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Artículo de Investigación

Association between Periodontitis and Head and Neck Squamous Cell Carcinoma: a Systematic Review

Asociación entre periodontitis y carcinoma de células escamosas de cabeza y cuello: una revisión sistemática

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ABSTRACT

Introduction: Periodontitis remains a global health challenge and has been implicated in the pathogenesis of various systemic diseases, including cancer. However, findings on its association with head and neck squamous cell carcinoma (HNSCC) remain inconsistent across observational studies.

Objective: To systematically review observational studies assessing the association between periodontitis and HNSCC, and explore potential biological mechanisms underlying this relationship.

Methods: A systematic review of observational studies published in Scopus, PubMed, ScienceDirect, and Web of Science until December 2025 was conducted following the PRISMA 2020 guidelines. Eligible studies evaluated the association between periodontitis and HNSCC. Risk of bias was assessed using the ROBINS-I tool.

Results: Fourteen observational studies involving 22,000 participants were included. Most reported a positive association between periodontitis and HNSCC; twelve studies reported odds ratios ranging from 1.09 to 10.9. Current evidence suggests that periodontal pathogens and chronic inflammation may contribute to HNSCC development through multiple mechanisms of carcinogenesis.

Conclusions: The available observational data support an association between periodontitis and HNSCC, but current evidence is insufficient to establish a causal relationship. Further high-quality prospective studies are needed to clarify whether this association is causal.

RESUMEN

Introducción: La periodontitis continúa siendo un problema de salud mundial que influye en la patogénesis de algunas enfermedades sistémicas, incluido el cáncer. Sin embargo, la evidencia sobre su asociación con el carcinoma de células escamosas de cabeza y cuello (CCECC) sigue siendo inconsistente entre los estudios observacionales.

Objetivo: Revisar sistemáticamente los estudios observacionales sobre la asociación entre la periodontitis y el CCECC, y explorar los posibles mecanismos biológicos subyacentes en esta relación.

Métodos: Se realizó una revisión sistemática de estudios observacionales publicados en Scopus, PubMed, ScienceDirect y Web of Science hasta diciembre de 2025, teniendo en cuenta las directrices PRISMA 2020. Los estudios elegibles valoran la asociación entre la periodontitis y el CCECC. El riesgo de sesgo fue evaluado mediante la herramienta ROBINS-I.

Resultados: Se incluyeron catorce estudios observacionales con un total de 22 000 participantes. La mayoría reportó una asociación positiva entre la periodontitis y el CCECC; 12 proporcionaron razones de momios que oscilaron entre 1.09 y 10.9. La evidencia actual sugiere que los patógenos periodontales y la inflamación crónica podrían contribuir al desarrollo del CCECC a través de múltiples mecanismos de carcinogénesis.

Conclusiones: Los datos observacionales respaldan una asociación entre la periodontitis y el CCECC, pero la evidencia actual es insuficiente para establecer una relación causal. Se requieren futuros estudios prospectivos cualitativos para esclarecer si esta relación es causal.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is a malignant neoplasm arising from the mucosal epithelium of the oral cavity, pharynx (including

oropharynx and hypopharyng), and larynx. Data obtained from GLOBOCAN 2020 show HNSCC as the seventh most frequent cancer worldwide, accounting for approximately 4.5% of all cancers diagnosed. Most cases present as cancers of the lip and oral cavity with around 380,000 cases, followed by cancers of the larynx (185,000), nasopharynx (130,000), oropharynx (98,000), and hypopharynx (84,000). HNSCC is accounts for 450,000 cancer deaths annually (4.6% of the global total). It is projected that by 2030, the incidence of HNSCC will rise by 30%, driven by lifestyle trends which are established as risk factors for HNSCC.[1,2]

Periodontitis is a chronic inflammatory disease triggered by a dysbiotic dental plaque biofilm and modified by environmental and genetic risk factors, which destruct the periodontium. Clinically it is characterized by bleeding on probing (BOP), alveolar bone loss (ABL), periodontal pocket formation, gingival recession, furcation involvement, clinical attachment loss (CAL), and tooth mobility, eventually leading to tooth loss.[3] This disease remains a global health problem. A latest meta-analysis (2011-2020) estimated that 61.6% of the oldest population is affected, with 23.6% presenting severe forms of the disease.[4]

New studies have produced growing evidence suggesting an association between periodontitis and several systemic disorders,[5] including various cancers.[6] Proposed biological mechanisms involve chronic systemic inflammation and virulence factors from periodontal pathogens, which promote the release of free radicals and cytokines and the degradation of the extracellular matrix. These have been shown to be involved in carcinogenesis and tumor progression.[7]

Despite increasing recognition of periodontitis as a potential contributor to systemic disease, findings on its link with HNSCC remain inconsistent. Therefore, this study aimed to systematically review observational studies evaluating the association between periodontitis and HNSCC risk and to explore the underlying biological mechanisms supported by current evidence.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to evaluate the association between periodontitis and the risk of HNSCC. The protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews) under ID CRD420251271345.

Eligibility Criteria

Eligibility criteria were structured using the Population, Exposure, Comparison, Outcome, and Study (PECOS) framework. (Table 1)

Studies were included if they: (1) were observational studies examining the association between periodontitis and HNSCC; (2) were published in any language, provided that an English translation was available; and (3) were available in full-text in a peer-reviewed journal. Reviews, expert opinions, editorials, case reports, case series, books, theses, dissertations, and studies unrelated to the periodontitis-HNSCC relationships were excluded. No restrictions were placed on publication year; studies published up to December 2025 were eligible.

Table 1. PECOS framework

Element	Details
Population	Any population
Exposure	Individuals diagnosed with periodontitis
Comparison	Individuals with clinically healthy periodontium
Outcome	Head and neck squamous cell carcinoma
Study	Case-control, cross-sectional, and cohort studies

Information Sources and Search Strategy

A comprehensive search was performed by two authors (F.M.R. and R.A.) independently, in Scopus, PubMed, ScienceDirect, and Web of Science. Backward and forward citation searches were also conducted to additional relevant studies. This literature search was conducted in January 2024 with an update in December 2025. Search terms included MESH and free-text keywords: "periodontitis", "head and neck cancer", "oral cancer", "mouth neoplasm", "oropharyngeal cancer", "pharyngeal cancer", "cancer", "neoplasm", "squamous cell carcinoma", "malignancy", and "carcinoma", combined using Boolean operators "AND"/"OR". The detailed search strategies applied in each database are available in Supplementary Table 1.

Study Selection Process

Search results were exported to Mendeley, and duplicates were removed automatically and verified manually. Records with missing titles, incomplete bibliographic information, or irrelevant studies, were excluded before screening. After that, an initial screening based on titles and abstracts was performed by two authors (F.M.R and R.A.) to exclude irrelevant records. Potentially eligible studies underwent full-text assessment against PECOS criteria. Finally, studies that fulfilled all eligibility requirements were qualitatively reviewed in this systematic review. The selection process was documented in a PRISMA flow diagram.

Data Collection Process

Two authors (F.M.R. and R.A.) independently extracted data using a standardized form. Extracted data included: author, publication year, country; study design, sample size, periodontitis diagnosis criteria, methodand main findings. Following a systematic summary of the important information from each of the included articles, authors analyzed the data qualitatively and the results are presented in the discussion.

Synthesis Methods

Due to clinical and methodological heterogeneity in study designs, as well as exposure and outcome variability, a quantitative synthesis was not performed. Instead, a narrative synthesis of the findings was carried out. Data from the included studies were summarized and presented using descriptive tables and figures to facilitate comparison across studies. Effect estimates reported by individual studies, such as odds ratio (OR), were descriptively summarized without statistical pooling. The risk of bias assessment was also presented in graphical format using Rev Man 5.4 for Windows.

Risk of Bias Assessment

Risk of bias was evaluated using the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) tool by two assessors (F.M.R. and R.A.) independently. Discrepancies were resolved by consensus or arbitration, by the senior researcher A.I. Results were summarized graphically

Ethical Considerations

This study was conducted as a systematic review based on previously published data. As no primary data were collected and no human participants were directly involved, ethical approval was not applicable for this research.

RESULTS

A comprehensive literature search of the databases was conducted using predefined search terms. After the removal of duplicate records, a total of 3,980 records were identified. Prior to screening, 3,011 records were removed with missing titles, incomplete bibliographic metadata, and irrelevant studies, resulting in 969 records eligible for screening. A further 77 articles were subjected to eligibility assessment, resulting in 64 articles being excluded due to unavailable full-text, irrelevant objectives, unclear methodology, or ineligible publication types (e.g. reviews, case reports and case series, and editorials, as well as cases involving non-HNSCC. In addition to the aforementioned database searches, citation searching identified two additional articles, but only one was

included because the other had an irrelevant study aim. Finally, this systematic review included a total of 14 studies[8-21] for review. (Figure 1)

Characteristics of included studies

Fourteen articles involving 22,000 subjects were included in this systematic review: 13 case-control studies[8-20] and one cross-sectional study.[21] Studies were conducted in several countries: Taiwan,[8] USA,[9,19-21] Cuba,[10] Hungary,[11] Canada,[12] Germany,[13] Brazil,[14] Romania,[15] India,[16] Sweden,[17] and South Korea.[18] Three studies included more than 1,000 participants.[8,9,21] Periodontitis assessment methods varied across studies, ICD-9-CM codes,[8] self-report,[9] missing teeth/tooth loss,[10,17] PPD and/or CAL with or without radiographic ABL,[11,14,16,21] radiographic ABL with BOP, plaque index (PI), and degree of tooth mobility,[15] only radiographic ABL,[13,18-20] and gingival inflammation and recession.[12] General study characteristics are summarized in Table 2.

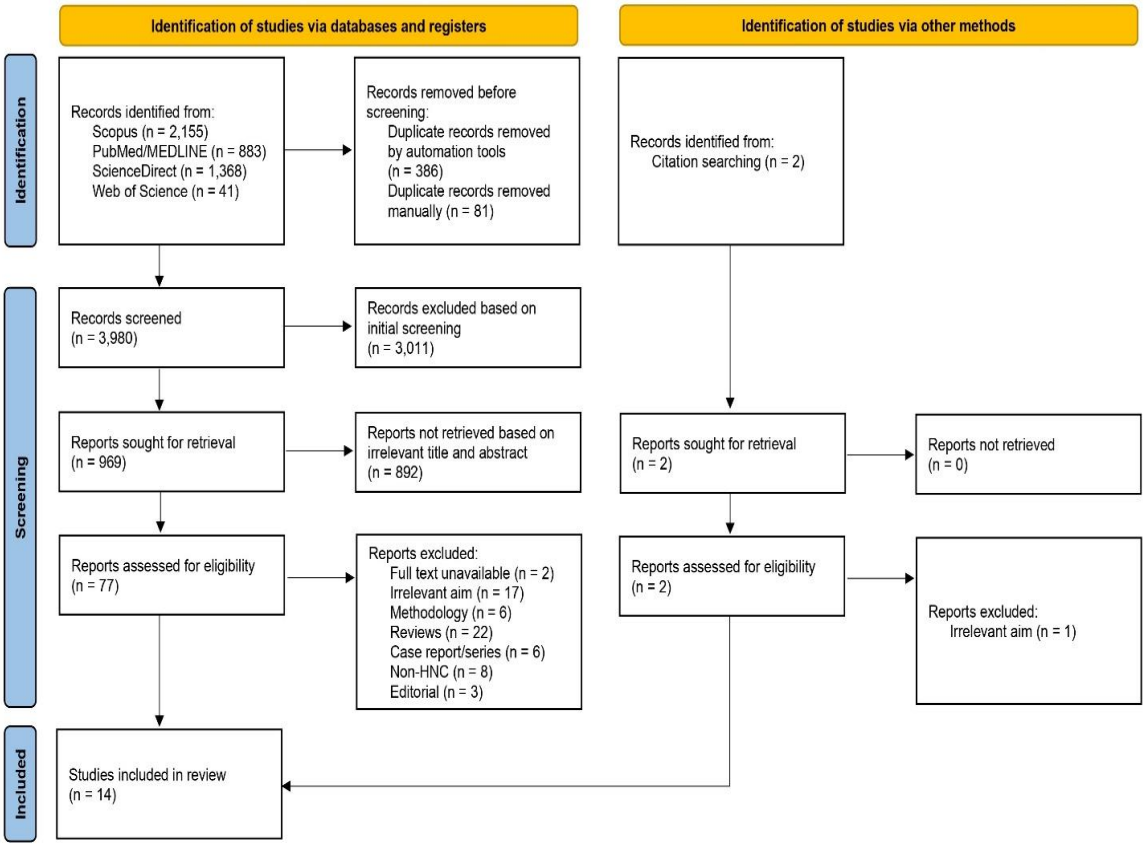

Fig. 1. PRISMA flowchart.

Regarding the main findings, twelve studies reported odds ratios (OR),[8-10,12-15,17-21] and two studies reported prevalence.[11,16] All the main findings from the eligible studies are summarized in Table 3.

Risk of Bias Assessment

Five studies[8,14,16,18,20] were rated as having a low risk of bias, while two[15,21] were rated as moderated, and seven[9-13,17,19] as having high risk, primarily due to limitations in controlling for confounding factors, exposure misclassification, and outcome measurement issues. High risk studies were retained due to the scarcity of evidence, but their results were interpreted cautiously as their methodological limitations may influence the strength and reliability of the reported association. Figure 2 shows the risk of bias results.

Table 2. Characteristics and summary of included studies

Study	Country	Study design	Participants (*n*)	Periodontitis assessment
Chen et al.	Taiwan	Case-control	3,876	ICD-9-CM
Eliot et al.	USA	Case-control	1,080	Self-reported
Garrote et al.	Cuba	Case-control	400	Missing teeth
Komlós et al.	Hungary	Case-control	200	PPD, CAL, BOP
Laprise et al.	Canada	Case-control	634	Gingival inflammation and recession
Moergel et al.	Germany	Case-control	301	Radiographic ABL
Moraes et al.	Brazil	Case-control	75	PPD, CAL, BOP, PI, GI
Nițescu et al.	Romania	Case-control	46	Radiographic ABL, BOP, PI, tooth mobility degree
Reddy et al.	India	Case-control	126	PPD, CAL, BOP, radiographic ABL
Rosenquist et al.	Sweden	Case-control	462	Missing teeth
Shin et al.	South Korea	Case-control	424	Radiographic ABL
Tezal et al.	USA	Case-control	105	Radiographic ABL
Tezal et al.	USA	Case-control	473	Radiographic ABL
Tezal et al.	USA	Cross-sectional	13,798	CAL

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PPD, probing pocket depth; CAL, clinical attachment loss; BOP, bleeding on probing; ABL, alveolar bone loss; PI, plaque index; GI, gingival index.

Table 3. Main findings in included studies

Study	Main findings
Chen et al.	Periodontitis is associated with pharyngeal SCC, especially oropharyngeal SCC (OR=1.57 [1.17-2.10]).
Eliot et al.	Periodontal disease is associated with HNSCC (OR=1.09 [1.02-1.16]), oral (OR=1.07 [1.00-1.13]) and pharyngeal (OR=1.07 [1.00-1.15]) SCC; not laryngeal SCC (OR=1.05 [0.99-1.10]).
Garrote et al.	Tooth loss (>16 teeth) linked to oral/pharyngeal SCC (OR=2.74 [1.23-6.12]).
Komlós et al.	Periodontitis in 57.1% of oral SCC vs. 28.6% of controls
Laprise et al.	Gingival recession associated with oral SCC (OR=1.83 [1.10-3.04]); gingival inflammation not significant (OR=2.02 [0.90-4.55]).
Moergel et al.	Chronic periodontitis is linked to oral SCC (OR=2.4 [1.5-3.8]).
Moraes et al.	Severe chronic periodontitis associated to oral /or oropharyngeal SCC (OR=10.9 [1.9-61.2]).
Niţescu et al.	Periodontitis increases risk of HNSCC (OR=4.36), oral (OR=4.52), oropharyngeal (OR=3.64), and laryngeal SCC (OR=2.27).
Reddy et al.	Oral SCC higher in periodontitis group (63.9% vs. 30.6%).
Rosenquist et al.	Tooth loss (>20 teeth) associated with oropharyngeal SCC (OR=3.4 [1.4-8.5]).
Shin et al.	Chronic periodontitis independently associated with oral SCC (OR=3.66 [1.46-9.23].
Tezal et al.	Periodontitis associated with tongue SCC (OR=5.23 [2.64-10.35]).
Tezal et al.	Periodontitis as HNSCC risk factor (OR=4.36 [3.16-6.01]); oral (OR=4.52 [3.03-6.75]), oropharyngeal (OR=3.64 [2.54-5.22]), laryngeal SCC (OR=2.72 [1.78-4.16]).
Tezal et al.	Periodontitis linked to oral neoplasms (OR=4.57 [2.25-9.30]).

OR, *Odds ratio*; HNSCC, head and neck squamous cell carcinoma; SCC, squamous cell carcinoma.

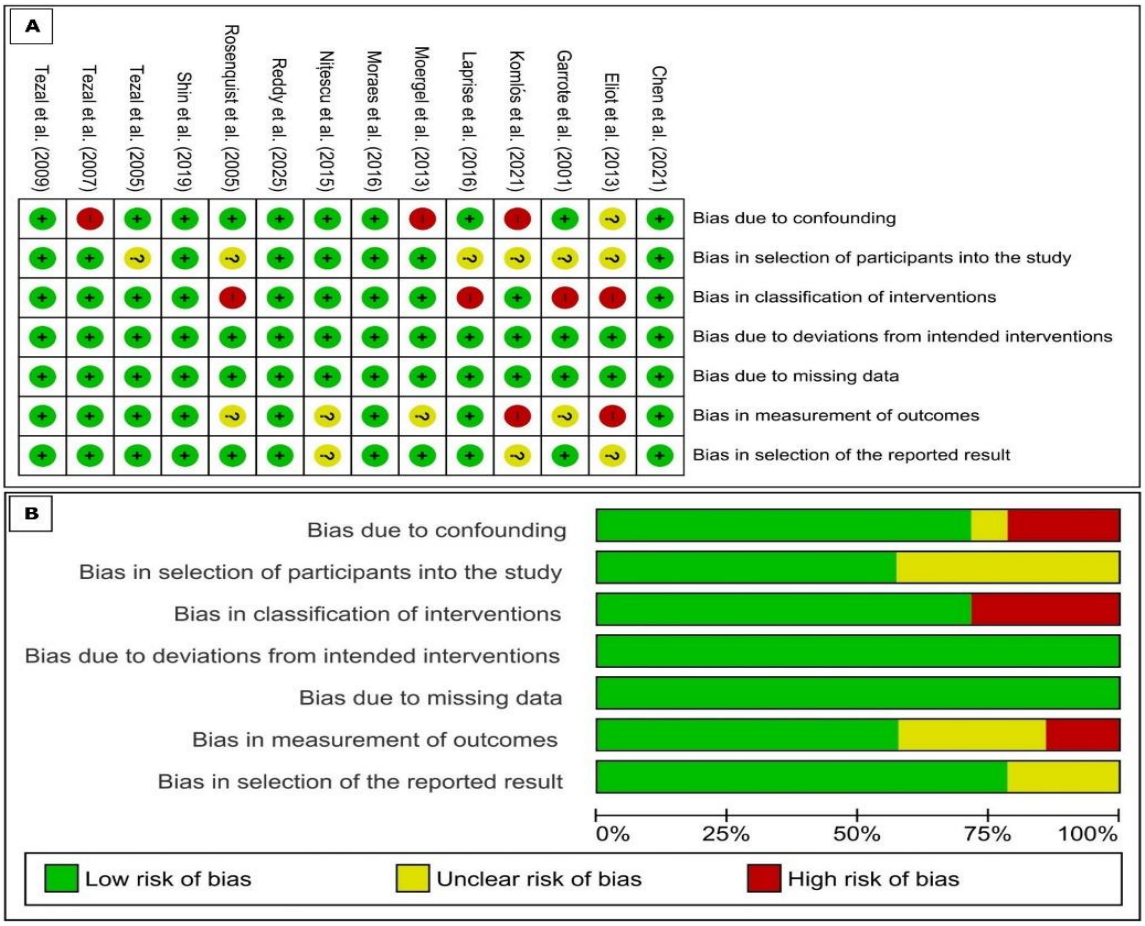

Fig. 2. Risk of bias assessment: (A) Risk of bias summary and (B) risk of bias graph.

DISCUSSION

This systematic review included 14 observational studies, most of which reported that periodontitis was associated with an increased risk of head and neck squamous cell carcinoma (HNSCC) after adjustment for confounders. Twelve studies provided odds ratios (OR) ranging from 1.09 to 10.9.[8-10,12-15,17-21] Evidence consistently links periodontitis to HNSCC subsites, including oral cavity (comprising tongue,[9-15,16-21] oropharynx,[8, 14-17,19] pharynx,[9,10] and larynx.[15,20] Only one study found no significant association with laryngeal SCC.[9] Collectively, these findings support a positive association between periodontitis and HNSCC, though causality cannot be inferred from observational data. Notably, seven of the 14 studies were rated as high risk bias, and substantial heterogeneity existed in HNSCC subtypes and periodontitis definitions, warranting cautious interpretation.

There remains a controversy on the diagnostic criteria for periodontitis. The gold standard combines clinical probing (assessing probing pocket depth [PPD],

clinical attachment loss [CAL], and bleeding on probing with radiographic evaluation of alveolar bone loss [ABL].[22] Ten studies used these standard methods either clinical,[11,14,21] radiographic,[13,18-20] or both;[15,16] one used the ICD-9-CM classification.[8] Three other studies used non-specific proxies: two defined periodontitis by tooth loss,[10,17] and one by gingival inflammation and recession.[12] Tooth loss is not only caused by periodontitis, but also by other periodontal diseases, untreated dental caries, dental trauma, and orthodontic extractions.[23] One study used self-reported periodontitis,[9] which risk misclassifying individuals with gingivitis or no disease. These methodological variations introduce significant bias. Therefore, future research should to use the 2017 World Workshop classification for periodontitis diagnosis.

A possible mechanism by which periodontitis may promote HNSCC is through chronic inflammation. The chronic inflammatory and immune-mediated conditions of periodontitis contribute to changes in the genetic structure, which ultimately undergo malignant transformation.[24] According to Surlari, et al.,[25] the oral periodontitis-related microbiota has been shown to contribute to the carcinogenesis process and HNSCC initiation. *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans are key periodontal pathogens* driving carcinogenesis via multiple mechanisms.[26] *P. gingivalis* activates anti-apoptotic pathways (AKTFOXO1, P13K/AKT, JAK/STAT), suppresses pro-apoptotic proteins (Bax, Bad), and up-regulates BLC-2.[27-29] It also enhances tumor invasion by stimulating protease-activated receptor-2(PAR2)/NF-kB, p38/HSP27, and ERK1-ETs1 pathways, inducing matrix metalloproteinase (MMP)9 and pro-inflammatory cytokines (IL-6, IL-8, MCP-1, sICAM-1).[30,31] IL-6and IL-8 further up-regulate MMP-1 and MMP-10, facilitating oral SCC cell invasion.[27]

Moreover, F. nucleatum and P. gyngivalis block apoptosis, arrest the cell cycle at S-phase, inhibit checkpoint kinase OCHK1), and overexpress the NLRP3 inflammasome.[31,32] Their lipopolysaccharide (LPS) activates Toll-like receptors (TLRs), triggering TNFα and Il-6 release, which in turn activate NF-kB and STAT3, transcription factors that upregulate genes involved in angiogenesis proliferation, anti-apoptosis, and immunosuppression. Supporting this, Dailey et al.[33] reported significantly elevated IL-8 and NF-kB levels in individuals with both periodontitis and HNSCC compared to controls. Additionally, leucotoxin LtxA) from A. actinomycetemcomitants stimulates IL-1β and IL-18 production, which are implicated in HNSCC development.[34] These mechanisms underscore the biological plausibility of the observed epidemiological association.

Emerging evidence also suggest that periodontal therapy may reduce HNSCC risk. Cheng at al.[8] found that scaling and toot planning (SRP) significantly lowered pharyngeal cancer risk, Similarly, Yeh at al.[35] reported that SRP was associated with a 25% reduction in oral SCC risk (OR=0.75) in a cohort over 4,800 patients. Although data remain limited, these findings imply that reducing periodontal inflammation may mitigate HNSCC development.

This review has limitations. First, seven studies had high risk of bias, primarily from inadequate control of confounders and exposure/outcome misclassification. Second, heterogeneous periodontitis definitions, including non-standard criteria like tooth loss, introduce misclassification bias. Third, studies originated from only 11 countries, limiting global generalizability.

Despite these limitations, the findings of the study support an association between periodontitis and HNSCC, with plausibly biological mechanisms and preliminary evidence that periodontal treatment may be protective. Future research should prioritize large, prospective studies using standardized periodontitis diagnostics and conduct meta-analyses to quantify risk. Interventional studies assessing whether periodontal therapy reduces HNSCC incidence are also warranted.

CONCLUSION

Available observational evidence suggests an association between periodontitis and head and neck squamous cell carcinoma (HNSCC). However, the evidence synthetized in this review is insufficient to establish a causal relationship, primarily due to the observational design and methodological heterogeneity of included studies. Biologically, current data indicates that periodontal pathogens and chronic inflammation contribute to HNSCC development through multiple carcinogenic pathways. These findings underscore the importance of periodontal health and highlight the need for greater awareness among oral health professionals, particularly general dentists and periodontists. Future well-designed studies employing standardized diagnostic criteria for periodontitis and larger, diverse populations are needed to clarify this association and to determine whether periodontal therapy can modify HNSCC risk or prognosis.

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Conflict of interest

All authors declared that they have no conflict of interest.