International Dental & Medical Journal of Advanced Research (2018), 4, 1–6

META - ANALYSIS

Usefulness of salivary biomarkers in oral precancer and cancer

Alberto Rodriguez-Archilla, M. Beatriz Carrion-Ruiz

Department of Stomatology, Faculty of Dentistry, Oral Medicine Unit, University of Granada, Colegio Maximo, Spain

Keywords:
Biomarkers, early diagnosis, mouth neoplasms, prognosis, saliva

Correspondence:
Alberto Rodriguez-Archilla, Department of Stomatology, Faculty of Dentistry, Oral Medicine Unit, University of Granada, Colegio Maximo, s/n. Campus de Cartuja, 18071-Granada, Spain. E-mail: alberodr@ugr.es. Phone: +34 958 244 085

Received 09 July 18;
Accepted 20 August 18

doi: 10.15713/ins.idmjar.91

Abstract

Background: Oral and pharyngeal cancer is the sixth most common cancer in the world. Tumoral biomarkers are important for the early diagnosis of oral cancer and to establish prognostic criteria for these lesions.

Aim: The aim of this study is to assess the possible influence of salivary biomarkers on potentially malignant and malignant oral lesions.

Methodology: A PubMed search through April 2018, using the following Medical Subjects Headings terms, was performed: "Mouth neoplasms," "biomarkers," and "saliva." Studies with findings on several salivary biomarkers on potentially malignant and malignant oral lesions were comprised. A total of 180 articles (156 of them full-text articles) were found. 142 articles were excluded for several reasons: Different measurement units/detection methods (95), studies with no usable data (34), studies with no oral cancer patients group (7), and studies about malignant salivary gland tumors (6). For continuous outcomes, the estimates of effects of an intervention were expressed as mean differences (MD) using the inverse variance method together with 95% confidence intervals.

Results: Fourteen studies on salivary biomarkers on potentially malignant and malignant oral lesions were included in this meta-analysis. Biomarkers with significant diagnostic and prognostic relevance in oral cancer were as follows: Interleukin 8 (IL-8) ($P < 0.001$), endothelin 1 ($P < 0.001$), IL-6 ($P < 0.001$), cytokeratin fraction 21-1 ($P < 0.001$), and carcinoembryonic antigen ($P = 0.01$).

Conclusion: Salivary biomarkers have a important relevance in oral cancer. In the case of potentially malignant oral disorders, their relevance seems less evident.

Clinical Significance: Saliva is an useful fluid to identify possible diagnostic and prognostic biomarkers in oral cancer.

Introduction

Oral and oropharyngeal cancer is the sixth most common cancer in the world. Oral squamous cell carcinoma (OSCC) accounts for more than 90% of the malignant tumors of the head and neck that derive from oral squamous epithelial cells. It has different degrees of differentiation and trends to cervical lymph node metastases. Despite advances in research and treatment, survival rates have not improved significantly in recent decades. Oral cancer continues to show high rates of both morbidity (40%) and mortality (46%) at 5 years' survival rate.[1]

A tumoral biomarker is a molecule secreted by cancer cells or by immune cells as a specific host response to cancer. Tumoral biomarkers can be used for the assessment of cancer patients or as prognostic parameters that inform on the evolution of the neoplastic process. Saliva is an accessible fluid with a non-invasive extraction method and useful as a diagnostic and prognostic tool in various oral diseases, including malignant ones.[2]

Unfortunately, most oral cancers are diagnosed in advanced stages, which lead to a poor prognosis and a low survival rate at 5 years' survival rate. Several biomarkers have been studied in oral cancer to try to achieve an early diagnosis of this disease in its initial stages and to establish appropriate prognostic criteria.[3] The aim of this study was to assess the possible influence of various salivary biomarkers in potentially malignant and malignant lesions of the oral mucosa.

Methodology

A PubMed search of studies on salivary biomarkers related to premalignant and malignant oral lesions was conducted. Search strategies included the combination of the following terms from the Medical Subjects Headings (MeSH): "Mouth neoplasms," "biomarkers," and "saliva." A total of 180 articles from 1984 to April 2018 were found.

The inclusion criteria were as follows: (a) Type of studies (clinical trials, clinical studies, comparative studies, and multicenter studies). All the studies had to have two or more comparable study groups, (b) studies with the same detection method, enzyme-linked immunosorbent assay, and the same measurement units, and (c) studies with full-text availability. Exclusion criteria were studies with different measurement units and/or different detection methods, with irrelevant or no usable data, without oral cancer patients group or studies with non-OSCC malignant lesions.

After applying the inclusion and exclusion criteria, 14 studies were included in this meta-analysis [Figure 1].

Statistical analysis

For the meta-analysis, the data were processed with the statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For the continuous variables, the inverse of the variance (IV) was used for the MD with 95% confidence intervals (95% CI). Heterogeneity was determined according to the *P* values and the Higgins statistic (I^2). In cases of high heterogeneity, the random effect model was applied. The significance level was set at $P < 0.05$.

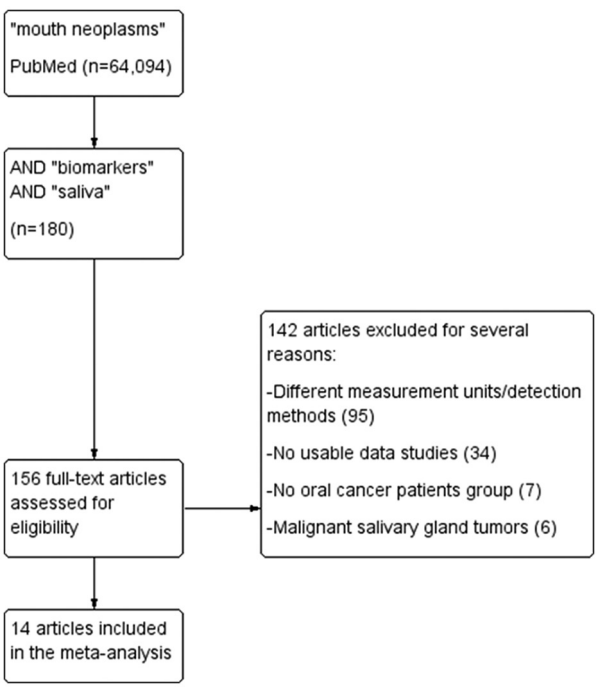

Figure 1: Study flow diagram

Results

A total of 180 articles (156 of them full-text articles) were found. 142 articles were excluded for several reasons: Different measurement units/detection methods (95), studies with no usable data (34), studies with no oral cancer patients group (7), and studies about malignant salivary gland tumors (6).

Table 1 presents the descriptive characteristics of the 14 included studies in the meta-analysis.[4-17]

The different salivary biomarkers analyzed in different population groups (patients with OSCC, patients with oral potentially malignant disorders, and controls) are shown in Table 2.

Six studies[4-9] analyzed the salivary levels of interleukin-8 (IL-8) in OSCC patients and a control group. All studies found quite higher levels of IL-8 in OSCC patients compared to controls. After the statistical analysis of the data, highly significant differences were observed (DM: 820.81, 95% CI: 594.65–1046.97, $P < 0.001$).

Three studies[7-9] examined the salivary levels of IL-8 in patients with OSCC and in patients with oral potentially malignant disorders (OPMD). In this case, higher levels of IL-8 were also found in OSCC patients in contrast to OPMD patients with a statistically significant association (MD: 741.17, 95% CI: 19.83–1462.51, $P = 0.04$). These same three studies[7-9] also compared the salivary levels of IL-8 in OPMD patients and a control group. OPMD patients had higher levels of IL-8 with a statistically significant relationship (DM: 219.39, 95% CI: 42.03 yo 396.76, $P = 0.02$).

Three studies[10-12] assessed the salivary levels of endothelin-1 (ET-1) in OSCC patients and a control group. Higher levels of ET-1 were found in OSCC patients compared to controls with statistically significant differences (MD: 3.30, 95% CI: 2.43–4.16, $P < 0.001$).

Two studies[11,12] assessed the salivary levels of ET-1 in OSCC patients and OPMD patients. The OSCC patients showed the highest levels of ET-1 although no statistically significant association was found (DM: 2.68, 95% CI: −2.38–7.74, $P = 0.30$). These two studies[11,12] also investigated the salivary levels of ET-1 in OPMD patients and in a healthy control group. Higher levels of ET-1 were observed in OPMD patients. However, there was no statistically significant relationship (DM: 1.25, 95% CI: −0.27–2.76, $P = 0.11$).

Three studies[4,6,8] considered the salivary levels of IL-6 in OSCC patients and a control group. OSCC patients showed quite higher levels of IL-6 compared to controls with highly significant statistical differences (DM: 133.13, 95% CI: 75.49–190.78, $P < 0.001$).

Three studies[13-15] analyzed the salivary levels of the carcinoembryonic antigen (CEA) in OSCC patients and controls. OSCC patients had higher levels of CEA with a statistically significant association (DM: 22.80, 95% CI: 5.46–40.14, $P = 0.01$).

Two studies[16,17] examined the levels of the soluble fragment of cytokeratin fraction 21-1 (Cyfra 21-1) in OSCC patients and

Table 1: Descriptive characteristics of included studies

Authors	Years	Country	Study populations (mean age, gender M/F)	Salivary biomarker assessed	Remarks
Katakura *et al.*[4]	2007	Japan	19 OSCC, 60.9 yr, 9M/10F 20 controls, 32.0 yr, 15M/5F	IL-8 IL-6	More significant differences in IL-6 expression in OSCC patients versus controls
Arellano-Garcia *et al.*[5]	2008	USA	20 OSCC, 59.1 yr, 12M/8F 20 controls, 38.7 yr, 14M/6F	IL-8	Significantly higher IL-8 levels in OSCC patients
Korostoff *et al.*[6]	2011	USA	18 OSCC, 56.5 yr, 12M/6F 56 controls, NR	IL-8 IL-6	Salivary levels of IL-8 and IL-6 are correlated to the progression of OSCC
Punyani *et al.*[7]	2013	India	25 OSCC, 53.2 yr, 16M/9F 25 OPMD, 32.2 yr, 19M/6F 25 controls, NR	IL-8	IL-8 may be a biomarker for OSCC but non-conclusive for oral potentially malignant lesions
Lisa-Cheng *et al.*[8]	2014	USA	18 OSCC, 59.4 yr, 11M/7F 41 OPMD, 62.1 yr, 13M/28F 21 controls, 62.9 yr, 9M/12F	IL-8 IL-6	IL-8 and IL-6 can be biomarkers for OSCC detection
Rajkumar *et al.*[9]	2014	India	100 OSCC, NR, 68M/32F 100 OPMD, NR, 71M/29F 100 controls, NR, 65M/35F	IL-8	IL-8 may be a biomarker for the differential diagnosis of OPMD and OSCC
Pickering *et al.*[10]	2007	USA	8 OSCC, 57.5 yr, 7M/1F 8 controls, 31.0 yr, 4M/4F	ET-1	ET-1 is useful to monitor patients at risk for OSCC
Cheng *et al.*[11]	2011	USA	33 OSCC, 62.9 yr, 23M/10F 49 OPMD, 63.1 yr, 13M/36F 24 controls, 62.9 yr, 11M, 13F	ET-1	ET-1 could be a good biomarker for OSCC development but not for detecting recurrence of OSCC
Nosratzehi *et al.*[12]	2017	Iran	25 OSCC, NR, 12M/13F 25 OPMD, NR, 7M/18F 25 controls, NR, 6M/19F	ET-1	ET-1 can be used as a biomarker for OPMD and OSCC lesions
He *et al.*[13]	2009	China	80 OSCC, 57.0 yr, 52M/28F 80 controls, 37.0 yr, 42M/38F	CEA	Salivary CEA level can be useful as prognostic indicator in early diagnosis of OSCC
Honarmand *et al.*[14]	2016	Iran	27 OSCC, 53.8 yr, 15M/12F 26 controls, 52.8 yr, 14M/12F	CEA	Salivary CEA levels may be useful for the early detection of OSCC
Li *et al.*[15]	2016	China	26 OSCC, 64.7 yr, 13M/13F 10 controls, NR	CEA	Salivary CEA levels may be a reliable marker for the early detection of OSCC
Zhong *et al.*[16]	2007	China	30 OSCC, NR 30 controls, NR	Cyfra 21-1	Salivary Cyfra 21-1 concentrations have a potential clinical value for OSCC detection
Rajkumar *et al.*[17]	2015	India	100 OSCC, NR, 68M/32F 100 controls, NR, 65M/35F	Cyfra 21-1	Salivary Cyfra 21-1 can be used as a biomarker in the early detection of OSCC

OSCC: Oral squamous cell carcinoma; OPMD: Oral potentially malignant disorders; yr: years; M: Male; F: Female; NR: Not reported. IL Interleukin, ET-1: Endothelin-1, CEA: Carcinoembryonic antigen, Cyfra 21-1: Cytokeratin fraction 21-1

a control group. OSCC patients had much higher levels of Cyfra 21-1 compared to controls. After the statistical analysis, a highly significant relationship was found (DM: 61.43, 95% CI: 34.59–88.28, $P < 0.001$).

Discussion

In the present meta-analysis on the possible influence of various salivary biomarkers in potentially malignant and malignant lesions of the oral mucosa, data from 14 studies have been included.

IL-8 is a chemotactic cytokine with other biological functions that may play an important role in the cancer progression. Overexpression of IL-8 can induce tumor cell proliferation, angiogenesis, and migration of cancer cells.[9] IL-8 has been identified as a mediator of proliferation in diverse tumor types, including gliomas, melanoma, colorectal cancer, or ovarian cancer.[18]

The six studies[4-9] that considered the levels of IL-8 in patients with OSCC, all of them noticed higher levels of IL-8 in these patients, with highly significant statistical differences ($P < 0.001$). Elevated levels of IL-8 correlate with increased tumor growth and a worse prognosis.[19] Overexpression of IL-8 favors tumor angiogenesis, and it is associated with an increased risk of metastasis and recurrence in oral cancers.[6] The determination of IL-8 in OSCC patients could be an easy diagnostic test used as a prognostic indicator of evolution in patients undergoing treatment.[7]

The levels of IL-8 in OSCC patients and with potentially malignant disorders of the oral mucosa (OPMD) were also

Table 2: Different salivary biomarkers in OPMD, OSCC patients, and controls

Biomarker	n	Study groups	MD	95% CI	I^2 (%)	*P* value
IL-8[4-9]	6	OSCC versus Controls	820.81	594.65, 1046.97	95	<0.001*
	3	OSCC versus OPMD	741.17	19.83, 1462.51	96	0.04*
	3	OPMD versus Controls	219.39	42.03, 396.76	89	0.02*
ET-1[10-12]	3	OSCC versus Controls	3.30	2.43, 4.16	19	<0.001*
	2	OSCC versus OPMD	2.68	−2.38, 7.74	84	0.30
	2	OPMD versus Controls	0.62	−1.26, 2.51	15	0.11
IL-6[4,6,8]	3	OSCC versus Controls	133.13	75.49, 190.78	92	<0.001*
CEA[13-15]	3	OSCC versus Controls	22.80	5.46, 40.14	94	0.01*
Cyfra 21-1[16,17]	2	OSCC versus Controls	61.43	34.59, 88.28	61	<0.001*

n: Number of studies, MD: Mean difference, 95% CI: 95% confidence interval, I^2: Higgins statistic for heterogeneity, *Statistically significant. IL Interleukin, ET-1: Endothelin-1, CEA: Carcinoembryonic antigen, Cyfra 21-1: Cytokeratin fraction 21-1, OSCC: Oral squamous cell carcinoma, OPMD: Oral potentially malignant disorders

examined,[7-9] with significantly higher salivary IL-8 levels in OSCC patients ($P = 0.04$). When the salivary levels of IL-8 were compared in OPMD patients and in controls, expression of IL-8 was higher in OPMD patients with a statistically significant association ($P = 0.02$). The three studies that analyzed this biomarker established a direct relationship between premalignant oral lesions and levels of IL-8.[7-9]

Other factors such as tobacco and/or alcohol consumption can influence the expression of IL-8. However, the findings are contradictory. Some studies[6] found an increase in salivary levels of IL-8 in current smokers and/or drinkers, others not.[19] IL-8 could behave as an indicator of proliferative activity in both potentially malignant and malignant lesions of the oral mucosa.

ET-1 is a vasoactive peptide synthesized by keratinocytes with a potent vasoconstrictive action that intervenes in processes such as inflammation, wound healing, or carcinogenesis.[5] Some patients with systemic diseases had elevated salivary ET-1 expression. In congestive heart failure, these increased levels are correlated with disease severity and with treatment.[20] ET-1 appears overexpressed in various malignant tumors (prostate, lungs, breast, liver, and colon) including the OSCC where it seems that the expression of ET-1 is related to the invasion and oral metastases.[10]

In the present study, OSCC patients had higher levels of salivary ET-1 than controls with highly significant statistical differences ($P < 0.001$). Probably ET-1 can help tumor metastasis indirectly through the induction of angiogenic factors that promote the angiogenesis stimulation.[12] When comparing the expression of ET-1 in OSCC patients and OPMD subjects, higher salivary ET-1 levels were found in OSCC patients but without statistically significant association ($P = 0.30$). However, these results might be conditioned by the type of premalignant lesion studied, the degree of dysplasia of the lesions, or a possible selection bias since the population groups considered have great differences related to age and sex.[11,12]

In the case of ET-1 levels in OPMD patients and in controls,[11,12] the first ones presented higher levels although no statistically significant differences were found ($P = 0.11$). The potential role of ET-1 as a marker of malignant transformation of an OPMD into oral cancer is currently controversial.[11]

IL-6 is a multifactorial cytokine that plays a role in the progression and severity of diverse types of cancer. Some studies have suggested the involvement of elevated levels of IL-6 in human carcinogenesis. However, it remains unclear the real relevance of IL-6 on cancer.[21] The increase in IL-6 levels correlates with an increase in tumor burden, a worse prognosis, and a higher probability of metastasis. IL-6 is involved in angiogenesis, which is also associated with an increased risk of metastasis and recurrence of OSCC.[11]

Sharma *et al*.[22] observed a direct correlation between the degree of epithelial dysplasia and IL-6 levels. As in the case of IL-8, other factors as tobacco consumption stimulate the production of IL-6 and smokers have higher levels of this interleukin. There are many confounding factors that can alter expression of IL-6, and therefore, larger studies are needed in OSCC patients to determine the possible value of IL-6 as a diagnostic or prognostic tumoral marker.[23]

CEA, considered as a tumoral marker, is a glycoprotein that occurs during fetal development, and it is usually not detectable in the blood of healthy adults. Its use as a screening technique for the early cancer detection is not recommended because its sensitivity is low. Nevertheless, it is useful to assess the evolution of colorectal cancer after treatment and to detect tumoral recurrences.[24]

The results showed a higher expression of CEA in OSCC patients with significant statistically differences ($P = 0.01$). Three studies[10-12] obtained matching results, indicating a higher expression in patients with oral cancer compared to controls. Although there are differences between serum and salivary levels of CEA depending on the type of patients, serum CEA levels between the OSCC patients and the non-cancer patients are very close. Particularly, in oral cancer patients, serum CEA levels are not increased but that in the saliva raise significantly. This may be due to CEA is present on the surface of tumor cells and together with the constant shedding of them from the surface tissue layer, CEA could enter the saliva, increasing its levels in

this fluid. Moreover, CEA levels are gradually increased with cancer progression. Hence, detecting the salivary CEA levels might be one method to effectively detect early cancer.[15]

Cyfra 21-1 is considered as a important tumoral biomarker with high sensitivity and specificity in non-small cell lung cancer and, especially in squamous cell carcinoma, including OSCC.[17]

In this meta-analysis, salivary Cyfra 21-1 levels found in OSCC patients were significantly higher than in healthy control subjects ($P < 0.001$).[16,17] The highest levels of Cyfra 21-1 are found in patients with tumors of worse histological differentiation and with recurrent lesions, evidencing a possible usefulness as a marker of disease progression, tumoral prognosis, and survival.[25]

In general, new studies with larger populations of all these markers measured in saliva are required to assess their real influence on the diagnosis and evolution of oral neoplastic lesions.

Early detection of potentially malignant and malignant lesions of the oral mucosa is critical for prognosis and survival rates, especially in the case of OSCC. Saliva has an increasing role as a diagnostic fluid because sampling is easy, inexpensive, and not invasive. These are its main advantages.[26]

All findings of this meta-analysis must be interpreted with caution due to the high heterogeneity of the studies included and the presence of different bias. The differences among studies could be conditioned by the study design, the methods used to collect data, the type of analysis used, the characteristics of the study populations and samples, or the duration of the studies.

Conclusions

In this meta-analysis, the possible salivary markers with diagnostic and prognostic relevance in oral cancer were as follows: IL-8 ($P < 0.001$), ET-1 ($P < 0.001$), IL-6 ($P < 0.001$), Cyfra 21-1 ($P < 0.001$), and CEA ($P = 0.01$). In the case of potentially malignant oral disorders (OPMD), their relevance seems less evident.

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How to cite this article: Rodriguez-Archilla A, Carrion-Ruiz MB. Usefulness of salivary biomarkers in oral precancer and cancer. Int Dent Med J Adv Res 2018;4: 1-6.