

Saliva as a Diagnostic Tool in Oral Malignancies.

Sadia Minhas¹ & Zohaib Khurshid.²

Affiliations: ¹Department of Oral Pathology, Akhtar Saeed Medical and Dental Colleges, Lahore, Pakistan. ²Prosthodontics and Implantology, College of Dentistry, King Faisal University, Al-Ahsa 31982, Saudi Arabia.

Corresponding author: Zohaib Khurshid. Prosthodontics and Implantology, College of Dentistry, King Faisal University, Al-Ahsa 31982, Saudi Arabia. Phone: (966) 558420410. E-mail: drzohaibkhurshid@gmail.com

Worldwide, head and neck malignancies are the eighth most frequent cause of cancer mortality, and comprises about 8-10% of all cancers.¹ Cancer is a pathological condition in which uncontrollable growth of cells invade and start damaging surrounding tissue. These cells are called malignant or cancerous cells. Oral cancer or mouth cancer mainly occurs on the lower lip, inside the mouth, on salivary glands, tonsils, on the back of the throat, on the area behind the third molars (retromolar trigone), esophagus, and on the tongue and soft tissues of the mouth.² According to the *National Institute of Dental Craniofacial Research* (NIDCR), it accounts for around 3% of all malignancies or cancers diagnosed yearly in the United States. *Cancer Research UK* reported 7800 new cases each year of mouth and oropharyngeal cancer. The statistics regarding mouth cancer incidence is alarming for the next generation, so early diagnosis by a non-invasive approach is useful for controlling it. Recognition of oral squamous cell carcinoma (OSCC) presently relies on skilled clinical investigation and histological study of suspicious areas, but at sites not easily visibly, it might be go by unnoticeable.² Consequently, precise and sensitive biomarkers for oral squamous cell carcinoma might be supportive in early diagnosis of high-risk patients.³

Human oral fluid consists mainly of saliva produced by the salivary glands, gingival crevicular fluid (GCF), secretions from labial mucosal glands and oropharyngeal glands secretions.⁴⁻⁶ The main component of oral fluid is saliva, and it contains much-hidden information of the human health status. Previously our group reported on the importance of human saliva as a diagnostic fluid and how to do the sampling and extraction of salivary proteins.^{7,8} The value of saliva as a means for detection of oral malignancies has been increasing in parallel with recent diagnostic technological advances.⁶ Both saliva and blood are the most widely considered body fluids and may provide definitive biomarkers for early cancer detection.⁵ Employing saliva is a non-invasive and cost-effective technique compared to serum analysis and is a useful body fluid comprising a collection of components (DNA, mRNA, protein) which are used as biomarkers for translation, clinical applications, western blot assays, enzyme-linked fluorescence assays and polymerase chain reaction.⁹⁻¹¹ Whole saliva can be collected non-invasively, by the patients themselves with no specialized technique with no requirements of specialized apparatus, and it is also favorable for use in children as it is associated with a higher acceptance rate. Salivary detection tools are of utmost significance as it helps in screening, early detection of high-risk groups, patients with previous cancer history as well as patients with pre-malignant lesions and it might

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be used to assess the effectiveness of cancer treatment.¹² Saliva investigation for early recognition of oral cancers also has the considerable advantage that this fluid contains shed desquamated cells of the oral cavity, making it as a first choice for the screening and recognition of biomarkers. Circulatory markers and salivary tumor markers have been studied in multiple studies of oral squamous cell carcinoma that reported specific and sensitive results regarding the prognosis and early diagnosis.^{2,13} Similarly, in oral squamous cell carcinoma studies, salivary defensin-1 levels were found to be increased, and a significant association was noticed between serum levels of squamous cell carcinoma antigens and salivary defensin-1.^{14,15} When compared with healthy individuals, raised levels of salivary nitrite and nitrate in oral cancer patients, as well as increased activity of nitrate reductase, were noticed and reported in multiple studies.¹⁶ Fliss *et al.*, reported that mitochondrial DNA mutations are useful to distinguish the exfoliated oral squamous cell carcinoma cells in saliva. By direct sequencing of saliva samples from OSCC patients, mutations were identified in 67% of those samples.¹⁷ St John *et al.*,¹⁸ reported that IL-8 and IL-6 can be useful biomarkers

in the saliva of OSCC patients.

Increased IL-8 levels have an essential role in chemotaxis of granulocytes and macrophages and stimulation and proliferation of angiogenesis, which are a well-known part of OSCC stroma; similarly, raised IL-6 levels lead to immune unresponsiveness and initiation of cachexia, hypercalcemia and wasting; both IL-8 and IL-6 levels have been found to be increased above the cutoff values.^{18,19} This diagnostic fluid can be beneficial for the future of point-of-care (POC) technology and sensor development for low-cost diagnosis.²⁰

Thus, in conclusion, saliva sampling and its screening is a good choice for the early detection and screening of high risks patients for oral squamous cell carcinoma (OSCC). It is a non-invasive as well as cost-effective technique. Large-scale studies are still needed to check the sensitivity and specificity of the saliva for detection of OSCC. The advancements in salivary fluid sampling devices and -omics science is helping researchers to do more in-depth studies and explore as of yet unidentified biomarkers. The whole paradigm is to revolutionize point-of-care (POC) and biosensor technology is for the betterment of humanity.

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