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REVIEW ARTICLE

Possible association of periodontal disease with oral cancer and oral potentially malignant disorders: a systematic review

Adriana Colonia-García[a], Mariana Gutiérrez-Vélez[b], Andrés Duque-Duque[b] and Cleverton Roberto de Andrade[c]

[a]School of Dentistry, São Paulo State University (UNESP), Araraquara, Brazil; [b]Basic and Clinical Dentistry Group, School of Dentistry, CES University, Medellín, Colombia; [c]Department of Physiology and Pathology, School of Dentistry, São Paulo State University (UNESP), Araraquara, Brazil

ABSTRACT

Background: Periodontitis has been associated with several systemic diseases and medical conditions, including oral cancer (OC). However, most studies reporting an association between OC and periodontal disease have used different clinical and radiographic criteria to define periodontal disease. This review aimed to evaluate the currently available evidence to determine an association between periodontal disease (extension and severity), OC, and oral potentially malignant disorders (OPMDs).

Material and methods: A systematic search of studies published up to August 2018 was performed following the PRISMA guidelines in the electronic databases MEDLINE (PubMed) and COCHRANE (OVID). A methodological evaluation was made using the *Strengthening the Reporting of Observational studies in Epidemiology* (STROBE) checklist.

Results: Eight studies (case-control, cross-sectional and cohort) were included. An increased clinical attachment loss, plaque index, bleeding on probing, and radiographic bone loss was found in patients with OC and OPMDs. Differences in the methodological characteristics, case definition used for periodontal diseases, and OC location did not allow estimating the odds ratio required to conduct a meta-analysis.

Conclusion: Some studies suggest a positive relationship between periodontal disease, OC, and OPMDs; however, the currently available evidence is insufficient to draw solid conclusions.

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KEYWORDS
Oral cancer; oral potentially malignant disorders; periodontal diseases; periodontitis

Introduction

Over the past decade, an alarming increase in cancer incidence has been reported. In 2018, GLOBOCAN reported a total of 18 million new cases of cancer and 9.5 million cancer-related deaths globally [1]; nearly more than 4 million new cases and 1.5 million related deaths compared to those reported in 2012 [2]. Oral cancer (OC) is the 18th most common type of cancer [1], being oral squamous cell carcinoma (OSCC) the most frequently encountered histologic subtype, accounting for up to 94% of the cases [3].

Chronic inflammation has been associated with carcinogenesis since Virchow first postulated in the 19th century that chronic inflammation might predispose to cancer development [4]. Indeed, several clinical and epidemiological studies have suggested an association between inflammation and different types of cancer [3,4]. In humans, 15%–20% of the tumours initiate with an inflammatory process [5], and inflammatory molecules have been shown to activate growth signalling and to promote malignant cell proliferation [4].

Periodontal disease is an inflammatory condition that affects the tooth-supporting structures [6]. The Global Burden of Disease (GBD, 1990–2010) study reported that severe periodontitis is the sixth most common disease worldwide, with a prevalence of 11.2% [7]. The incidence rate of chronic periodontitis (CP) increases with age, and similarly, OC affects people typically over 40 years of age [8]. In patients with concomitant CP and OC, the tumour microenvironment is likely exposed to pro-inflammatory molecules and numerous periodontal pathogenic bacteria. Thus, CP has been suggested to be involved in the modulation of neoplastic cells [9]. A link between cancer and the inflammatory response caused by different microorganisms has also been proposed [10]. Besides, *in vitro* studies suggest that *Porphyromonas gingivalis*—a Gram-negative oral anaerobe involved in the pathogenesis of CP—increases tumour aggressiveness and invasion potential. However, the exact molecular mechanisms linking CP to OC remain to be elucidated [9,11].

To date, CP has been associated with several systemic diseases and medical conditions, including cardiovascular diseases, diabetes mellitus, preterm labour, and low birth weight [12]. More recently, CP has been linked to various types of cancer, including oral cancer [13,14]. However, most studies reporting an association between periodontal disease and OC have not used a standardized clinical and radiographic criteria to diagnose periodontal disease. For instance, a recent systematic review that assessed the association

CONTACT Adriana Colonia-García acolonia@ces.edu.co School of Dentistry, São Paulo State University (UNESP), Araraquara 01049-010, Brazil
Supplemental data for this article can be accessed here.

between periodontal disease and OC used inaccurate diagnostic criteria for the former condition, such as tooth loss and level of oral hygiene [14]. In this review, we have used additional diagnostic criteria to determine the extent and severity of periodontal disease: clinical attachment loss (CAL), plaque index (PI), bleeding on probing (BOP), probing depth (PD), and radiographic bone loss (RBL) [15]. In addition to clinical and radiographic criteria, salivary biomarkers have also been used to investigate the association between periodontal disease and OC and oral potentially malignant disorders (OPMDs) [16].

The purpose of this systematic review was to evaluate the currently available evidence on the association between periodontal disease and OC and OPMDs. Briefly, we addressed the following question: is there a relationship between periodontal status and OC and OPMDs?

Materials and methods

Protocol and registration

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist [17]. The protocol was registered in the International prospective register of systematic reviews (PROSPERO), under the registration number 74314.

Study selection

Studies meeting the following criteria were included in the analysis:

- Observational (descriptive and analytical) studies in humans; retrospective, prospective, and cross-sectional studies that evaluated the odds of developing OC and OPMD by comparing healthy individuals with patients diagnosed with periodontal disease.
- Studies that have been published between January 2000 and August 2018.
- Studies that have been written in English or Spanish language.

Studies were excluded when:

- The diagnostic criteria used for periodontal disease, OC, and OPMDs were not clearly described.

Eligibility criteria for study participants

Individuals with periodontal disease of any age and gender participating in studies meeting the above-described inclusion criteria were considered eligible.

Types of exposure

- Periodontally healthy patients
- Patients with gingivitis (Plaque index = PI, Gingival index = GI)
- Patients with chronic periodontitis (CAL, BOP, PD, and RBL).

Information sources and search strategies

Electronic literature searches using the following search string were performed in the databases MEDLINE (PubMed) and COCHRANE (OVID): Periodontal diseases AND ('Mouth Neoplasms' [Mesh] OR 'oral cancer'). Also, a manual search for publications referenced on the identified articles was conducted.

Literature selection and data extraction protocol

Titles and abstracts yielded by the searches were independently screened by two of the authors (ACG and MGV). Full-texts were obtained from those studies meeting the inclusion criteria. Disagreements were resolved by discussion between the two reviewers or settled by a third author (ADD).

Variable registration

Once the included studies were selected, the data corresponding to the variables of interest were tabulated in a Microsoft Excel spreadsheet.

Summary of outcome measures

Primary outcome:

- Prevalence of OC and OPMDs.

Secondary outcomes:

- Mortality.
- Quality of life or life satisfaction.
- Adverse events.

Risk of bias assessment in single studies

A methodological evaluation of each article was performed using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist [18]. The studies were awarded one point for each criterion met and further classified as low risk of bias (20–22 points), moderate risk of bias (15–19 points), and high risk of bias (less than 15 points) [19].

The items in the STROBE checklist for observational studies were scored in 6 blocks (title and abstract, introduction, methods, results, discussion, and other information), and given a final score that ranged from 5 to 22 points. Besides, a traffic-light system (green: meets all criteria; yellow: criteria lacks clarity; red: does not meet criteria) was used to identify the most relevant criteria of the STROBE checklist regarding methodological quality [20].

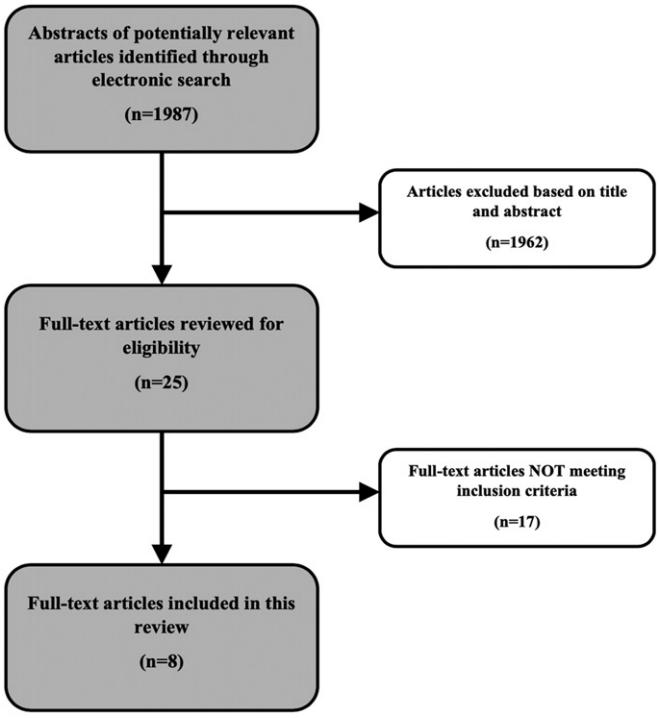

Figure 1. Flowchart of the study selection process.

Results

Study selection

The systematic search of the electronic databases identified 1,987 articles. After title and abstract screening, 1,962 studies were excluded, and full texts of the remaining 25 studies were evaluated. Of these, 17 were further excluded: nine because they did not report the parameters used for periodontal disease diagnosis; two because they were *in vitro* studies; two because they did not describe which of the reported cancer cases were OC; two because they measured salivary biomarkers in biopsies; and two studies due to methodological inconsistencies when applying the STROBE checklist (Figure 1 and Supplementary Appendix 1). Thus, eight studies were included in this review (Table 1).

Characteristics of the selected studies

Among the included studies, six were case-control studies, one was a cohort study, and one was a cross-sectional study. The studies were published between 2005 and 2016. A total of 168,967 individuals participated in these studies. Sample sizes ranged from 40 to 153,566 individuals. The age of the participants ranged from 20 to 87 years at the time of data collection.

According to the STROBE checklist, the risk of bias was classified as low for six studies [13,21–25], and moderate for two studies [16,25] (Supplementary Appendix 2). Regarding the traffic light system, the criteria related to the sample size calculation lacked clarity (yellow light) or were not met (red light) in all the included studies [13,16,21–26] (Figure 2).

Summary of results

The eight studies included agreed on the possible relationship between periodontal disease, OC, and OPMDs. However, differences in the methodological characteristics (Figure 2), case definition used for periodontal disease, and oral cancer location were identified. Therefore, the current evidence is weak to support an association [13,16,21–26] between periodontal disease, OC, and OPMDs. We were unable to estimate the odds ratio required to perform a meta-analysis, and thus a connection between the prevalence of OC and OPMDs in patients with periodontal disease could not be established.

Relationship between bleeding on probing, oral cancer, and oral potentially malignant disorders

One study [21] found a BOP of 25.9% and 18.6% in patients with and without OC, respectively. However, this difference was not statistically significant. Another study [23] reported a BOP of 46% and 35% in patients with and without leukoplakia, respectively. The authors also reported that a greater BOP increased the risk of leukoplakia in a dose-dependent manner (adjusted to socioeconomic factors and smoking) as follows: calculated OR for the second quartile was 2.0 (CI 0.8–4.90), for the third quartile was 2.9 (CI 1.1–7.8), and for the fourth quartile was 3.8 (CI 1.5–9.8).

Relationship between plaque index, oral cancer, and oral potentially malignant disorders

A significant difference in PI (presence or absence of bacterial plaque on four surfaces per tooth) was found between patients with OC (34.7%) and controls (23.1%) [21].

Relationship between clinical attachment loss, oral cancer, and oral potentially malignant disorders

Patients with CAL ($>$1.5 mm) exhibited an increased risk of malignant tumours (OR 4.57; CI 2.25–9.30) or precancerous lesions (OR 1.55; CI 1.06–2.27) [24]. A dose-dependent response between CAL and the probability of having leukoplakia has also been shown [23]. Patients with leukoplakia displayed more sites with an insertion loss $\geq$4mm (35%) than those without leukoplakia (20%). Similarly, Moraes et al. [21] reported that patients with oral or oropharyngeal cancer had more sites with CAL 4–5 mm (44.5%) and CAL $\geq$6mm (29.0%) than the control group (patients without cancer) (16.1% with CAL 4–5 mm and 9.4% with CAL $\geq$6mm). Altogether, these data suggest that patients with OC or OPMDs exhibited a higher insertion loss than the controls.

Relationship between periodontal disease, salivary biomarkers, oral cancer, and oral potentially malignant disorders

Sharma et al. [16] reported significantly increased levels of salivary IL-6 in patients with concomitant periodontitis and leukoplakia (414.94 ± 36.69 pg/ml) compared to those with

Table 1. Characteristics of the included studies.

Reference	Country	Type of study	Sample size (subjects)	Oral cancer or oral potentially malignant disorder	Evaluated parameters	Reported results
Rosenquist et al. [22]	Sweden	Case-control	452	OSCC and OPSCC	Education and civil status; medical history and use of medications; oral hygiene; oral health status; panoramic x-ray; oral mucosal lesions; oral sex habits; HPV infection; cigarette use; alcohol intake	No association was identified between marginal bone loss (determined by panoramic x-rays) and OPSCC after adjusting for tobacco and alcohol use. Individuals with poor plaque control had greater risk of presenting OSCC. No association between OPSCC and gingival index or RBL was identified.
Tezal et al. [24]	United States of America	Cross- sectional	13798	Non-specific tumour, pre-cancerous lesion, any soft tissue lesion	CAL (>1.5mm); dental caries (>1 tooth); prosthesis (present); dental fillings (>8 teeth); tobacco use	Periodontal disease was defined as CAL ≥1.5 mm. Insertion loss and tobacco smoking was related to the presence of tumours (OR = 4.77; 95% CI: 2.25–9.30), and pre-cancerous lesions (OR = 1.5; 95% CI: 1.06–2.27).
Tezal et al. [13]	United States of America	Case-control	105	OTSSC	Alveolar bone loss (mm); decayed teeth; filled teeth; crowns per tooth; root canal treatments per tooth; missing teeth; alveolar bone loss in cases and controls; stratified smoking status	Each mm of alveolar bone loss was associated with a 5.23-fold increased risk of tongue cancer (CI 95%: 2.64–10.45). Positive correlation between bone loss and squamous cell carcinoma, independent of smoking habits.
Tezal et al. [26]	United States of America	Case-control	473	OSCC, OPSCC and larynx cancer	Age at diagnosis; sex; race/ethnicity; marital status; smoking status; alcohol use; alveolar bone loss; number of missing teeth	Each mm of alveolar bone loss was associated with a 4-fold increased risk of HNSCC (adjusted OR = 4.36; CI: 3.16–6.01). The association was stronger for OSCC (OR = 4.52; CI: 3.03–6.75), followed by OPSCC (OR = 3.74; CI: 2.54–5.22) and larynx cancer (OR = 2.72; CI: 1.78–4.16). A positive correlation between smoking status and bone loss with HNSCC. No significant association was found between history of periodontitis and tumour stage and differentiation.
Sharma et al. [16]	India	Case-control	40	Oral leukoplakia	Salivary IL-6; smoking habits; presence or absence of leukoplakia and periodontal disease	The presence of periodontitis (with or without leukoplakia), and tobacco habits were significantly associated with increased levels of IL-6. Increased levels of IL-6 were correlated with increased grades of dysplasia. Higher levels of IL-6 were found in patients with concomitant periodontitis and leukoplakia, compared to patients with periodontitis (without leukoplakia), and to healthy patients.
Meisel et al. [23]	Germany	Case-control	348	Oral leukoplakia	Education level; frequency of dental visits; denture wearing in the upper/lower jaw; monthly income; BMI; alcohol intake, smoking habits	Risk of leukoplakia was higher with increased BOP, being the fourth quartile of BOP the one associated with the highest risk of leukoplakia (OR = 3.52; CI: 1.45–8.51) even after adjusting for smoking. Despite being associated, the correlation between insertion loss and the risk of leukoplakia attenuated after adjusting for smoking.
Wen et al. [25]	Taiwan	Retrospective cohort	153566	OSCC and other types of cancer such as pharyngeal, oesophageal, stomach, colon, pancreas, larynx, lung, breast, uterus, prostate, bladder, kidney, thyroid, and haematologic.	Type of cancer; age; sex; diabetes; hypertension; hyperlipidaemia	Cancer IRR was higher in patients with periodontitis (IRR = 1.14; CI: 1.11–1.17) than in those with gingivitis. The adjusted HR (1.05; CI: 1.00–1.11) was not significant. Patients with periodontitis exhibited greater risk of developing OC (adjusted HR 1.79; CI: 1.42–2.25) compared to those with gingivitis. Females presented a higher adjusted HR (2.23; CI: 1.18–4.23). This study did not include a control group (patients without periodontal disease).
Costa de Moraes et al. [21]	Brazil	Case-control	75	Tumours of the floor of the mouth, gingival border, palate, base of tongue, lateral border of tongue tonsils, oropharynx epiglottis	Extent and severity of periodontal disease; tobacco and alcohol use	The prevalence of generalised CP among patients with OSCC or OPSCC was 80%, compared to 25% in the control group. Severe CP was found in 88.6% of cases and 32.5% of controls ($p < .05$). The extent and severity of periodontal disease was a risk factor for OSCC and OPSCC, even after adjusting for alcohol and tobacco use.

OSCC: oral squamous cell carcinoma; OPSCC: oropharyngeal squamous cell carcinoma; HPV: human papillomavirus; RBL: radiographic bone loss; OTSCC: oral tongue squamous cell carcinoma; HNSCC: head and neck squamous cell carcinoma; BMI: body mass index; IRR: incidence rate ratio; HR: hazard ratio; OC: oral cancer; CP: chronic periodontitis.

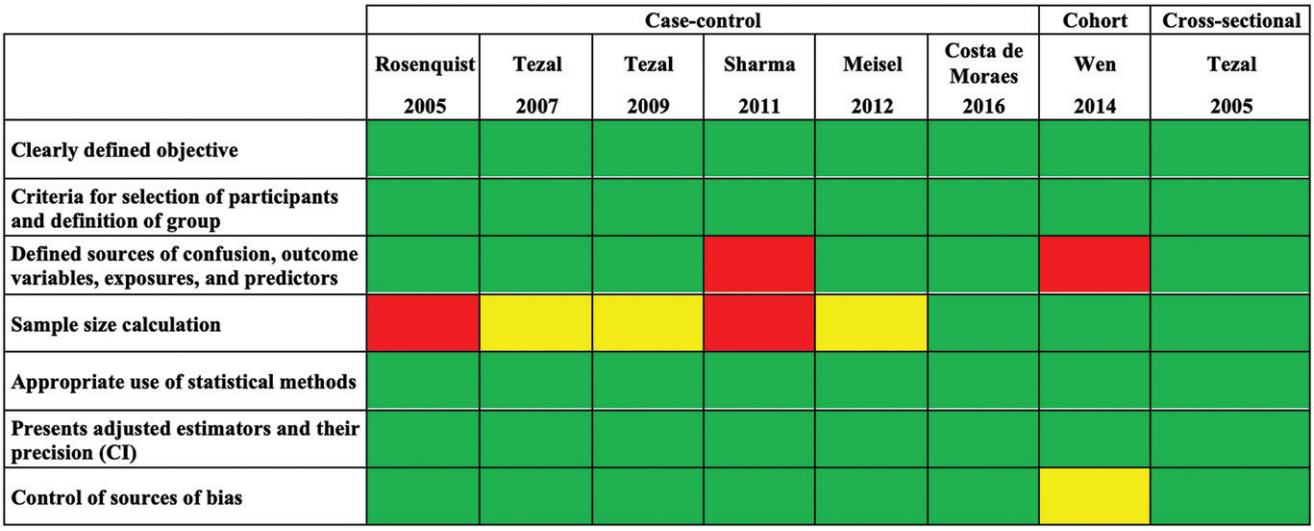

Figure 2. Most relevant items in the STROBE checklist regarding the methodological quality of the included studies (Green: meets all criteria; Yellow: criteria lack clarity; Red: does not meet criteria).

periodontitis but without leukoplakia (311.35 ± 11.51 pg/ml), and to healthy patients (17.15 ± 8.44 pg/ml).

Relationship between radiographic bone loss, oral cancer, and oral potentially malignant disorders

Some studies [13,21,26] used bone loss measured in panoramic radiographs as the criterium to determine the extent and severity of periodontal disease. No relationship between marginal bone loss and the presence of oropharyngeal squamous cell carcinoma (OPSCC) was found in one of these studies (OR 3.0; 95% CI 1.0–8.7) [22], nor after adjusting for alcohol and tobacco use. In contrast, Tezal et al. [13] reported $a > 5$-fold increased risk (OR 5.23; CI 2.64–10.45) of presenting oral tongue squamous cell carcinoma (OTSCC) for each mm of bone loss. The same group of authors later reported $a > 4$-fold increased risk of head and neck squamous cell carcinoma (HNSCC) for each mm of bone loss (adjusted OR 4.36; CI 3.16–6.01) [26]. This association was stronger for the oral cavity (OR 4.52; CI 3.03–6.75), followed by the oropharynx (OR 3.74; CI 2.54–5.22) and the larynx (OR 2.72; CI 1.78–4.16).

Relationship between periodontal disease, oral cancer location and stage, and oral potentially malignant disorders

In patients with concomitant periodontal disease and OC, the most prevalent type of OC was OTSCC, which was found in 22% ($n = 132$) of the patients (stage I, $n = 12$; stage II, $n = 6$; stage III, $n = 6$, stage IV, $n = 5$) [22]. Nineteen per cent of these patients presented floor of the mouth cancer (stage I, $n = 6$; stage II, $n = 11$; stage III, $n = 1$; stage IV, $n = 7$). Another study [21] reported that 36% of the patients in the case group (periodontal disease) had tongue cancer (21% in the lateral border and 15% in the base) and 12% had floor of the mouth cancer. Of the total number of cases ($n = 35$), 3% were classified as stage I, 19% as stage II, 34% as stage III, and 44% as stage IV. Additionally, Tezal et al. [26] reported that 67.2% of the patients with periodontitis presented with well to moderately differentiated OSCC and 32.8% with poorly differentiated OSCC. Among patients with periodontitis and OSCC, 44.4% were classified as stage 0–II and 55.6% as stage III–IV.

Wen et al. [25] reported the incidence rate ratio and adjusted hazard ratio of cancer sub-divisions among patients in different stages of periodontal disease. The authors showed that patients with periodontitis exhibited the highest risk of developing oral cancer (adjusted HR 1.79; 95% CI 1.42–2.25) and a significantly lower oral cancer-free rate compared to patients with gingivitis.

Discussion

In recent years, the incidence of OC has increased significantly. Despite improved early detection and treatment strategies, the prognosis of patients with oral malignancies is still poor. The 5 year survival rate of OC is approximately 50%, being one of the lowest amongst all types of cancer [27]. This low rate is mainly due to late diagnosis since most of the patients with OC seek medical help in advanced stages (III and IV) [16,21,26]. Therefore, early diagnosis and treatment are essential to improve survival rates and quality of life in patients with OC [28]. The majority of oral malignant tumours derives from OPMDs such as erythroplakia, leukoplakia, and oral lichen planus [23].

Two biological mechanisms may explain the relationship of periodontitis with OC. The first is direct exposure to microorganisms and their products (toxins, enzymes, and other by-products), which can induce mutations in tumour suppressor genes and proto-oncogenes, or alter signalling pathways that regulate epithelial cell proliferation and survival. Microbial products also stimulate host cells such as neutrophils, macrophages, monocytes, lymphocytes, fibroblasts, and epithelial cells to generate reactive oxygen and nitrogen species, reactive lipids, matrix metalloproteases, and metabolites. These molecules may damage the epithelial cell DNA, which

in turn produces chemical signals and cytokines that promote cell survival, proliferation, migration, angiogenesis, and inhibition of apoptosis in the tumoral microenvironment. The second is an indirect mechanism, in which inflammation exposes epithelial cells to potentially mutagenic substances [13]. However, more studies are necessary to establish the exact mechanism involved in the pathogenesis of periodontal disease and its association with the development and progression of OC and OPMDs.

In this systematic review, we identified some studies that suggest a positive relationship between periodontal disease and OC and OPMDs [16,29–32]. Clinical and radiographic parameters such as CAL [21,23,24], PI [21], BOP [21,23] and RBL [13,26] were increased in patients with OC and OPMD. On the other hand, biological parameters such as salivary levels of IL-6 were elevated in patients with concomitant periodontitis and leukoplakia [23].

Several systematic reviews and meta-analyzes on the relationship of periodontal disease and oral cancer have recently been published [14,33,34]. Javed et al. [14] reported a 2- to 5-fold increased risk of OC among patients with periodontal disease. A systematic review with a meta-analysis of 5 studies found that patients with periodontal disease have 2.66 times greater risk of developing OC, concluding that periodontal disease is an independent risk factor for OC [33]. Similar results were found in a systematic review with a meta-analysis of 11 studies [34]. However, since the eligibility criteria of the clinical parameters that could evidence a periodontal inflammatory process were more rigorous in this review, we were unable to establish the risk, unlike previous systematic reviews. Additionally, we excluded the studies in which the diagnostic criteria were not clearly described or when the diagnosis was based on self-reported data, questionnaires, interviews and medical history.

Some clinical findings such as the number of missing teeth or level of oral hygiene not always correlate with periodontal disease. Thus, their use in the diagnosis of this condition could explain the lack of association with OC. Regarding the number of missing teeth, this could be related to other causes different from periodontal disease, such as local trauma, dental caries or endodontic treatment failure [29,35]. Due to the heterogeneity in the study designs, methodology, study populations, clinical and radiographic criteria or biomarkers used to define periodontal disease, it was not possible to establish an association between periodontal disease, OC and OPMDs. However, the absence of a statistical association does not exclude periodontal disease as a risk factor for OC.

For periodontal disease, it is necessary to adopt standard clinical parameters to define its extension, severity, and longitudinal progression of clinical attachment loss to establish a correlation with OC and OPMDs. OC research should follow the guidelines of the newest classification of periodontal disease by stages and grades [15]. The literature suggests that OC is more associated with periodontal disease than with gingivitis [13,24,29]. However, these results should be interpreted with caution since some of the studies use tooth loss as an indicator of periodontal disease [36]. Several studies have shown that tobacco use and alcohol intake are two major risk factors for OSCC and OPSCC [22,37,38]. Nonetheless, other aspects such as poor oral hygiene, increased BOP, RBL, periodontal status, oral mucosa lesions, missing teeth, decayed teeth, filled teeth, alimentary habits, ill-fitting prosthesis, and betel nut chewing also play a significant role in the development of OC [13,22,24,39].

The prevalence of OC and periodontal disease is low in young individuals. However, the number of OC cases has significantly increased in adolescents and young adults (under 45 years of age) during the last decades [40]. Prospective studies evaluating early gingivitis and clinical parameters such as BOP in young patients with OSCC should be conducted, to explore the relationship between age, periodontal status, and OC.

It is also essential to consider the location of OC. Both floor of the mouth and tongue cancer has been associated with more aggressive and invasive behaviour. Besides, in OTSCC, the site of origin (base or oral tongue) correlates with the survival rate [41,42]. Thus, the lack of data regarding OC location may be a significant source of analysis bias when exploring this association. The use of clinical guidelines such as those from the *Instituto Nacional del Cáncer* (INCA), which describes the anatomical regions of the oral cavity (the lips, anterior two-thirds of the tongue, buccal mucosa, floor of the mouth, upper and lower gums, hard palate, and retromolar area) can help to identify the cancer location at onset and thus increase the quality of the data [24]. If a causal association is established in the future, it could be hypothesized that the treatment of periodontal disease, as an independent risk factor for OC, could result in a lower incidence and higher survival rates. Future studies require an individualized, multifactorial risk assessment approach, since the aetiology of OPMD and OC, as well as of periodontal disease, is multicausal.

Although we aimed to assess secondary outcomes, such as mortality, quality of life, life satisfaction, and adverse events, no results regarding these variables were identified. Hence, future research, analysing these variables and also controlling for confounding factors, is required to provide data on such outcomes.

In summary, although there is no consensus in the literature and the currently available evidence is still insufficient, some studies suggest a positive relationship between periodontal disease, OC and OPMDs. We suggest that patients with periodontal disease should be examined for OC or OPMDs.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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