

## Review Article

## Salivary biomarkers in oral squamous cell carcinoma – An insight



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## ABSTRACT

Oral cancer refers to the malignancies that occur in the oral cavity, lip and pharynx with 90% of oral cancers being squamous cell carcinomas (OSCC). OSCC has the highest mortality ratio compared to other carcinomas. Although oral cavity is easily accessible, most oral cancers are detected at a later stage leading to lower survival rates. Early detection of OSCC is a key factor in improving the prognosis and survival rate of the patient. Rapid advancement in the field of diagnosis has enabled early diagnosis of many potentially malignant conditions even before its clinical manifestations. One such diagnostic modality that has gained much relevance in the field of molecular biology has been the discovery of salivary biomarkers (DNA, RNA and protein markers). These salivary biomarkers have been shown to play a non-invasive role in the diagnosis and surveillance of oral cancer. The direct contact between the saliva and the oral cancer lesions makes it a most sensitive and specific, screening method in diagnosis, staging and follow-up. This review aims to discuss the effectiveness and the potential of salivary biomarkers as a screening tool in OSCC.

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## 1. Introduction

Oral cancer ranks sixth among the cancers occurring worldwide with 90% of them being diagnosed as OSCC. However, the prognosis of OSCC is good with a survival rate of 90% in case of early detection. The gold standard for diagnosis of OSCC is biopsy followed by histopathological examination, the major drawback in this technique is delay in detection. The biomarkers which are the measurable indicators of physiological and pathological process are useful in the diagnosis and influence the prognosis of disease.

Salivary biomarkers have proven to be cost effective adjoins in diagnosis and follow-up of oral and oropharyngeal carcinoma. This review summarizes the current knowledge regarding the classification, criterias, rationale, applications, merits and demerits of salivary biomarkers in relation to oral squamous cell carcinoma.

## 2. Biomarkers

Biomarkers are molecular signatures that are unique to a certain disease (e.g., oral cancer), and has been defined by 'WHO' as

any substance, structure or process that can be measured in the body or its products and influences or predicts the incidence of outcome or disease.<sup>1</sup> Biomarkers are also defined as "a characteristic that is an objectively measured and evaluated indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention" (National Institutes of Health, 1998).<sup>2</sup> Biomarkers could be analyzed in different analytes like blood and saliva.

## 3. Classification of cancer biomarkers

Biomarkers have been classified based on biomolecules and disease states (Table 1).<sup>3</sup>

3.1. Applications of biomarkers<sup>4</sup>

1. Biomarkers help in predicting the preventive measures that could be formulated.
2. Aids in detection of various stages of oral malignant transformation.
3. Evaluates the molecular changes related to oral carcinogenesis.
4. Enhances the prognosis, diagnosis, and treatment of oral carcinomas.
5. Helps in manipulating the drugs used for the treatment of cancer.

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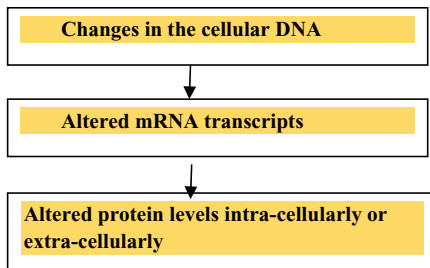
E-mail address: [radhikasashi26@gmail.com](mailto:radhikasashi26@gmail.com) (T. Radhika).

**Table 1**  
Classification of cancer biomarkers.<sup>3</sup>

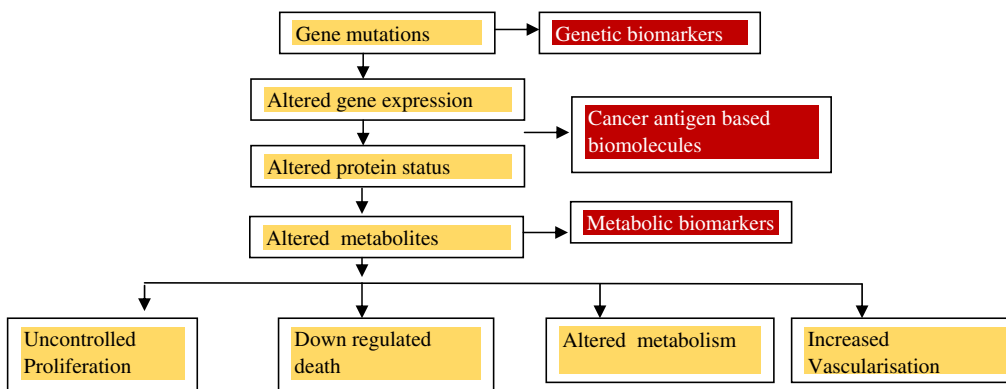
Based on biomolecules	Based on disease state
a. DNA biomarkers	a. Diagnostic biomarkers
b. RNA biomarkers	b. Prognostic biomarkers
c. Protein biomarkers	

#### 4. Salivary biomarkers in the detection of oral cancer

Saliva, the readily available specimen containing large number of proteins and peptides is used as a biomarker for diagnosing various oral and systemic diseases. It is one of the most reliable tool for diagnosing oral squamous cell carcinomas because of their direct contact with oral cancer lesions. FD Shah et al. (2011) in their review on salivary genomics in oral cancer has insisted saliva as the potential biomarker for squamous cell carcinoma because of their locally expressed proteins such as alpha amylase, lactoferrins, lysozymes, proline-rich proteins, mucins, histatins, cystatins and transferrin.<sup>5</sup> Molecular diagnosis of OSCC can be pursued in three levels. This was proved by Markopoulos et al. in their original study on salivary biomarkers for oral cancer detection.<sup>6</sup> These include:



Salivary biomarkers can be a genetic marker, a protein or a metabolomic marker.<sup>1</sup>



#### 5. Rationale behind the use of salivary biomarkers<sup>7</sup>

- (1) Saliva contains a wide range of compounds
- (2) Easily accessible
- (3) Patient comfort
- (4) Non-invasive method of disease detection
- (5) Safe to handle
- (6) Low chances of transmission compared to blood samples
- (7) Easy to store
- (8) Saliva does not clot

#### 6. Salivary biomarkers – an update

More than 100 potential salivary biomarkers have been reported till date. Numerous analytes have been detected in saliva using various techniques (Table 2).<sup>8</sup> Dearth of studies confirming the potential of many salivary biomarkers in detection of oral cancer is available in scientific literature (Table 3).

##### 6.1. Peptides

Defensins possess antimicrobial and cytotoxic properties. The azurophil granules of polymorphonuclear leukocytes contain defensins. Studies by Mizukawa et al. have reported that OSCC can be detected even in their earlier stages by the elevated levels of salivary defensin-1 compared with healthy controls.<sup>9</sup>

##### 6.2. Proteins

Several salivary protein markers such as interleukins (8, 6, 1 $\beta$ ), matrix metalloproteinase (MMP 2, 9), transforming growth factor (TGF-1), Ki67, cyclic D1, Cyfra 21.1, transferrin,  $\alpha$  amylase, tumor necrosis factor (TNF- $\alpha$ ) and catalase have been detected in oral squamous cell carcinoma by various studies.<sup>10</sup>

Franzmann et al. reported elevated levels of CD 44 in saliva (oral rinse) of oral squamous cell carcinoma patients ( $n = 102$ ) compared to controls ( $n = 69$ ).<sup>11</sup>

St John et al. detected higher concentrations of IL-8 in saliva and higher concentrations of IL-6 in serum of patients with OSCC and concluded that IL-8 in saliva and IL-6 in serum are the informative biomarkers for OSCC.<sup>12</sup>

##### 6.3. DNA

Boyle et al. in their comparative study identified p53 mutations in 71% of saliva samples from patients with OSCC by using plaque hybridization technique.<sup>13</sup> Rosas et al. identified aberrant methylation of p16, MGMT and DAP-K in OSCC patients.

##### 6.4. Salivary mRNAs

According to Liu et al, oral carcinogenesis can be detected by the elevation of salivary mRNAs which includes six mRNA molecules such as DUSP1, H3F3A, IL 1B, IL 8, SAT and S100.<sup>14</sup>

###### 6.4.1. DUSP1 (dual specificity phosphatase 1)

DUSP mRNA participates in the MAPK (Mitogen Activated Protein Kinase) pathway. It is involved in protein modification, oxidative stress, and signal transduction. Molecular studies

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