proteomic analysis may even be useful for health safety applications. Despite the oral cavity being very accessible, most cases of oral cancer are not detected until cancer has developed into advanced stages. There is much research effort dedicated to investigating salivary biomarkers as reliable early-stage diagnostic.[14,30]

Proteins are vital building blocks of life, and a large number of investigators has viewed proteomics as promising to discover specific biomarkers of oral cancer. De Jong *et al.* used advanced mass spectrometry-based quantitative proteomics analysis of the pooled soluble fraction of the whole saliva from 12 individuals with premalignant lesions and 4 with malignant lesions. Actin and myosin proteins displayed increases in their abundance levels in soluble saliva from those with malignant lesions, compared to those with pre-malignant lesions. Other studies show increases in myosin abundance have been reported in proteomic studies of Oral Squamous Cell Carcinoma tissue. The observed increases in protein abundance were due to increased actin and myosin expression within the exfoliated cells with the onset of invasive oral malignancy, and not simply an increase in the number of cells in saliva. Actin and myosin are key cytoskeletal proteins enabling cell motility and invasion, behaviour central to epithelial tumorigenesis.[28,31,32] The study of oral cancer biomarkers via proteomic approaches has yielded another progress. Frederico et al. conducted an example study where the proteomics profile was examined in a patient population, the protein concentration of IL-8 and IL1ß was significantly higher in oral squamous cell carcinoma patients than controls and dysplasia patients.[33]

Elevated salivary IL-8 levels in patients reported with experience of tumour diseases were found in a recent study, which is in line with a study performed by Wei and coauthors who investigated salivary IL-8 levels of patients with oral cancer.[34] In addition, IL-8 has been shown to be elevated in both serum and saliva in patients with head and neck squamous cell cancer. Salivary IL-8 appears to be a good marker for evaluation of head and neck cancer, as well as in other clinical settings, such as muscle and joint diseases and inflammatory bowel disease.[35]

In another study, the increase in salivary transferrin levels in OSCC patients strongly correlated with the size and stage of the tumour. The area under the receiver-operating characteristics curves showed that salivary transferrin-based ELISA was highly specific, sensitive and accurate for the early detection of OSCC. Based on Yu et al. findings, they have identified salivary transferrin as a biomarker for the detection of early-stage OSCC. This finding provides a promising basis for the development of a non-invasive diagnostic test for early-stage OSCC.[36]

TRANSCRIPTOMICS

Transcriptomics studies the full global complement of mRNA molecules expressed in cells and tissues. Salivary transcriptomics is based on the analysis of the oral transcriptome, the set of all mRNA molecules that can be found in the salivary milieu. In order to analyze the transcriptome of a patient, saliva is collected and then RNA extraction is performed. Following the extraction, the RNA is amplified for analysis. After quantification of the nucleic acid content present in the saliva, comparisons can be made with known transcriptomic information.[29,37]

Saliva contains an assortment of extracellular RNA species, including mRNA, miRNA, and other small non-coding RNAs. The human salivary transcriptome was initially described using microarray technology. In various cancers, such as oral, oesophagal, lung, pancreatic, breast, and ovarian cancers, certain RNA biomarkers have been discovered in saliva and proposed as possible biomarkers.[29,38]

MicroRNA (miRNA) is small noncoding RNA sequences with strong regulatory potential for normal biological processes ranging from cell growth, and differentiation to death. It has been demonstrated that genes for miRNAs genes are dysregulated in various types of cancer and that miRNAs themselves can act as both oncogenes and as tumour suppressors. Many research groups have shown that miRNAs are differentially expressed in various cancer cells compared with normal cells, and it seems that miRNAs can more accurately classify different types of solid tumours than can mRNA, suggesting that miRNAs can be used to detect cancer.[37,39]

Li et al. have found potential salivary RNA biomarkers, such as *IL8, IL1* ß, *DUSP1, HA3, OAZ1, S100P*, and *SAT*. The combinations of these biomarkers yielded sensitivity (91%) and specificity (91%) in distinguishing oral squamous cell carcinoma from the controls. The serum level of IL1ß is higher in patients with oral squamous cell carcinoma of the oral cavity.[27] Also, it has been reported that the level of IL1ß is significantly increased in the ascitic fluid of women with ovarian cancer.[40]

Cytokines are intercellular signalling proteins that play a role in normal growth, cellular proliferation, tissue repair, and angiogenesis. Cytokines are also involved in the immune response against infection and inflammation. Katakura et al has reported cytokines level, in 2007, examined 20 healthy patients and 19 patients with oral cancer and checked levels of cytokines (IL-6, IL-8, IL-β1) and osteopontin in saliva through ELISA, which showed higher levels of cytokines in oral cancer patients as compared to the control group; IL 6 levels showed significant elevation in oral cancer patients while this was not detected in the control group. Indicate that IL-8 and IL-6 in saliva hold promise as biomarkers for OSCC.[41]

Park et al. found miR-125a and miR-200a were present at significantly lower levels ($P<0.05$) in the saliva of OSCC patients than in controls. However, their sensitivity and specificity were not satisfactory.[42] But in the other study, miR-200a is present at higher levels in various oral squamous cell lines. This discrepancy could be due to observing the cell-free state of miRNAs compared with the ones in living cells. Because the supernatant saliva is the cell-free phase of saliva, some of the miRNAs in supernatant saliva are likely by-products of cell death. It is possible that cancer-specific miRNAs undergo a more rapid degradation and/or have a

Table 1 Recent publications of biomarkers for Oral Squamous Cell Carcinoma (OSCC)

Year	Author	Biomarker Studied	Study Findings
2004	Li et al	IL8, IL1B, DUSP1, HA3, OAZ1, S100P, SAT	Elevated levels of IL8, IL1B, DUSP1, HA3, OAZ1, S100P, and SAT in oral cancer
2007	Katakura et al	cytokines (IL-6, IL-8, IL-β1) and osteopontin	Showed higher levels of cytokines in oral cancer patients as compared to the control group
2009	Park et al	miR-125a and miR-200a	Lower levels in the saliva of OSCC patients than in controls
2009	Wei et al	IL-8	Elevated salivary IL-8 levels in patients reported with experience of tumour diseases
2010	Yu et al	transferrin	Increase in salivary transferrin levels in OSCC patients
2011	Stott et al	MMP-1	Shown to be higher in OSCC patients than controls.
2016	Frederico et al	IL8 and IL1ß	Significantly higher in oral squamous cell carcinoma patients than controls and dysplasia patients

DUSP: dual specificity phosphatase; HA: hemagglutinin; IL: Interleukin; MMP: matrix metalloproteinase; OAZ: ornithine decarboxylase antizyme; S100P: protein S100-P; SAT: spermidine N1-acetyltransferase

shorter half-life during cell death, similar to the degradation of regulatory mRNAs.[43]

The matrix metalloproteinases (MMPs) may play a key role in cancer development, as they cause degradation of the extracellular matrix and basement membranes. MMPs have been studied as potential cancer biomarkers and been associated with tumour invasion and metastasis. In a recent study, MMP transcripts are over-expressed in Oral Squamous Cell Carcinoma patients and MMP-1 and MMP-9 have been associated with the progression of dysplasia to cancer. MMP-1 transcript levels in saliva are higher in OSCC patients than controls. Additional studies have reported saliva biomarkers for OSCC that may increase the feasibility of using saliva for discriminatory OSCC detection in future combination biomarker studies (Table 1).[44]

CONCLUSION

Recent research has identified a multitude of potential markers that have a significant role in the surveillance of oral squamous cell carcinoma. In this review, despite the inherent limitations, we identified several potential biomarkers of particular interest that appear to carry prognostic significance. Sensitive technology is needed to detect biomarkers in low quantities for saliva to be a useful diagnostic medium. Furthermore, salivary biomarkers can be used between biopsies to assist in monitoring the disease status of OSCC patients. Taking together all these aspects, it can be concluded that there are abundant possibilities in saliva diagnostics already at present, and the immediate future of this area is even more promising.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

FUNDING

None.

AUTHOR CONTRIBUTION

Ni Made Ista Prestiyanti is responsible for the study from the conceptual framework, literature search, data gathering, until synthesis the findings through narrative sentences in the literature study.

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