

Influence of interleukins on prognosis of patients with oral squamous cells carcinoma

Influência de interleucinas no prognóstico de pacientes portadores de carcinoma de células escamosas intraoral

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ABSTRACT

Squamous cell carcinoma is a malignant neoplasm that affects the structures and tissues of the oral cavity. Interleukins (IL) synthesized from a tumor modulate a cascade reaction that may influence the prognosis of the disease. We aim to investigate in the literature whether interleukins are mediators that negatively or positively influence the prognosis of patients with oral squamous cell carcinoma. A systematic review study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) instructions. PubMed (including MedLine), Scopus, Web of Science, SciELO and Latin American and Caribbean Health Sciences (LILACS) databases were used as the primary sources for the study; OpenGrey and OpenThesis were used to search for “gray literature”. The search conducted in seven general databases resulted in a set of 858 studies, while the search conducted in two databases for gray literature resulted in 82 studies, totaling 940 studies. From these, 15 studies were selected for this systematic review (eight studies presented low bias risk; four studies presented moderate bias risk; and three studies presented high risk of bias). Although they may act on the anti-tumor immune response pathways, the IL evaluated in the present systematic review (IL-4, IL-6, IL-8, IL-10, IL-12 and IL-13) tend to present a response associated with the intensification of carcinogenesis and poor prognosis in patients with oral squamous cell carcinoma.

Key words: neoplasms; interleukins; head and neck neoplasms; oral squamous cell carcinoma.

RESUMO

O carcinoma de células escamosas é uma neoplasia maligna que afeta as estruturas e os tecidos da cavidade oral. Interleucinas (IL) sintetizadas a partir de um tumor modulam uma cascata de reações que poderá influenciar o prognóstico da doença. Objetivava-se investigar na literatura se as interleucinas são mediadores que influenciam negativa ou positivamente o prognóstico de pacientes com carcinoma de células escamosas intraoral. Um estudo de revisão sistemática foi realizado segundo as instruções do Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). As bases de dados PubMed (incluindo MedLine), Scopus, Web of Science, SciELO e Latin American and Caribbean Health Sciences (LILACS) foram utilizadas como fontes de estudo primárias; OpenGrey e OpenThesis, utilizadas para pesquisar a “literatura cinzenta”. A busca realizada em sete bases de dados gerais resultou em um conjunto de 858 estudos, enquanto a realizada em duas bases de dados para literatura cinza, em 82 estudos, totalizando 940 pesquisas. Destas, 15 foram selecionadas para a presente revisão sistemática (oito estudos apresentaram baixo risco de viés; quatro, moderado risco de viés; e três, alto risco de viés). Apesar de poderem atuar nas vias de resposta imune antitumoral, as IL avaliadas nesta revisão (IL-4, IL-6, IL-8, IL-10, IL-12 e IL-13) tendem a apresentar uma resposta associada à intensificação do processo de carcinogênese e ao prognóstico desfavorável em pacientes portadores do carcinoma de células escamosas intraoral.

Unitermos: neoplasias; interleucinas; neoplasias de cabeça e pescoço; carcinoma de células escamosas intraoral.

RESUMEN

El carcinoma de células escamosas es una neoplasia maligna que afecta las estructuras y los tejidos de la cavidad oral. Interleucinas (IL) sintetizadas a partir de un tumor modulan una cascada de reacciones que puede influenciar el pronóstico de la enfermedad. Nuestro objetivo es investigar en la literatura si las IL son mediadoras que influyen negativamente o positivamente en el pronóstico de pacientes con carcinoma oral de células escamosas. Un estudio de revisión sistemática fue realizado bajo las instrucciones del Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Las bases de datos PubMed (incluyendo MedLine), Scopus, Web of Science, SciELO y Latin American and Caribbean Health Sciences (LILACS) fueron usadas como fuentes primarias de estudio; OpenGrey y OpenThesis, para pesquisar la literatura gris. La búsqueda realizada en siete bases de datos generales resultó en un conjunto de 858 estudios, mientras la búsqueda realizada en dos bases de datos para literatura gris resultó en 82 estudios, totalizando 940 investigaciones. Entre ellas, 15 fueron elegidas para la presente revisión sistemática (ocho estudios presentaron bajo riesgo de sesgo; cuatro, riesgo moderado; tres, riesgo alto). A pesar de poder actuar en vías de respuesta inmune antitumoral, las IL evaluadas en esta revisión (IL-4, IL-6, IL-8, IL-10, IL-12, y IL-13) suelen presentar una respuesta asociada a la intensificación del proceso de carcinogénesis y al pronóstico desfavorable en pacientes portadores de carcinoma oral de células escamosas.

Palabras clave: neoplasias; interleucinas; neoplasias de cabeza y cuello; carcinomas de células escamosas de la boca.

INTRODUCTION

Squamous cell carcinoma (SCC) is a malignant neoplasm that affects the structures and tissues of the oral cavity⁽¹⁾. This condition may originate from a precancerous primary lesion that arises in the mouth or from metastasis⁽²⁾. Its etiology is multifactorial; smoking and alcohol consumption are the habits that most influence oral cancer^(1,3). Men are often more affected than women because they are more involved with risk factors⁽⁴⁾. According to the literature, oral cancer is the eighth leading cause of death, with oral squamous cell carcinoma (OSCC) representing the most common malignant neoplasm in the mucous membranes of the oral and oropharynx mucosa⁽⁵⁾.

Interleukins (IL) are a group of cytokines and are one of the main molecules that act in the immune system, transmitting signals among cells⁽⁶⁾. Interleukin 1 (IL-1) and 6 (IL-6) are produced in SCC and play a key role in the progression of the carcinogenesis process. IL-1 is produced in order to mediate the host defense system when there is an aggression, as well as to stimulate immune cells and fluids leakage. IL-6 production occurs through the activation of nuclear factor kappa B (NF- κ B) by stimulating lymphoid cells; it acts similarly to IL-1, however with more specific activities, such as differentiation and growth factors for T and B cells⁽⁷⁾. IL-10 also favors tumor progression; this cytokine regulates immune cell differentiation and proliferation and contributes to immune evasion of anti-tumor immunity⁽⁸⁾.

Cytokines synthesized from a tumor may modulate a cascade reaction that will eventually act on the progression of the carcinogenesis process⁽⁷⁾. The production of IL-6 in high quantities is known to be present in pathological processes, constituting an

important diagnostic biological marker⁽⁹⁾. Thus, in OSCC, salivary levels of IL-1, IL-6 and IL-8 are highly sensitive parameters to verify the progression of the neoplasia^(9, 10). Moreover, IL-37, a member of the IL-1 family, has innate immunity inhibitory properties, with the potential to influence inflammatory tumors, and it is suggested as a new diagnostic biomarker⁽¹¹⁾.

In the absence of specific indications on the general role of IL in the carcinogenesis process, this systematic review aims to investigate the literature on IL as mediators that negatively or positively influence the prognosis of patients with OSCC.

MATERIAL AND METHODS

This is a systematic review study conducted according to the instructions of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (www.prisma-statement.org). PubMed (including MedLine), Scopus, Web of Science, SciELO and Latin American and Caribbean Health Sciences (LILACS) databases were used as primary sources for the study; OpenGrey and OpenThesis, used to search for "gray literature". Additional information regarding the search strategy used is shown in **Table 1**.

The Medical Subject Headings (MeSH) feature selected the key words: *oral cavity, mouth, carcinoma squamous cell, carcinoma, oral cavity, squamous cell, squamous cell carcinoma, squamous carcinoma, epidermoid carcinoma, planocellular carcinoma, interleukin, interleukin-1, interleukin-6, interleukin-8, IL-1, IL-6 and IL-8*, connected together by the Boolean operators "and" and "or".

TABLE 1 – Search strategy used to search the databases

Database	Search strategy	Total
	Key words	
PubMed http://www.ncbi.nlm.nih.gov/pubmed/	("mouth" [all fields] OR "mouth" [MeSH terms] OR "oral cavity" [all fields]) AND ("carcinoma, squamous cell" [all fields] OR "carcinoma, squamous cell" [MeSH Terms] OR "squamous cell carcinomas" [all fields] OR "squamous carcinoma" [all fields] OR "epidermoid carcinoma" [all fields] OR "planocellular carcinoma" [all fields]) AND ("interleukins" [all fields] OR "interleukin" [all fields] OR "interleukins" [all fields] OR "interleukin-1" [all fields] OR "interleukin-1" [MeSH terms] OR "IL-1" [all fields] OR "interleukin-6" [MeSH terms] OR "IL-6" [all fields] OR "interleukin-6" [all fields] OR "interleukin-8" [MeSH terms] OR "Interleukin-8" [all fields] OR "IL-8" [all fields])	288
Scopus http://www.scopus.com/	((("mouth" OR "oral cavity") AND ("carcinoma squamous cell" OR "squamous cell carcinomas" OR "squamous carcinoma" OR "epidermoid carcinoma" OR "planocellular carcinoma") AND ("interleukins" OR "interleukin")))	525
Web of Science http://apps.webofknowledge.com/	((("mouth" OR "oral cavity") AND ("carcinoma, squamous cell" OR "squamous cell carcinomas" OR "squamous carcinoma" OR "epidermoid carcinoma" OR "planocellular carcinoma") AND ("interleukins" or "interleukin")))	16
LILACS http://lilacs.bvsalud.org/	tw:(carcinoma squamous cell AND interleukin) AND (instance:"regional") AND (db:("LILACS"))	10
	tw:(epidermoid carcinoma AND interleukin) AND (instance:"regional") AND (db:("LILACS"))	8
	tw:(planocellular carcinoma AND interleukin) AND (instance:"regional") AND (db:("LILACS"))	8
SciELO http://www.scielo.org/	carcinoma squamous cell AND interleukin	3
	epidermoid carcinoma AND interleukin	0
	planocellular carcinoma AND interleukin	0
OpenGrey http://www.opengrey.eu/	("planocellular carcinoma" OR "carcinoma squamous cell" OR "epidermoid carcinoma") AND ("interleukin")	0
OpenThesis http://www.openthesis.org/	("planocellular carcinoma" OR "carcinoma squamous cell" OR "epidermoid carcinoma") AND ("interleukin")	82
	Total	940

The following were included: 1. observational studies without restriction of period, language and publication status; 2. studies that identified the relationship among the IL(s) analyzed and their influence on OSCC prognosis. The following were excluded: 1. studies that did not displayed as content the objective of the present systematic review; 2. *in vitro* studies; 3. animal studies; 4. case reports, letter to editor and/or editorials, literature review, books and book chapters, indexes and abstracts; 5. studies that analyzed IL levels but did not assess the relationship with prognosis in OSCC patients.

Data collection was performed in two phases: in the first, the titles and abstracts were systematically examined by the reviewer to check the eligibility criteria (with access to the names of the authors and journals). Those who presented titles according to the eligibility criteria, but the abstracts were not available were also obtained and analyzed in full. In the second phase, the preliminary eligible studies had the full text evaluated to verify if they met the eligibility criteria. In specific cases, when the study potentially eligible presented incomplete data, the authors were contacted by email to provide further information. After complete screening, the texts of the selected articles were reexamined and their data

extracted in a standardized form, containing: authorship, year of publication and place of study, IL, type of study, sample, methods of disclosure of IL(s) levels and main outcome.

The selected studies were assessed for risk of bias and individual quality using the checklist obtained through the critical assessment tools from the Joanna Briggs Institute allowed for systematic reviews⁽¹²⁾. The reviewer assessed the risk of bias and the individual quality of the studies, which were classified as high, moderate or low risk of bias. At that point, the review was blinded to the authors and journals, avoiding any selection bias and possible conflicts of interest. The search was performed in August 2017. The results were exported to Mendeley 1.13.3 software desktop (Mendeley TM Ltd, London, UK), where duplicity was verified.

RESULTS

Study selection

The flowchart shown in **Figure** demonstrates our selection profile.

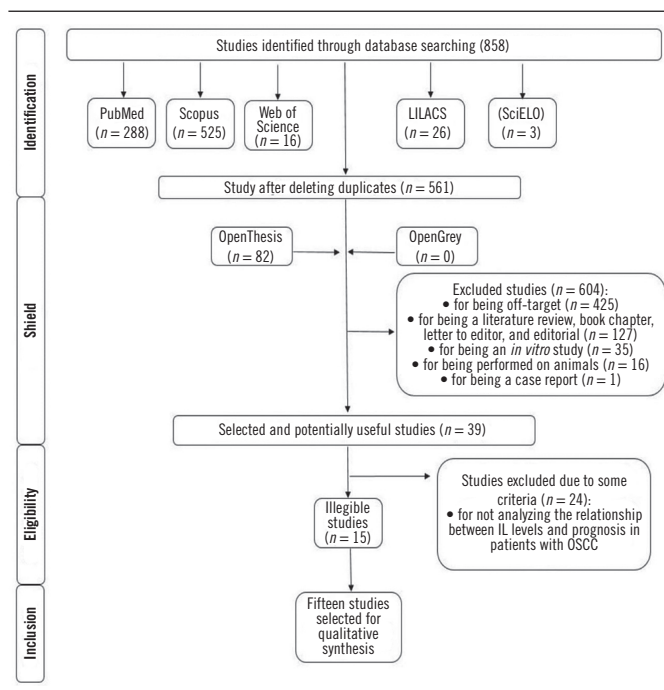


FIGURE – Flowchart that defines the search strategy result

IL: interleukins; OSCC: oral squamous cell carcinoma.

Characteristics of studies

All included studies were published in English. One study was conducted in Brazil⁽¹³⁾; one in China⁽¹⁴⁾; two in Croatia^(15, 16); two in India^(17, 18); one in England⁽¹⁹⁾; one in Iran⁽²⁰⁾; three in Japan⁽²¹⁻²³⁾; one in Pakistan⁽²⁴⁾; one in the United Kingdom⁽²⁵⁾; and two in Taiwan^(26, 27). A summary of the descriptive characteristics of the included articles can be found in **Table 2**.

Risk of individual bias of the studies

Among the 15 studies selected, eight showed low risk of bias^(14-19, 25-27); four, moderate risk of bias^(20, 22-24); and three, high risk of bias^(13, 16, 21). Detailed information on the assessment of risk of individual bias of the studies is shown in **Table 3**.

Summary of results

There was a certain degree of heterogeneity between the included studies, which showed differences on the type of study, the types of IL evaluated, the methods of disclosure of IL, and the main outcome. Therefore, it was not possible to perform a meta-analysis.

IL-4 was evaluated in three studies^(13, 20, 24). Only one of them presented results⁽²⁴⁾ showing that high levels of IL-4 in patients with OSCC seem to be related to poorer prognosis. IL-6 was evaluated in

seven studies^(13, 15, 16, 18, 21, 23, 26). Except in one study⁽¹³⁾, the results of others showed that high levels of IL-6 in patients with OSCC seem to be related to poorer prognosis. IL-8 was evaluated in three studies^(13, 17, 22). Except for one study⁽¹³⁾, the results of others showed that high levels of IL-8 in patients with OSCC seem to be related to poorer prognosis. IL-10 was evaluated in six studies^(14, 19, 20, 24, 25, 27). According to the results of half of them^(14, 24, 27), increased levels of IL-10 in OSCC patients seem to be related to poorer prognosis. IL-12 was evaluated in two studies^(13, 19). The results of these surveys showed that increased levels of IL-12 in patients with OSCC do not seem to be related to a poorer prognosis. IL-13 was evaluated in one study⁽²⁴⁾. High levels of IL-13 in patients with OSCC seem to be related to poorer prognosis.

DISCUSSION

We sought to verify the general role of IL in the carcinogenesis process, correlating its actions with the prognosis of patients with OSCC. According to the results of the studies included in the present review, it was noticeable that most of the analyzed IL is associated with poor prognosis in patients with OSCC.

Immunosuppression in cancer patients is a well-established phenomenon and may include changes in cytokines and in the balance of immune cell populations⁽²⁸⁾. Helper T lymphocytes play a key role in controlling the immune response and are subdivided into T-helper 1 (Th1) and T-helper 2 (Th2). Their differences lie in synthesized mediators and induced responses. The Th1 lineage is responsible for promoting cell-mediated immunity and acting in anti-tumor pathways, secreting mediators, such as interferon- γ (IFN- γ), which activates macrophages, cytotoxic T lymphocytes and natural killer cells (NK). The Th2 lineage induces humoral response and is responsible for IL secretion, such as IL-4, which favors tumor progression by inhibiting mediators secreted by a Th1 cells^(29, 30). Functional imbalance between mediators secreted by Th1 and Th2, which favor IL secreted by Th2 cell lineages, was responsible for the progression of head and neck SCC⁽³¹⁾.

IL-4 presents antiangiogenic properties that may inhibit tumor progression⁽³²⁾. However, this same IL presents antiapoptotic property, which may help in the tumor's immune protection, besides favoring tumor growth⁽³³⁾. This dual action of IL-4 has influenced the increase of its levels and the poorer prognosis of patients with OSCC⁽²⁴⁾.

According to the results of the present review, increased IL-6 levels seem to be related to unfavorable prognosis in patients with OSCC. The relationship between lymphatic metastases and IL-6

TABLE 2 – General characteristics of the studies

Interleukins	Authors, year of publication and place of study	Type of study	Sample	Interleukin level disclosure method	Main outcome
IL-4	Oliveira <i>et al.</i> (2009) Brasil	Prospective	35 patients with OSCC (26 M and 9 F)	Tissue biopsy and immunohistochemistry	Increased levels of IL-4 do not seem to be associated with a poorer prognosis in patients with OSCC
	Mojtahedi <i>et al.</i> (2012) Irã	Cross sectional	87 patients (control group: 53; OSCC group: 34)	ELISA in blood samples	Increased levels of IL-4 do not seem to be associated with a poorer prognosis in patients with OSCC
	Aziz <i>et al.</i> (2015) Paquistão	Cross sectional	63 patients [51 M and 12 F (control group: 33; OSCC group: 30)]	ELISA in saliva samples	Increased levels of IL-4 seem to be associated with a poorer prognosis in patients with OSCC
IL-6	Oliveira <i>et al.</i> (2009) Brasil	Prospective	35 patients with OSCC (26 M and 9 F)	Tissue biopsy and immunohistochemistry	Increased levels of IL-6 do not seem to be associated with a poorer prognosis in patients with OSCC
	Sato <i>et al.</i> (2010) Japão	Prospective	48 patients [27 M and 21 F (control group: 19; OSCC group: 29)]	ELISA in saliva samples	Increased levels of IL-6 seem to be associated with a poorer prognosis in patients with OSCC
	Chang <i>et al.</i> (2013) Taiwan	Cross sectional	466 patients (control group: 125; pre-malignant lesions group: 104; OSCC group: 237)	ELISA in blood samples	Increased levels of IL-6 seem to be associated with a poorer prognosis in patients with OSCC
	Juretic <i>et al.</i> (2013) Croácia	Cross sectional	57 patients [31 M e 26 F (control group: 19; pre-malignant lesions group: 19; OSCC group: 19)]	ELISA in saliva samples	Increased levels of IL-6 seem to be associated with a poorer prognosis in patients with OSCC
	Skrinjar <i>et al.</i> (2015) Croácia	Prospective	67 patients [49 M and 18 F (control group: 31; OSCC group: 36)]	ELISA in saliva samples	Increased levels of IL-6 seem to be associated with a poorer prognosis in patients with OSCC
	Jinno <i>et al.</i> (2015) Japão	Cross sectional	78 patients with OSCC (52 M e 26 F)	Tissue biopsy and immunohistochemistry	Increased levels of IL-6 seem to be associated with a poorer prognosis in patients with OSCC
	Panneer e Sdaksharam (2015) Índia	Crss sectional	75 patients [63 M e 12 F (control group: 25; leukoplakia group: 25; OSCC group: 25)]	ELISA in saliva samples	Increased levels of IL-6 seem to be associated with a poorer prognosis in patients with OSCC
IL-8	Oliveira <i>et al.</i> (2009) Brasil	Prospective	35 patients with OSCC (26 M and 9 F)	Tissue biopsy and immunohistochemistry	Increased levels of IL-8 do not seem to be associated with a poorer prognosis in patients with OSCC
	Fujita <i>et al.</i> (2014) Japão	Cross sectional	58 patients [37 M and 21 F (control group: 8; OSCC group: 50)]	ELISA in blood samples	Increased levels of IL-8 seem to be associated with a poorer prognosis in patients with OSCC
	Rajkumar <i>et al.</i> (2014) Índia	Cross sectional	300 patients [204 M and 96 F (control group: 100; leukoplakia group: 50; submucous fibrosis group: 50; OSCC group: 100)]	ELISA in saliva and blood samples	Increased levels of IL-8 seem to be associated with a poorer prognosis in patients with OSCC

IL-10	Alhamarneh <i>et al.</i> (2011) Reino Unido	Cross sectional	61 patients (control group: 40; OSCC group: 21)	ELISA in blood samples	Increased levels of IL-10 do not seem to be associated with a poorer prognosis in patients with OSCC
	Green <i>et al.</i> (2012) Inglaterra	Cross sectional	61 patients (control group: 40; OSCC group: 21)	ELISA in blood samples	Increased levels of IL-10 do not seem to be associated with a poorer prognosis in patients with OSCC
	Mojtahedi <i>et al.</i> (2012) Irã	Cross sectional	87 patients (control group: 53; OSCC group: 34)	ELISA in blood samples	Increased levels of IL-10 do not seem to be associated with a poorer prognosis in patients with OSCC
	Chen <i>et al.</i> (2013) Taiwan	Retrospectivo	325 patients (252 M and 73 F)	Tissue biopsy and immunohistochemistry	Increased levels of IL-10 seem to be associated with a poorer prognosis in patients with OSCC
	Wang <i>et al.</i> (2014) China	Cross sectional	Group with OSCC: 240 (152 M and 88 F)	Tissue biopsy and immunohistochemistry	Increased levels of IL-10 seem to be associated with a poorer prognosis in patients with OSCC
	Aziz <i>et al.</i> (2015) Paquistão	Cross sectional	63 patients [51 M and 12 F (control group: 33; OSCC group: 30)]	ELISA in saliva samples	Increased levels of IL-10 seem to be associated with a poorer prognosis in patients with OSCC
IL-12	Oliveira <i>et al.</i> (2009) Brasil	Prospective	35 patients with OSCC (26 M and 9 F)	Tissue biopsy and immunohistochemistry	Increased levels of IL-12 do not seem to be associated with a poorer prognosis in patients with OSCC
	Green <i>et al.</i> (2012) Inglaterra	Cross sectional	61 patients (control group: 40; OSCC group: 21)]	ELISA in blood samples	Increased levels of IL-12 do not seem to be associated with a poorer prognosis in patients with OSCC
IL-13	Aziz <i>et al.</i> (2015) Paquistão	Cross sectional	63 patients [51 M and 12 F (control group: 33; OSCC group: 30)]	ELISA in saliva samples	Increased levels of IL-13 seem to be associated with a poorer prognosis in patients with OSCC

IL: interleukins; OSCC: oral squamous cell carcinoma; M: male; F: female; ELISA: enzyme linked immunosorbent assay.

TABLE 3 – Risk of specific individual bias for each type of study

Authors and year	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8		% yes/risk	Risk of bias		
Alhamarneh <i>et al.</i> (2011)	√	√	√	√	U	U	√	√		75%	+		
Green <i>et al.</i> (2012)	√	√	√	√	U	U	√	√		75%	+		
Mojtahedi <i>et al.</i> (2012)	U	√	√	√	U	U	√	√		62.5%	++		
Chang <i>et al.</i> (2013)	√	√	√	√	U	U	√	√		75%	+		
Chen <i>et al.</i> (2013)	√	√	√	√	U	U	√	√		75%	+		
Juretic <i>et al.</i> (2013)	√	√	√	√	U	U	√	√		75%	+		
Fujita <i>et al.</i> (2014)	U	√	√	√	U	U	√	√		62.5%	++		
Rajkumar <i>et al.</i> (2014)	√	√	√	√	U	U	√	√		75%	+		
Wang <i>et al.</i> (2014)	√	√	√	√	U	U	√	√		75%	+		
Aziz <i>et al.</i> (2015)	U	√	√	√	U	U	√	√		62.5%	++		
Jinno <i>et al.</i> (2015)	U	√	√	√	U	U	√	√		62.5%	++		
Panner and Sadaksharam (2015)	√	√	√	√	U	U	U	√		75%	+		
Authors and year	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Q.9	Q.10	Q.11	% yes/risk	Risk of bias
Oliveira <i>et al.</i> (2009)	√	√	√	--	--	--	√	U	U	U	√	45.4%	+++
Sato <i>et al.</i> (2010)	--	√	√	--	--	--	√	U	U	U	√	36.3%	+++
Skrinjar <i>et al.</i> (2015)	--	√	√	--	--	--	√	√	U	U	√	45.4%	+++

Cross-sectional studies – Q.1: were the inclusion criteria of the sample clearly defined? Q.2: was the methodological structure of the studies described in detail? Q.3: has exposure been measured validly and reliably? Q.4: were the criteria used to measure the condition objective? Q.5: were confounders factors identified? Q.6: were strategies approached to address the confounders factors identified? Q.7: were the results measured validly and reliably? Q.8: was proper statistical analysis used?

Cohort studies – Q.1: were the two groups similar and recruited in the same population? Q.2: were exposures measured similarly to assign people to exposed and unexposed groups? Q.3: has exposure been measured validly and reliably? Q.4: were the confounders factors identified? Q.5: were strategies addressed to deal with the confounders factors identified? Q.6: were the groups/participants free of the outcome at the beginning of the study (or at the time of exposure)? Q.7: were the results measured validly and reliably? Q.8: has the follow-up time been reported and sufficient for the results to occur? Q.9: was follow-up complete and otherwise the reasons for loss of follow-up were described and explored? Q.10: have strategies been implemented to address incomplete follow-up? Q.11: was proper statistical analysis used?

√: yes; --: no; U: uncertain; NA: not applicable; +++: high; ++: moderate; +: low.

occurs by stimulating lymph vessel proliferation by signaling the expression of vascular endothelial growth factor C (VEGF-C), which is regulated by the PI3K-Akt pathway and stimulated by IL-6R signaling. IL-6 binding to IL-6R initiates gp130 homodimerization and triggers signaling cascades via the JAK-STAT, Ras-MAPK and PI3K-Akt pathways; which is essential for the regulation of VEGF-C messenger ribonucleic acid (RNAm) expression by IL-6 in tumor cells, favoring both the development of lymphatic metastases and the poorer prognosis of the disease⁽³⁴⁾. Gp130 homodimerization and activation of signaling cascades, in one sample study, were related to constitutive activation of signal transducers and activators of transcription (STAT3) as a contributing factor to the carcinogenesis process in a variety of malignancies. The authors also observed the association with IL-6, showing that STAT3 activation occurred between IL-6 and IL-6R in the tumor microenvironment, showing us that high cytokine expression was positively correlated with tumor progression and poorer prognosis⁽²³⁾.

A study⁽³⁵⁾ evaluated the polymorphisms expression of matrix metalloproteinase-1 (MMP-1) and IL-8 in tongue SCC; the data from this research suggest that these proteins are not strongly associated with the carcinogenesis process of this pathology, although they may contribute during the progression of this neoplastic lesion through positive regulation of the gene for MMP-1 and IL-8. Metalloproteinases act as a tool for tumor growth, either modulating the extracellular matrix, or regulating the release of growth factors and/or inducing angiogenesis⁽³⁶⁾. MMP-1 was involved in the degradation process of type I collagen, favoring tumor invasion and metastasis⁽³⁷⁾.

A study verified the presence of two receptors (IL-8A and IL-8B) for IL-8 in head and neck SCC, and receptor type A was related to poorer prognosis⁽³⁸⁾. Receptor A is specific for IL-8, whereas several cytokines also present affinity for receptor type B⁽³⁵⁾. Therefore, these authors suggest a positive relationship between IL-8 and tumor lesion progression together with the metastasis process.

In the research of one of the studies selected for this review⁽²²⁾, 27 out of 50 sample components were in an early stage (stage I/II) of OSCC, presented lower serum levels of IL-8 and tended to survive longer when compared to individuals at more advanced stages (stage III/IV) and with higher serum levels of this IL. It is possible that the presence of increased levels of IL-8 leads to poor prognosis through the generation and activation of M2 macrophages, which also secrete IL-8 and VEGF-C – proteins that enhance angiogenesis in the tumor environment

and favor tumor expansion⁽³⁹⁾. Furthermore, the authors of this research⁽²²⁾, through in vitro results, assume that the increase in M2 macrophage generation may cause an unfavorable clinical outcome through the secretion of IL-10, an immunosuppressive cytokine.

The main source of IL-10 is tissue macrophages, as well as their synthesis may occur through T lymphocytes, B lymphocytes, mast cells, eosinophils and keratinocytes⁽⁴⁰⁾. This interleukin regulates the differentiation and proliferation of immune cells, as well as contributes to immune evasion of anti-tumor immunity by interfering with regulation of Class I major histocompatibility complex (MHC) expression or inhibition of T cell activation and function⁽⁷⁾. According to results from two studies^(14, 27), high levels of IL-10 seem to be related to poorer prognosis of OSCC. IL-10 induces a polarized M2 phenotype and inhibits the synthesis of proinflammatory cytokines, such as IFN- γ and tumor necrotic factor alpha (TNF- α), which favor the emergence of local immunosuppression and allow tumor progression⁽⁴¹⁾.

Although evidence reinforces the role of IL-10 in tumor progression, studies^(19, 25) have shown results contrary to this statement. According to data from these studies, there was no significant difference in IL-10 levels between patients with OSCC and the control group, nor influence on prognosis and survival time. These results were opposite when the carcinoma site was located in another region of the head and neck. Thus, some authors suggest that there may be specificity in the profile of the tumor immune response correlated with the primary site of SCC development⁽¹⁹⁾.

Generally, tumor growth is associated with the ability to evade the attack instituted by the host immune system. In the carcinogenesis process, there is a change in immune function between Th1 and Th2 cells, which favors the immunosuppressive response Th2 cell-mediated, and stimulates tumor progression⁽³⁰⁾. One of the possible determinants for functional dysregulation between these two cell lineages involves the IL imbalance participating in the integration of their functions⁽⁴²⁾. A study found that after administration of IL-12 in the intratumoral region, there was increased expression of the immune response through Th1 cells⁽⁴³⁾. In addition, another study found longer survival time in patients with higher IL-12 expression in tumor tissue⁽⁴⁴⁾. Therefore, it is assumed that the performance of this IL in a tumor environment may increase the survival time⁽¹⁹⁾.

Among the studies included in this review, only one evaluated the role of IL-13 in the carcinogenesis process, which

was associated with poorer prognosis in patients with OSCC⁽²⁴⁾. IL-13 may inhibit IFN- γ secretion and cytotoxic T lymphocyte activity, thus hindering the action of the anti-tumor immune response⁽⁴⁵⁾. IL-13 aids tumor cell defense against immune response, also acts as an autocrine growth factor and stimulates tumor progression, metastasis and antiapoptotic response in some malignant neoplasms⁽²⁴⁾.

REFERENCES

1. Johnson NW, Jayasekara P, Amarasinghe HK. Squamous cell carcinoma and precursor lesions of the oral cavity: epidemiology and aetiology. *Periodontol.* 2000; 57(1): 19-37.
2. Rivera C, Venegas B. Histological and molecular aspects of oral squamous cell carcinoma (Review). *Oncol Lett.* 2014; 8(1): 7-11.
3. Dissanayaka WL, Pitiyage G, Kumarasiri PVR, et al. Clinical and histopathologic parameters in survival of oral squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2012; 113(4): 518-25.
4. Bauer T, Göhlmann S, Sinning M. Gender differences in smoking behavior. *Health Econ.* 2007; 16(9): 895-909.
5. Varsha BK, Radhika MB, Makarla S, et al. Perineural invasion in oral squamous cell carcinoma: case series and review of literature. *J Oral Maxillofac Pathol.* 2015; 19(3): 335-41.
6. Gleeson M. Interleukins and exercise. *J Physiol.* 2000; 1(1): 529.
7. Woods KV, Storz KA, Clayman GL, et al. Interleukin-1 regulates interleukin-6 secretion in human oral squamous cell carcinoma in vitro: possible influence of p53 but not human papillomavirus E6/E71. *Cancer Res.* 1998; 58(14): 3142-9.
8. Matsuda M, Salazar F, Petersson M, et al. Interleukin 10 pretreatment protects target cells from tumor- and allo-specific cytotoxic T cells and downregulates HLA class I expression. *J Exp Med.* 1994; 180(6): 2371-6.
9. Lotfi A. Serum level of interleukin-6 in patients with oral tongue squamous cell carcinoma. *Iran J Otorhinolaryngol.* 2015; 27(80): 207-11.
10. Rhodus NL, Ho V, Miller CS, et al. NF- κ B dependent cytokine levels in saliva of patients with oral preneoplastic lesions and oral squamous cell carcinoma. *Cancer Detect Prev.* 2005; 29(1): 42-5.
11. Lin L, Wang J, Liu D, et al. Interleukin-37 expression and its potential role in oral leukoplakia and oral squamous cell carcinoma. *Sci Rep.* 2016; 6(26): 757.
12. Joanna Briggs Institute. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews. Checklist for Randomized Controlled Trials. 2017. Available at: <http://joannabriggs.org/research/critical-appraisal-tools.html>.
13. Oliveira MV, Fraga CAC, Gomez RS, et al. Immunohistochemical expression of interleukin-4, -6, -8, and -12 in inflammatory cells in surrounding invasive front of oral squamous cell carcinoma. *Head Neck.* 2009; 31(11): 1439-46.
14. Wang S, Sun M, Gu C, et al. Expression of CD163, interleukin-10, and interferon-gamma in oral squamous cell carcinoma: mutual

CONCLUSION

According to the results of the studies selected for this systematic review, IL-4, IL-6, IL-8, IL-10 and IL-13 tend to present a response related to the intensification of the carcinogenesis process, whereas increased IL-12 levels were not associated with an unfavorable prognosis in patients with OSCC.

relationships and prognostic implications. *Eur J Oral Sci.* 2014; 122: 202-9.

15. Juretic M, Cerovic R, Belušić-Gobić V, et al. Salivary levels of $\text{tnf-}\alpha$ and il-6 in patients with oral premalignant and malignant lesions. *Folia Biol.* 2013; 59(2): 99-102.
16. Skrinjar I. Evaluation of pretreatment serum interleukin-6 and tumour necrosis factor alpha as a potential biomarker for recurrence in patients with oral squamous cell carcinoma. *Med Oral Patol Cir Bucal.* 2015; 20(4): 402-7.
17. Rajkumar K. 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. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2014; 118(3): 309-19.
18. Panneer SN, Sadaksharam J. Salivary interleukin-6 in the detection of oral cancer and precancer. *Asia Pac J Clin Oncol.* 2015; 11(3): 236-41.
19. Green V, Irune E, Prasai A, et al. Serum IL10, IL12 and circulating CD4+CD25 high T regulatory cells in relation to long-term clinical outcome in head and neck squamous cell carcinoma patients. *Int J Oncol.* 2012; 40(3): 833-9.
20. Mojtahedi Z, Khademi B, Yehya U, et al. Serum levels of interleukins 4 and 10 in head and neck squamous cell carcinoma. *Laryngol Otol.* 2012; 126(2): 175-9.
21. Sato J. Changes in saliva interleukin-6 levels in patients with oral squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2010; 110(3): 330-6.
22. Fujita Y, Okamoto M, Goda H, et al. Prognostic significance of interleukin-8 and CD163-positive cell-infiltration in tumor tissues in patients with oral squamous cell carcinoma. *PLoS One.* 2014; 9(12): 103-78.
23. Jinno T, Kawano S, Maruse Y, et al. Increased expression of interleukin-6 predicts poor response to chemoradiotherapy and unfavorable prognosis in oral squamous cell carcinoma. *Oncol Rep.* 2015; 33(5): 2161-8.
24. Aziz S. Salivary immunosuppressive cytokines IL-10 and IL-13 are significantly elevated in oral squamous cell carcinoma patients. *Cancer Invest.* 2015; 33(7): 318-28.
25. Alhamarneh O, Agada F, Madden G, et al. Serum IL 10 and circulating CD(+) CD25(high) regulatory t cell numbers as predictors of clinical outcome and survival in patients with head and neck squamous cell carcinoma. *Head Neck.* 2011; 33(3): 415-23.
26. Chang KP, Kao HK, Wu CC, et al. Pretreatment interleukin-6 serum levels are associated with patient survival for oral cavity squamous cell carcinoma. *Otolaryngol Head Neck Surg.* 2013; 148(5): 786-91.

27. Chen CJ, Sung WW, Su TC. High expression of interleukin 10 might predict poor prognosis in early stage oral squamous cell carcinoma patients. *Clin Chim Acta.* 2013; 415: 25-30.
28. Jebreel A, Mistry D, Loke D, et al. Investigation of interleukin 10, 12 and 18 levels in patients with head and neck cancer. *J Laryngol Otol.* 2007; 121(3): 246-52.
29. Salazar-Onfray F, Lopez MN, Mendoza-Naranjo A. Paradoxical effects of cytokines in tumor immune surveillance and tumor immune escape. *Cytokine Growth Factor Rev.* 2007; 18: 171-82.
30. Agarwal A, Agrawal U, Verma S, et al. Serum Th1 and Th2 cytokine balance in patients of superficial transitional cell carcinoma of bladder pre- and post-intravesical combination immunotherapy. *Immunopharmacol Immunotoxicol.* 2010; 32(2): 348-56.
31. Hoffmann TK, Sonkoly E, Homey B, et al. Aberrant cytokine expression in serum of patients with adenoid cystic carcinoma and squamous cell carcinoma of the head and neck. *Head Neck.* 2007; 29(5): 472-8.
32. Volpert OV, Fong T, Koch AE, et al. Inhibition of angiogenesis by interleukin 4. *J Exp Med.* 1998; 188(6): 1039-46.
33. Conticello C, Pedini F, Zeuner A, et al. IL-4 protects tumor cells from anti-CD95 and chemotherapeutic agents via up-regulation of antiapoptotic proteins. *J Immunol.* 2004; 172(9): 5467-77.
34. Shinriki S, Jono H, Ueda M, et al. Interleukin-6 signalling regulates vascular endothelial growth factor-C synthesis and lymphangiogenesis in human oral squamous cell carcinoma. *J Pathol.* 2011; 225(1): 142-50.
35. Shimizu Y, Kondo S, Shirai A, et al. A single nucleotide polymorphism in the matrix metalloproteinase-1 and interleukin-8 gene promoter predicts poor prognosis in tongue cancer. *Auris Nasus Larynx.* 2008; 35(3): 381-9.
36. Nelson AR, Fingleton B, Rothenberg ML, Matrisian LM. Matrix metalloproteinases: biologic activity and clinical implications. *J Clin Oncol.* 2000; 18(5): 1135-49.
37. Rigel DS, Friedman RJ, Kopf AW, Silverman MK. Factors influencing survival in melanoma. *Dermatol Clin.* 1991; 9(4): 631-42.
38. Horikawa T, Kaizaki Y, Kato H, et al. Expression of interleukin-8 receptor A predicts poor outcome in patients with nasopharyngeal carcinoma. *Laryngoscope.* 2005; 115(1): 62-7.
39. Tartour E, Pere H, Maillere B, et al. Angiogenesis and immunity: a bidirectional link potentially relevant for the monitoring of antiangiogenic therapy and the development of novel therapeutic combination with immunotherapy. *Cancer Metastasis Rev.* 2011; 30(1): 83-95.
40. Asadullah K, Sabat R, Wiese A, et al. Interleukin-10 in cutaneous disorders: implications for its pathophysiological importance and therapeutic use. *Arch Dermatol Res.* 1999; 291(12): 628-36.
41. Allavena P, Garlanda C, Borrello MG, et al. Pathways connecting inflammation and cancer. *Curr Opin Genet Dev.* 2008; 18(1): 3-10.
42. Mosser DM, Zhang X. Interleukin-10: new perspectives on an old cytokine. *Immunol Rev.* 2008; 226: 205-18.
43. Van Herpen CM, Looman M, Zonneveld M, et al. Intratumoural administration of recombinant human interleukin-12 in head and neck squamous cell carcinoma patients elicits a T-helper 1 profile in the locoregional lymph nodes. *Clin Cancer Res.* 2004; 10(8): 2626-35.
44. Paleri V, Pulimood A, Davies GR, Birchall MA. Interleukins 7 and 12 are expressed in head and neck squamous cancer. *Clin Otolaryngol Allied Sci.* 2001; 26(4): 302-6.
45. Terabe M, Matsui S, Noben-Trauth N, et al. NKT cell mediated repression of tumor immunosurveillance by IL-13 and the IL-4R-STAT6 pathway. *Nat Immunol.* 2000; 1(6): 515-20.

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