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Salivary Biomarkers in Oral Squamous Cell Carcinoma Diagnosis and Prognosis - A Review

Nunisa Phairingdao[1], Chandra, Deka, Akshay[1], Srinivasan, Vidhya[2]

[1]Department of Medical Laboratory Technology, Regional College of Health Sciences, Guwahati, Assam, India.
[2]Department of Medical Laboratory Technology, Girijananda Chowdhury University, Guwahati, Assam, India.

Corresponding Author: Vidhya Srinivasan

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ABSTRACT

Objectives: The purpose of this study is to investigate the increasing prevalence and consequences of oral cancer, a leading cause of cancer-related deaths worldwide. To explore the role of salivary biomarkers, in the diagnosis and progression of oral squamous cell carcinoma. To emphasize the potential of salivary biomarkers for advancing diagnostic methods and improving treatment options for oral cancer.
Materials and Methods: A comprehensive review of the existing literature was conducted using databases such as Google Scholar and PubMed. Search terms included "Salivary Biomarkers," "Oral Squamous Cell Carcinoma," "Head and Neck Squamous Cell Carcinoma," and "Adiponectin." Articles were filtered based on parameters such as tumor location, relevance to the study, and study region.
Results: Emerging salivary biomarkers, such as cytokines, show potential in diagnosing oral squamous cell carcinoma. Adiponectin, an adipokine with anti-inflammatory and metabolic properties, was highlighted as a key regulator of the inflammatory environment and tumor progression in oral cancer.
Conclusions: Salivary biomarkers, particularly cytokines and adiponectin, hold promise as non-invasive tools for the early detection and diagnosis of oral squamous cell carcinoma. Large-scale clinical trials are necessary to solidify the utility of adiponectin and other salivary biomarkers in personalized diagnostic and treatment strategies.

Keywords: Adiponectin, Adipokines, Biomarkers, Tumor.

INTRODUCTION

Oral cancer is one of the most common type cancers that is prevalent in the world today and it ranks sixth worldwide [1], it is highly prevalent in South Asia, and is primarily associated with alcohol and tobacco usage. It remains one of the most lethal conditions, with more than half the cases diagnosed annually [2], in part because most instances are only discovered when they are in advanced stages, even when routine examination of the oral cavity is reasonably easy. About one-third of the world's mouth cancer cases occur in India, where the disease is most prevalent [3]. Every year, approximately 52,000 deaths and 77,000 new cases are reported, making up almost one-fourth of all cases worldwide [4]. With the rising prevalence of oral cancer, one of the most common diseases in India, this should be of the greatest concern to all people. Oral cancer presents a major issue in India, where more than 70% of cases are estimated to be advanced. As the condition mostly remains undetected at an early stage, the odds of a cure are almost negligible; the documented 5-year survival rates have been

20% [5]. Oral Squamous Cell Carcinoma (OSCC) represents the most common malignancy of the oral cavity. Tobacco use, alcohol intake, betel quid chewing, and areca nut eating, together with genetic changes, are among the major risk factors for the development of OSCC [6,7]. Although biopsy represents the gold standard for the diagnosis of OSCC, its invasive nature, its high cost, and requirement of specialized medical personnel and equipment make it unsuitable for screening and follow-up. As a result, it is critical to create innovative, non-invasive, and user-friendly media and methods for early detection of OSCC.

MATERIALS & METHODS

Several Literatures were thoroughly researched and analyzed in this review. Collection of articles were done from websites such as Google Scholar and PubMed and thoroughly searched for topic-related terms. These included "Salivary Biomarkers", "Oral Squamous Cell Carcinoma", "Head and Neck Squamous Cell Carcinoma", and "Adiponectin". Articles were filtered by setting specific parameters such as tumor location, relevance to the study, and study region. Parameters were set to determine the significance of adiponectin as a relevant salivary biomarker for the diagnosis of OSCC. This review is a compilation of the research progress in oral cancer and it also sheds light on the potential Biomarkers.

RESULT

Salivary Markers

Saliva, and by extension salivary biomarkers are easy to collect and can give a clue about the systemic health due to that it has become a feasible, non-invasive technique to diagnose and monitor cancer. As such, most of the recent research in salivary biomarkers revolves mainly around malignancies like pancreatic, lung, breast, and oral cancers. Salivary biomarkers in oral cancer have been investigated with the objective of detecting and monitoring the progression of disease. Some proteins, for example osteopontin, and some cytokines like interleukin (IL), IL-6, and IL-8, have altered levels of expression in oral cancer patients [8]. These biomarkers have the ability to distinguish healthy individuals from those with cancer or other potently malignant mouth diseases.

Salivary biomarkers have been researched as a potential addition to current breast cancer diagnostic approaches. Researchers have investigated whether specific proteins, microRNAs, and DNA alterations found in saliva could indicate the onset of breast cancer. Further research is underway to determine whether the salivary biomarkers will be able to indicate therapy response and breast cancer subtypes [9]. The late presentation of pancreatic cancer has prompted research into non-invasive diagnostic techniques. Salivary biomarkers, including Carbohydrate antigen 19-9 (CA19-9), Kirsten rat sarcoma (KRAS) mutations, and other proteins are under study as a potential tool for early screening in order to detect signals linked with pancreatic cancer [10,11].

Salivary biomarkers such as C-reactive protein, Cytokeratin 19 Fragment (CYFRA 21-1), and other microRNAs are being studied to help in the diagnosis of lung cancer, one of the leading causes of death due to cancer. These biomarkers may enable the differentiation of patients with benign lung diseases or healthy controls from those with lung cancer [12,13]. Salivary biomarkers are also being further researched for their potential in therapy response assessment and cancer prognosis. Its non-invasive nature makes saliva collection a much desirable option for routine monitoring and for the development of personalised treatment methods.

Katakura et al. [14] investigated the expression of four cytokines in saliva as a potential indication of oral cancer. Saliva samples from 19 patients having squamous cell carcinoma of the oral cavity were compared to those from 20 healthy individuals. The cytokines evaluated were

the interleukins IL-1β, -6, -8, and osteopontin. Their results showed significantly higher levels for all four cytokines in oral cancer patients than in healthy controls. Hu et al. [15] identified different levels of protein biomarkers in human saliva in subjects with OSCC than in controls. Five validated biomarkers had a value of 93% in receiver operating characteristic, with 90% sensitivity and 83% specificity, thus showing the potential for accurate detection of OSCC by salivary proteins. In their research, Duffy et al. [16] assessed the predictive value of serum IL-6 levels at pretreatment in patients with head and neck squamous cell carcinoma. From this study, it had been realized that the pretreatment serum IL-6 level might be a good clinical predictor of recurrence and overall survival in patients suffering from head and neck squamous cell carcinoma (HNSCC). Using IL-6 as a biomarker could help in detecting disease recurrence early on and starting treatment to improve outcomes in head and neck malignancies. Cheng et al. [17] showed that levels of salivary IL-6 were significantly higher in patients with OSCC than in those with chronic periodontitis (CP), active or inactive Oral lichen planus (OLP), and healthy controls (all $p<0.001$). Therefore, this study identified the potential of salivary IL-6 and IL-8 to be biomarkers with diagnostic values to provide information about OSCC compared with other oral diseases and healthy individuals.

Compared with probably malignant lesions and healthy controls, Rajkumar et al. [18] showed that OSCC had much higher levels of blood and salivary IL-8. The results positioned salivary IL-8 as a strong marker, in a very useful position with diagnostic potential for the differentiation of oral squamous cell carcinoma from probably malignant diseases. Salivary IL-8 in differential diagnosis can help in improving the clinical management methods and the early detection of oral cancers. Dadhich et al. [19] determined the levels of sialic acid in serum and saliva from three groups of patients: healthy individuals, patients suffering from potentially malignant illnesses or Oral potentially malignant disorders (OPMD), and those diagnosed with oral cancer. Compared to controls, blood and salivary sialic acid levels increase dramatically in a manner that makes them potentially good predictors of this biomarker. The amount of sialic acid measurable in saliva underscores its value for clinical purposes in oral cancer diagnostics, suggesting saliva as a diagnostic fluid medium for the screening and early detection of mouth cancer.

In a recent study, Irfan et al. [20] did case-control analysis to evaluate the salivary levels of Endothelin-1 as a biomarker for oral cancer and precancer. The study comprised 72 participants in total, who were divided into the following three groups: 24 with premalignantly diagnosed histopathologic oral lesions, e.g. leukoplakia and submucous fibrosis; 24 with histopathologically diagnosed oral squamous cell type cancers; and 24 healthy controls having the same age and sex distribution, with no history of tobacco addictions. The results indicated that there was a substantial increase in the level of salivary Endothelin-1 among patients diagnosed with oral squamous cell carcinoma as compared to those with premalignant lesions or healthy controls. This fact may be quite supportive in ruling out premalignant lesions and being suggestive of oral cancer; therefore, it may appear as a probable biomarker for early detection.

Circulatory Cytokines

Cytokines are among the very important signaling molecules secreted by different cells in response to external stimuli. These signaling molecules activate immune cells and help generate protective immunity against a wide range of diseases. In addition, they control inflammation, proliferation, and differentiation of cells.

Cytokines are important in cancer research because they promote tumour growth,

angiogenesis, and immune response evasion. Engineered nanocarriers have been used by researchers to target and control cytokine distribution at specific areas inside the body, thereby increasing their efficacy in enhancing host immunity while lowering potential negative effects [21]. Tailored delivery strategies for cytokines enhance their response precision and administration efficiency, thereby improving their therapeutic potential in a wide range of diseases and disorders.

Several studies have identified cytokines as effective biomarkers for OSCC. They play an important role in the diagnosis and monitoring of OSCC, informing on their presence and progression. In this sense, cytokine levels and saliva profiles reflect the inflammatory state and immune responses associated with OSCC. Their expression profiles, therefore, can give an indication of inflammation and host immune responses to the presence of the tumor. Second, cytokine profiling in saliva can allow a non-invasive and easily accessible approach toward early detection and monitoring of OSCC for the purpose of allowing early intervention and a personalized treatment strategy for each case, thus potentially offering better outcomes for patients [22].

In a study, Dikova V et al. [23] compared salivary cytokine concentrations between healthy individuals, patients with oral leukoplakia, and patients with malignant lesions in search of the role of salivary cytokines as early biomarkers for the diagnosis of OSCC. This study analyzed IL-1α, IL-6, IL-8, IP-10, Monocyte Chemoattractant Protein-1(MCP-1), tumor necrosis factor alpha (TNF-α), hepatocellular carcinoma (HCC-1), and Platelet factor 4 (PF-4) in saliva. Compared to early OSCC stages, higher levels of IL-6 and TNF-α were observed in advanced stages. Higher levels of TNF-α and IL-6 correlated with the presence of neck metastases. Levels of the proinflammatory cytokine IL-6 in serum and saliva were described by Dineshkumar et al. [24] He showed that there were significant differences in the concentration of IL-6 and made some important observations. The ratio between salivary and serum levels was two to three times higher in all groups, stipulating the difference between OSCC and Potentially malignant lesions (PML) patients. This study demonstrated that the proinflammatory cytokine IL-6, said to be of diagnostic and/or prognostic value, is heightened in the saliva of patients with OSSC when matched against potentially malignant disorders (PMD) and controls.

Ameena M et al. [25] conducted research with the objective of evaluating the role of salivary TNF-α in leukoplakia and OSCC and determining whether it could be used as a marker for early diagnosis of OSCC. This research study was conducted on ninety subjects: thirty with OSCC, thirty suffering from leukoplakia, and thirty healthy individuals. Whole unstimulated saliva was collected and analysed by enzyme-linked immunosorbent assay (ELISA) test. TNF-α was found to be significantly higher in leukoplakia and even higher in OSCC compared to controls. TNF-α differed significantly amongst the different histopathological grades of leukoplakia and OSCC. Further, TNF-α levels differed significantly among the different clinical stages of OSCC. Therefore, it was concluded in this study that TNF-α can be used as a marker for predicting leukoplakia and oral cancer. Findings of the literature reviewed categorized by year of study, total number of cases, marker, and control variable are explained in (Table 1).

Table 1: Findings from studies categorized by year of study, total number of cases, marker, and control variable

Author (Year)	***Title***	***Cases***	***Marker***	***Control (Variables)***	***Findings***
Katakura et al. (2007) [14]	Comparison of Salivary Cytokine Levels in Oral Cancer Patients and Healthy Subjects	19 (T1/T2 tongue and gum cancer)	IL-1 β, -6, -8	20 (Healthy)	Saliva levels of interleukin (IL-1β, -6, -8), osteopontin, and other cytokines were tested in 19 oral cancer patients. IL-6 levels were significantly greater than in healthy individuals.
Hu et al. (2010) [15]	Salivary Proteomics for Oral Cancer Biomarker Discovery	64 (OSCC)	M2BP, MRP14, CD59, profilin, and catalase	64 (Healthy)	This proteomics study found five possible salivary biomarkers (M2BP, MRP14, CD59, profilin, and catalase) for OSCC, with a 93% ROC accuracy, 90% sensitivity, and 83% specificity in separating patients from healthy controls.
Duffy et al. (2008) [16]	Interleukin-6 predicts recurrence and survival among head and neck cancer patients	444 (HNSCC)	IL-6	0 (Healthy) age, sex, smoking, cancer site and stage, and comorbidities.	The median serum IL-6 level in patients was 13 pg/mL, with a 35.2% recurrence rate and 26.5% death rate after two years; multivariate analysis showed that elevated serum IL-6 levels and cancer site (oral/sinus) were significant independent predictors of recurrence and poor survival.
Cheng et al (2013) [17]	Salivary interleukin-6 and -8 in patients with oral cancer and patients with chronic oral inflammatory diseases	18 (OSCC) 21 (Disease active OLP) 20 (Disease inactive OLP)	IL-6, IL-8	21 (Healthy)	Salivary IL-6 levels were significantly higher in OSCC patients compared to those with CP, active OLP, inactive OLP, and healthy individuals, while IL-8 levels were marginally higher compared to healthy controls but significantly higher in OSCC patients compared to CP patients, with both standardised and non-standardized levels yielding consistent statistical findings.
Rajkumar K et al (2014) [18]	Validation of the diagnostic utility of salivary interleukin 8 in the differentiation of potentially malignant oral lesions and oral squamous cell carcinoma in a region with high endemicity	100 (OSCC) 100 (PML)	IL-8	100 (Healthy)	OSCC patients had significantly higher blood and salivary IL-8 levels than PMLs and healthy people, with salivary IL-8 being more sensitive in diagnosing OSCC and having a strong connection with OSCC histologic grading.
Dadhich M et al.	Serum and salivary sialic acid as a	25 (OPMD)	Sialic Acid	30 (Healthy)	Serum and salivary sialic acid levels were significantly greater in the OPMD and oral cancer groups compared to the normal group,

(2014) [19]	biomarker in oral potentially malignant disorders and oral cancer	30 (Oral Cancer)			with oral cancer patients displaying the highest levels. The increases were both significant ($P < 0.005$).
Dikova V et al. (2021) [23]	Potential Non-Invasive Biomarkers for Early Diagnosis of Oral Squamous Cell Carcinoma	33 (Early OSCC) 33 (Advanced OSCC) 33 (OL with homogenous) 33 (Proliferative verrucous)	IL-1α, IL-6, IL-8, IP-10, MCP-1, TNF-α, HCC-1, PF-4	25 (Healthy)	Advanced stages of OSCC exhibited significantly elevated levels of TNF-α and IL-6, with AUC values surpassing 0.8 for IL-6, IL-8, TNF-α, and HCC-1 in differentiating OSCC from control groups. Additionally, TNF-α and IL-6 were linked to neck metastases, indicating that these cytokines, along with PF-4, could aid in distinguishing between oral leukoplakia, OSCC, and healthy individuals, while also serving as potential markers for OSCC progression.
Dineshkumar T et al. (2016) [24]	Salivary and Serum Interleukin-6 Levels in Oral Premalignant Disorders and Squamous Cell Carcinoma: Diagnostic Value and Clinicopathologic Correlations	100 (OSCC) 100 (PML)	IL-6	100 (Healthy)	Marked differences in IL-6 levels were noted between OSCC and PML/C patients in both blood and saliva, with salivary IL-6 concentrations being 2–3 times greater than serum levels; salivary IL-6 exhibited 99% sensitivity and 96% specificity for the identification of PML, as determined by receiver operating characteristic analysis.
Ameena M (2019) [25]	Evaluation of tumor necrosis factor: Alpha in the saliva of oral cancer, leukoplakia, and healthy controls – A comparative study	30 (OSCC) 30 (Leukoplakia)	TNF-α	30 (Healthy)	The research indicated markedly increased TNF-α levels in leukoplakia, with further elevation observed in OSCC, showing significant variation across histological and clinical stages ($P \leq 0.01$ and $P \leq 0.05$, respectively). ROC curve analysis revealed high specificity and sensitivity in differentiating OSCC, leukoplakia, and healthy controls.
	IL: Interleukin; ELISA: Enzyme Linked Immunosorbent Assay; OSCC: Oral Squamous Cell Carcinoma; M2BP: Mac 2 Binding Protein; MRP14: Myeloid Related Protein 14; CD59: Inherited complete deficiency of 20-kilodalton homologous restriction factor; ROC: receiver operating characteristic; HNSCC: Head and and Neck Squamous Cell Carcinoma; OLP: Oral lichen planus; PML: Potentially Malignant Lesions; OPMD: Oral potentially malignant disorders; AUC: Area Under Curve; TNF: Tumor necrosis factor; MCC: Colorectal mutant cancer protein; HCP-1: Heme carrier protein-1.				

Salivary Adiponectin

Although adiponectin is primarily secreted by adipocytes in white fat (Adipose tissue), its production is also found in smaller amounts in brown adipose tissue, colon, ovaries, salivary glands, liver, and skeletal muscle. This suggests it may also exert autocrine and/or paracrine effects in these tissues. Adiponectin is a 244-amino acid protein and it had previously been demonstrated to contain an amino-terminal signal peptide including a species-specific variable domain, a collagen-like region consisting of 22 Gly-X-Y repeats, and a carboxyl-terminal globular domain. This globular domain interacts with adiponectin receptors and shows homology to C1q and the trimeric structure of TNF-α [26].

With the several physiological activities, and its possible relation to cancer, adiponectin is becoming the focus of much attention in current research. Several studies in the last twenty years have been carried out with the aim of trying to clarify the physiological activities of adiponectin in the setting of inflammatory, atherosclerotic, obesity, diabetes, and cardiovascular diseases [26-29]. Adiponectin has also been linked to being a biomarker for cervical cancer [30]. Indeed, several observational studies have also shown that low adiponectin levels are related to an increased risk for the development of breast, endometrial, ovarian, and prostate cancers [31-34].

There are studies pointing out the effect of adiponectin on vascular endothelial growth factor expression. Vidhya S et al. [35] performed a study meant to determine the role of adiponectin in modulating vascular endothelial growth factor (VEGF) and pigment epithelial-derived factor (PEDF) expression regarding ocular angiogenesis. Their evidence showed that adiponectin levels were inversely proportional to VEGF levels, hence proving the protective role of adiponectin against diseases mediated through angiogenesis.

Adiponectin has also been described to physiologically sensitize insulin and decrease inflammation [36], currently, two of the adipokines, leptin and adiponectin are used as biomarkers for severe insulin resistance and lipodystrophy syndromes, thus aiding in phenotyping and diagnostic direction [37]. Recent evidence has confirmed that it is physiologically involved in the initiation and tumor spread of cancer [38]. Many articles have provided studies on the relationship of adiponectin in cancers of the mouth, oesophageal, breast, and colon [39-43]. The results of the research are in general nuanced and context-dependent, reflecting the complexity of the interplay between adiponectin and cancer biology.

In a case-control study by Mantzoros et al. [44] a strong inverse relation with serum adiponectin level and breast cancer incidence was found in 174 newly diagnosed women with breast cancer and 167 controls: odds ratio, 0.84; 95% confidence interval, 0.71–0.99. This inverse association was most marked in the postmenopausal stratum relative to the premenopausal stratum (odds ratio, 0.82; 95% CI, 0.67–1.00) and was not observed in premenopausal women. The associations observed in this analysis were not explained by various potential confounding variables, components of the insulin-like growth factor (IGF) system, leptin, body mass index, sociodemographic variables, or known risk factors related to breast cancer. This study, therefore, lends weight to the need for more investigations to establish causality and elucidate mechanisms about adiponectin's action in breast cancer.

Sugiyama et al. [45] studied the effects of adiponectin on colorectal cancer cells. In these experiments, three cell lines of the human type of colorectal cancer, expressing both AdipoR1 and AdipoR2, were grown. As per the 3-(4,5-dimethylthiazolyl)-2,5-diphenyltetrazolium bromide (MTT) assay, the results obtained showed that the growth of human colorectal cancer cells was arrested by adiponectin. Adiponectin also activated 5′-adenosine monophosphate (AMP)-activated protein kinase AMPK while inhibiting mammalian target of

rapamycin (mTOR) pathways, which was further evidenced by Western blotting. A selective inhibitor of AMPK, compound C, was employed to reverse the adiponectin effect on inhibiting cell growth, thus confirming the specificity of the effect. These results can provide new insight into the role of adiponectin in colorectal cancer. It may suppress the growth of cancer cells by activating AMPK, followed by downregulation of the mTOR pathway. These molecular pathways give an insight into the development of therapeutic strategies that can exploit the anticancer features of adiponectin against colorectal cancer. Renal cell carcinoma, a form of kidney cancer, is also one of these several medical conditions for which investigators have studied the relation of circulating levels and activity of adiponectin [46].

In addition, there is also a possibility that adiponectin may turn out to be a useful marker for oral cancers by observing its serum and saliva levels in patients who suffer from mouth cancer and probably in pre-malignant conditions [47-49]. The results indicated potential use of adiponectin as a diagnostic marker for the progression of oral cancer, where changes in the levels depicted may serve. Although these exciting epidemiological and clinical studies present a link, more research is still needed to elucidate the molecular mechanisms leading to this linked factor in order to define whether adiponectin-based interventions have potential applications in cancer prevention or treatment strategies. Such close association of adiponectin with cancer necessitates in-depth research based on different categorizations of types of cancer, stages, and profiles of the patients.

In a majority of oral cancers, the origin of the pathology can be tied back to tobacco intake through smoking as well as via local applications of Gukta and Khaini. The long-term smoking process causes an inflammatory response, which is prooxidant and finally results in lipid peroxidation. Adipocyte releases adipokines essential for mediating these processes [50]. These released adipocyte inflammatory mediators exert broad-ranging effects, not only on different metabolic processes in organs such as liver, brain, and muscles but also in fat tissue. Adipokines are involved in the modulation of immune system and compose a complex network that links lipid peroxidation and inflammation caused by tobacco use with the emergence of oral malignancies. It has huge potential and has shown promise in current research into the salivary biomarkers in cancer, changing the facets of early detection, monitoring, and tailored treatment strategies for most cancers. Salivary biomarkers could be part and parcel of holistic cancer management in the near future with advances in technology and better understanding of molecular etiology of cancer.

(Table 2) describes results of studies that used adiponectin as a biomarker in cancer research of different research.

Table 2: Findings from studies utilizing adiponectin as a biomarker in cancer research.

Author (Year)	Title	Cases	Control	Findings
Diakowska et al. (2014) [39]	Serum Levels of Resistin, Adiponectin, and Apelin in Gastroesophageal Cancer Patients	85 (GEC)	60 (Healthy)	In patients with gastric esophageal cancer (GEC), levels of resistin and apelin were significantly increased, especially among cachectic individuals and those with metastasis. Conversely, adiponectin levels decreased in the presence of metastasis. Additionally, resistin and apelin concentrations were elevated in tumour tissues, exhibiting weak positive correlations between serum and tumour levels.
Mantzoros C et al. (2004) [44]	Adiponectin and Breast Cancer Risk	174 (Newly Diagnosed Breast Cancer, histologically confirmed)	167	The study found a statistically significant inverse correlation between serum adiponectin levels and breast cancer risk, especially in postmenopausal women, with no significant association in premenopausal women. The results held true when different factors were taken into account, indicating that more research is necessary to fully understand adiponectin's possible role in breast cancer.
Guo XH et al. (2013) [47]	Decreased adiponectin level is associated with aggressive phenotype of tongue squamous cell carcinoma	59 (TSCC)	50 (Healthy)	Serum adiponectin levels were lower in TSCC patients without metabolic or cardiovascular diseases, or smoking and drinking habits; in vitro tests revealed that adiponectin inhibited SCC15 cell migration, indicating that low adiponectin levels may increase TSCC risk. The study also found that as the TNM stage progressed, adiponectin levels in tumour tissue decreased, while receptor expression remained stable.
ÖZER NE et al. (2022) [48]	POTENTIAL BIOMARKERS FOR EARLY DETECTION OF ORAL CANCER: LEPTIN AND ADIPONECTIN	24 (OSCC) 12 (Oral Dysplasia)	16 (Healthy)	Adiponectin and leptin expression levels were non-significantly lower in the OSCC group and higher in the dysplasia group, although neither difference was statistically significant. Comparing the OSCC and dysplasia groups revealed that OSCC had higher levels of adiponectin and lower levels of leptin, and reclassifying into an increased risk group (OSCC+dysplasia) showed non-significant changes in both levels when compared to the healthy group.
Tandon D et al. (2024) [49]	RESISTIN GENE POLYMORPHISMS: POTENTIAL BIOMARKER FOR ORAL SQUAMOUS CELL CARCINOMA	200 (OSCC)	200 (Healthy)	According to the study, OSCC patients in the North Indian population who have the G/A heterozygous genotype of the RETN rs3219175 polymorphism are less likely to develop high-grade tumours than those who have the G/G homozygote, and smokers with a history of betel quid use are much more likely to develop OSCC than non-users.
Aksoy T et al. [51] (2020)	Significantly Lower Serum Adiponectin Levels in the Postmenopausal Age may be Specific for Breast Cancer Risk	59 (Breast Cancer)	47 (Healthy)	Although there was no correlation with Cerb-B2 expression, the study revealed significant differences in serum adiponectin levels and HOMA-IR values between patients and controls. Patients with postmenopausal breast cancer had lower adiponectin levels, and a serum adiponectin level below 4.46 mg/L may indicate a predisposition to postmenopausal breast cancer. This underscores the need for more research on the role of adiponectin in early detection.
	GEC: Gastroeosophaegal Cancer; hsCRP: High-sensitivity C-reactive protein; TSCC: Tongue and Oral Squamous Cell Carcinoma; TNM: tumor-node-metastasis; RETN: Resistin; HOMA-IR: Homeostatic Model Assessment of insulin resistance; Cerb-B2: Humanized epidermal growth factor receptor 2.			

DISCUSSION

The current surge of interest in salivary biomarkers for oral cancer is based mainly on its potential application in noninvasive and early detection and monitoring of oral cancer. Other studies have focused on various types of salivary biomarkers associated with oral cancer diagnosis and prognosis, which are discussed in this review. Salivary markers such as IL-6, IL-8, other cytokines, CA19-9, CRP, CYFRA 21-1, and different kinds of microRNAs have been widely studied and used due to a very good association or correlation with cancer presence and progression [10,11]. High levels of these markers in the saliva indicate a variety of malignancies, including oral, breast, lung, and gastrointestinal. These biomarkers reflect the inflammatory and tumorigenic processes taking place within, making a way for non-invasive and inexpensive early cancer detection, prognosis, and monitoring of treatment efficacy. Salivary levels and their presence in saliva are crucial indicators on the biological activity and burden of cancer, indicating its potential in clinical oncology.

Recently, salivary biomarkers have gained preference over serum biomarkers in the past due to a number of the assured practical, technical, and clinical advantages resulting from their use in the study. The collection of saliva is noninvasive, painless, and simple, which highly improves patient compliance in particular; for example, it is very helpful in children, the elderly, and individuals with chronic diseases in whom blood sampling is a burden. This also is less expensive, as it does not involve syringes or other phlebotomy materials, and samples are collected extra clinically, so no costs coming from logistics. This method is also bloodless, eliminating the substantial risk of infection from blood-borne pathogens and improving safety for both patients and healthcare personnel. Salivary-diagnostic biomarkers provide a comprehensive picture of local and systemic diseases, and the levels measured frequently correspond to illness stages earlier than blood biomarkers. The technical advancement of analytical techniques and point-of-care testing devices improves the sensitivity and specificity of the salivary biomarker, ensuring its reliability as a diagnostic tool. Its diverse set of biomarkers, which include proteins, nucleic acids, hormones, and metabolites, provides the most comprehensive profile for disease monitoring and real-time tracking of illness progression and treatment efficacy without causing discomfort to the patient. Saliva is especially helpful for oral health concerns because it immediately reflects the environment of the oral cavity and is more indicative of bioavailable hormone levels, which would be useful in hormonal research. Together, these features make saliva an appealing medium for early disease identification, continuous monitoring, and even personalised health care, signalling a substantial shift towards more patient-friendly diagnostic techniques. Salivary biomarkers are preferred for improving patient experience, safety, and better and more efficient health care delivery when altering diagnostic techniques and disease management strategies.

Of these, adiponectin seems to be one such vital and interesting molecule which has to be researched further. The consensus derived from these studies points toward the significant role of adiponectin in cancer research and, to be more precise, in cases of oral malignancy. The hormone produced by adipose tissue, such as adiponectin, is inversely associated with the risk of several malignancies of the breast, endometrium, colorectum, prostate, and oral cancer, with lower serum levels being associated with an increased risk and worse outcomes in cancer. concerning, especially for oral cavity neoplasms, because adiponectin possesses significant anti-inflammatory, insulin-sensitizing, and anti-proliferative properties [36-38]. Sample collection requires no invasive procedures, is painless, and simple to perform, with the potential for increased patient compliance; the procedure is performed without the use of syringes and phlebotomy supplies, at a significantly

lower cost, and with fewer infections associated with blood drawing. Practical implications for the salivary adiponectin test as a landmark in diagnostics and patient care include additional research to validate its efficacy as a biomarker for oral cancer diagnostic development and portable testing equipment for real-time clinical decision-making.

While salivary biomarkers present an exciting potential for cancer diagnostics, challenges highlight the need for further research into salivary adiponectin as a diagnostic tool. Questions about biological variability, such as diurnal and dietary influences on saliva composition, could affect the consistency of biomarker levels under investigation. Biological variances between patients, which are linked to genetic factors or pre-existing oral health issues, further complicate the establishment of standard reference ranges. Technical challenges arise from low biomarker levels, which necessitate very sensitive assays; yet, sampling contamination by oral bacteria and food residues may also create misleading results. As a result, salivary biomarkers must undergo extensive clinical validation to assure their reliability and diagnostic accuracy, as a standardised technique for saliva collection, processing, and analysis has yet to be created. Furthermore, the majority of salivary biomarkers are not specific to the disease under consideration in most situations, since their levels can accurately represent changes in a variety of systemic and local disorders, making it difficult to interpret the data. Other important considerations include sample stability during storage and transportation, as well as patient education on proper collection practices. However, noninvasiveness, painlessness, and low cost of saliva collection together with salivary characteristics that reflect local and systemic health states make salivary adiponectin quite an attractive cancer diagnostic candidate. These limitations can be addressed by additional research and technological advancements so that this molecule becomes more reliable and thus more clinically applicable, allowing the molecule to take its place among powerful tools in early cancer identification and personalized healthcare. This highlights the need of exploring and developing salivary adiponectin as a diagnostic tool, which has the potential to enhance patient outcomes and make it easier to give better health care.

CONCLUSION

Interest in salivary biomarkers of oral cancer has grown dramatically because they demonstrate the promise for noninvasive early detection and follow-up in the near future. Several studies have shown that biomarkers such as IL-6, IL-8, other cytokines, CA19-9, C-reactive protein (CRP), CYFRA 21-1, and microRNAs indicate cancer and its progression and are positively correlated with various malignancies, including oral, breast, lung, and gastrointestinal cancers. These biomarkers provide a non-invasive and accessible method to very early cancer detection, prognosis, and treatment efficacy monitoring by reflecting underlying inflammatory and tumorigenic processes. The advantages of salivary biomarkers over serum biomarkers are overwhelming. Saliva is collected in a non-invasive, painless, and uncomplicated manner, which considerably increases patient compliance, particularly in vulnerable groups like as children, the elderly, and people with chronic conditions. It is cost-effective since it saves money on logistics, syringes, and phlebotomy supplies while also eliminating the risk of blood-borne illnesses. Saliva reflects local and systemic diseases, allowing for earlier diagnosis than serum indicators.

Advancements in technology have made salivary biomarker detection more sensitive and specific, making it a highly dependable diagnostic tool. Among these, adiponectin stands out for its potential role in cancer research, particularly oral cancer. Adipose tissue produces adiponectin, which has an inverse relationship with the risk of numerous malignancies, including breast,

endometrial, colorectal, prostate, and oral cancers. Reduced serum levels are associated with an increased risk and poor cancer outcomes. Its anti-inflammatory, insulin-sensitizing, and anti-proliferative capabilities place it in the group of potentially promising biomarkers. Salivary adiponectin is associated with several advantages in oral cancer screening and monitoring due to non-invasive methods of collection that increase patient compliance, reduce costs, and infection risks. Several challenges must be addressed in identifying and fully bringing to life the potential of salivary biomarkers such as adiponectin. These include inter-individual variations and biological variability, technical challenges, a need for standardization of protocols, and clinical validation on large populations. Most salivary biomarkers are not specific to any particular disease and usually make result interpretation a little complicated. Practical concerns include ensuring sample stability and patient education regarding the correct technique of collection.

Regardless of the limitations listed in this review, the non-invasive character, painlessness, cost-effectiveness of saliva collection, and diagnostic potential of salivary adiponectin highlight the important need for continuing research in this area. Such limitations can be overcome by technological innovation and thorough validation, resulting in increased dependability and clinical adoption, eventually transforming it into a potent tool for early cancer detection and personalised healthcare. This ongoing research and development could significantly enhance patient outcomes and streamline healthcare delivery, making salivary adiponectin a promising candidate for diagnostic methods in the near future.

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