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The role of human papillomavirus in oral squamous cell and verrucous carcinomas: a systematic review with case series

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Introduction: Oral cancer (OC), particularly squamous cell carcinoma and its variants such as verrucous carcinoma, represents a growing public health concern due to increasing global incidence. While tobacco and alcohol remain the main risk factors, attention has turned to the potential role of human papillomavirus (HPV), particularly with particular consideration on high-risk genotypes.
Objective: This systematic review evaluates current evidence on the association between HPV and OC.
Methods: A structured search was conducted in PubMed, Scopus, and Web of Science using keywords including "oral carcinoma," "oral squamous cell carcinoma," "oral verrucous carcinoma," and "HPV." Screening followed PRISMA guidelines, and 15 articles were selected. Additionally, a case series of patients treated at the Department of Interdisciplinary Medicine, University of Bari "Aldo Moro," are presented to provide clinical context. Results. The evidence suggests a possible association between HPV infection, especially genotype 16, and a subset of oral squamous cell carcinomas. However, differences in detection techniques and study design contribute to variability in findings.
Conclusion: While HPV may play a role in oral carcinogenesis, further high-quality studies are required to clarify its impact. These findings may have implications for screening, prognosis, and prevention strategies, including HPV vaccination.

KEYWORDS
HPV, human papillomavirus, oral cancer, oral squamous cell carcinoma, verrucous carcinoma

1 Introduction

1.1 General background

Oral cancer (OC), especially oral squamous cell carcinoma (OSCC) and its variants like verrucous carcinoma (OVC), poses a significant global health challenge, with increasing incidence rates reported in both developed and developing nations (1, 2). Despite progress in diagnostic techniques and multidisciplinary treatments, OC prognosis remains poor, with 5-year survival rates stuck around 50%–60% (3–10). The latter highlights the need for a deeper understanding of its causes and biological mechanisms to enhance prevention, early detection, and targeted therapies (11–14).

1.2 Risk factors and HPV oncogenesis

Historically, the main risk factors for OC have been tobacco use and alcohol consumption, which work together to promote carcinogenesis (Figure 1) (15–22). However, recent evidence has highlighted the role of human papillomavirus (HPV) as a potential additional cause (23–25). HPV is a DNA virus with over 200 known genotypes, with high-risk types such as HPV16 and HPV18 recognized as strong oncogenic drivers (26–32). The oncogenic mechanism of HPV is mainly mediated by the persistent expression of the viral oncoproteins E6 and E7 (33–37). E6 promotes the degradation of the tumor suppressor p53, thereby impairing DNA repair and apoptosis, while E7 inactivates the retinoblastoma protein (pRb), leading to the release of E2F transcription factors and uncontrolled progression through the cell cycle (38–43). The combined loss of these two critical tumor suppressor pathways results in genomic instability, sustained cellular proliferation, and ultimately malignant transformation (44–50).

1.3 HPV and head and neck cancers

The causal relationship between HPV and cancers of the uterine cervix is well established, and growing evidence correlates HPV infection to a subset of head and neck squamous cell carcinomas (HNSCC), particularly in the oropharynx (51–57). HPV-positive oropharyngeal cancers are associated with distinct molecular profiles, improved treatment response, and better overall survival compared to HPV-negative tumors (58–64). This has prompted the inclusion of HPV status as a prognostic factor in staging systems and therapeutic decision-making (65–71).

According to the fifth Edition of the WHO Classification of Head and Neck Tumours (2022), both OSCC and OVC are not currently recognized as HPV-related entities. In contrast, HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) represents a distinct clinicopathological entity characterized by non-keratinizing morphology and a strong association with transcriptionally active high-risk HPV infection (72). The diagnosis of HPV-associated OPSCC is based primarily on p16 immunohistochemistry, which serves as a reliable surrogate marker for oncogenic HPV activity. p16 positivity is defined as diffuse nuclear and cytoplasmic staining in ≥70% of tumor cells with moderate to strong intensity. Direct HPV detection assays, such as DNA or RNA *in situ* hybridization and polymerase chain reaction (PCR), may be considered in selected situations—for instance, when p16 staining is equivocal, when morphological features do not match HPV-related patterns, or when required by clinical or research protocols (73, 74).

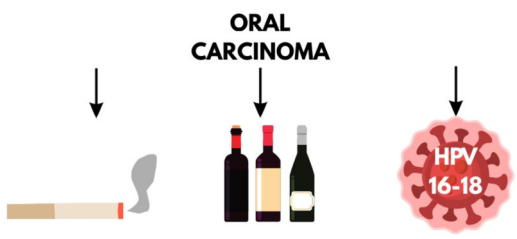

FIGURE 1
Schematic representation of the main risk factors for OC. Tobacco use, alcohol consumption, high-risk and HPV genotypes (16 and 18) are shown as key contributors to the development of OC.

These diagnostic criteria are essential to distinguish true HPV-driven tumors from those in which viral DNA may merely represent incidental infection.

1.4 Controversy of HPV in oral carcinogenesis

By contrast, the role of HPV in oral cavity carcinogenesis is still controversial (75–81). Several studies have reported the presence of HPV DNA, p16 overexpression, or E6/E7 mRNA transcripts in OSCC and OVC, suggesting that HPV may contribute to tumor initiation or progression (82–87). However, other investigations have found little or no evidence of HPV involvement in OC, with prevalence rates varying widely across geographic regions and depending on the detection methods used (88–92). These inconsistencies have generated ongoing debate about whether oral HPV infection is a true causative factor, a passenger infection, or a marker of other underlying processes (93–95).

1.5 Clinical and public health implications

Clarifying the role of HPV in OC carries important clinical and public health implications (96–101). If a significant causal association is confirmed, HPV vaccination programs might offer a preventive benefit beyond cervical and oropharyngeal cancers, potentially reducing the incidence of OSCC (102–105). Furthermore, HPV-positive oral tumors may have specific prognostic features that could influence the management, as already observed in HPV-related oropharyngeal cancers (106–109).

1.6 Oral VC

OVC is a rare, well-differentiated, low-grade variant of squamous cell carcinoma, first described by Ackerman in 1948 (110–116). It accounts for 0.5%–16% of OSCC and typically arises in the buccal mucosa, gingiva, and tongue, often consisting of abroad-based, outward-growing lesion with a rough, cauliflower-like surface. Such characteristic is histologically confirmed by its exophytic growing instead of a marked invasiveness which may help in differentially diagnose it from OSCC (117–121). Such a characteristic is histologically confirmed by its exophytic growth instead of a marked invasiveness which may help in differentially diagnose it from OSCC. Also, histological markers include a thick, hyperkeratotic squamous epithelium with minimal cytological

Abbreviations: APC, Article Processing Charge; DNA, Deoxyribonucleic Acid; DOI, Digital Object Identifier; EGFR, Epidermal Growth Factor Receptor; HNSCC, Head and Neck Squamous Cell Carcinoma; HPV, Human Papillomavirus; IHC, Immunohistochemistry; IRMA, Integrative Review and Meta-Analysis; OC, Oral Cancer; OSCC, Oral Squamous Cell Carcinoma; OVC, Oral Verrucous Carcinoma; p53, Tumor Protein p53; pRb, Retinoblastoma Protein; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RNA, Ribonucleic Acid; SCC, Squamous Cell Carcinoma; TT, Tumor Tissue; WoS, Web of Science.

TABLE 1 Indicators for database searches.

Article-screening strategy	Keywords: "oral carcinoma; oral squamous cell carcinoma; squamous cell oral carcinoma; oral verrucous carcinoma; HPV in oral carcinoma; human papillomavirus; HPV"
	Boolean indicators: OR and AND
	Timespan: June 2015 to July 2025
	Electronic databases: PubMed; Scopus; WOS.

atypia, prominent keratin plugs, and elongated rete ridges extending into the underlying stroma without true invasion of the basement membrane (122–126). Mitotic activity is generally low, and nuclear pleomorphism is scarce (127–133). Unlike OSCC, which shows infiltrative growth, marked nuclear atypia, higher mitotic activity, and a greater tendency for lymph node or distant metastasis, OVC usually demonstrates a pushing growth pattern, rare metastatic potential, and a more favorable short-term prognosis (134–138). While OVC rarely metastasizes, it can be locally aggressive and tends to recur if not completely excised (121, 139). In some cases, hybrid tumors containing foci of invasive squamous cell carcinoma may occur, conferring a worse prognosis (140–143). These histopathological characteristics are crucial for differential diagnosis, particularly in distinguishing OVC from benign verrucous hyperplasia, proliferative leukoplakia, and conventional SCC (144–147). Also, according to the most recent AJCC classification (2017), the main distinguishing feature in growth pattern is established by the parameter of depth of invasion (DOI), which plays a critical role in staging and prognosis establishment. A schematic representation of the histological features of OVC is presented below. The aim of this systematic review is therefore to critically evaluate and synthesize current evidence regarding the association between HPV and OC, with a focus on squamous cell and verrucous variants (148, 149). By analyzing the available literature, this work seeks to highlight both areas of consensus and points of controversy, providing a clearer perspective on the significance of HPV in oral carcinogenesis and its implications for prevention, prognosis, and treatment (150, 151).

2 Materials and methods

2.1 Protocol and registration

The current systematic review was conducted following the PRISMA guidelines (Preferred Reporting Items for SR and Meta-Analyses) and International Prospective Register of SR Registry procedures (ID PROSPERO: 1136400).

2.2 Search process

The following databases were combed from June 2015 to July 2025, to search for articles published over the last 10 years: PubMed, Web of Science (WoS), and Scopus. The search strategy was developed by combining terms relevant to the study's purpose. In the advanced search strings used in the databases (detailed search terms are given in Appendix A), the following keywords were applied using Boolean operators to combine terms pertinent to this study's purpose (Table 1).

2.3 Inclusion and exclusion criteria

The reviewers worked in groups to assess all relevant studies that evaluated:

- Open-access studies written in English
- Full-text articles accessible for review
- Studies conducted *in vivo* on human subjects aged 18 years or older
- Studies involving adults with a diagnosis of OSC or OCV
- Study laboratory-based on human samples,
- Studies with observational design (cross-sectional, case-control, cohort)
- Studies investigating the prevalence, etiological role, prognostic value, or clinicopathological associations of HPV in OSCC and/or OVC

Studies that fulfilled at least one of the following criteria were excluded:

- Systematic reviews, meta-analyses, case reports, or case series
- Letters to the editor, conference abstracts, or commentaries
- Animal model studies
- Exclusively *In vitro* studies
- Studies focusing exclusively on non-oral sites (e.g., oropharynx, larynx) without separate analysis for the oral cavity

2.4 PICO question

The PICO format is a framework used in qualitative research to structure clinical research questions. In this study, the PICO addressed the following question: "In adults diagnosed with OSCC compared with those diagnosed with oral verrucous carcinoma, are there differences in the prevalence and etiological role of HPV infection, as well as in associated clinicopathological characteristics and prognosis?? The PICO question was answered as follows:

P (Population)

Adults diagnosed with oral squamous cell carcinoma or oral verrucous carcinoma.

I (Intervention)

Presence of HPV infection (HPV DNA, p16 IHC, ISH, or E6/E7 mRNA).

C (Comparison)

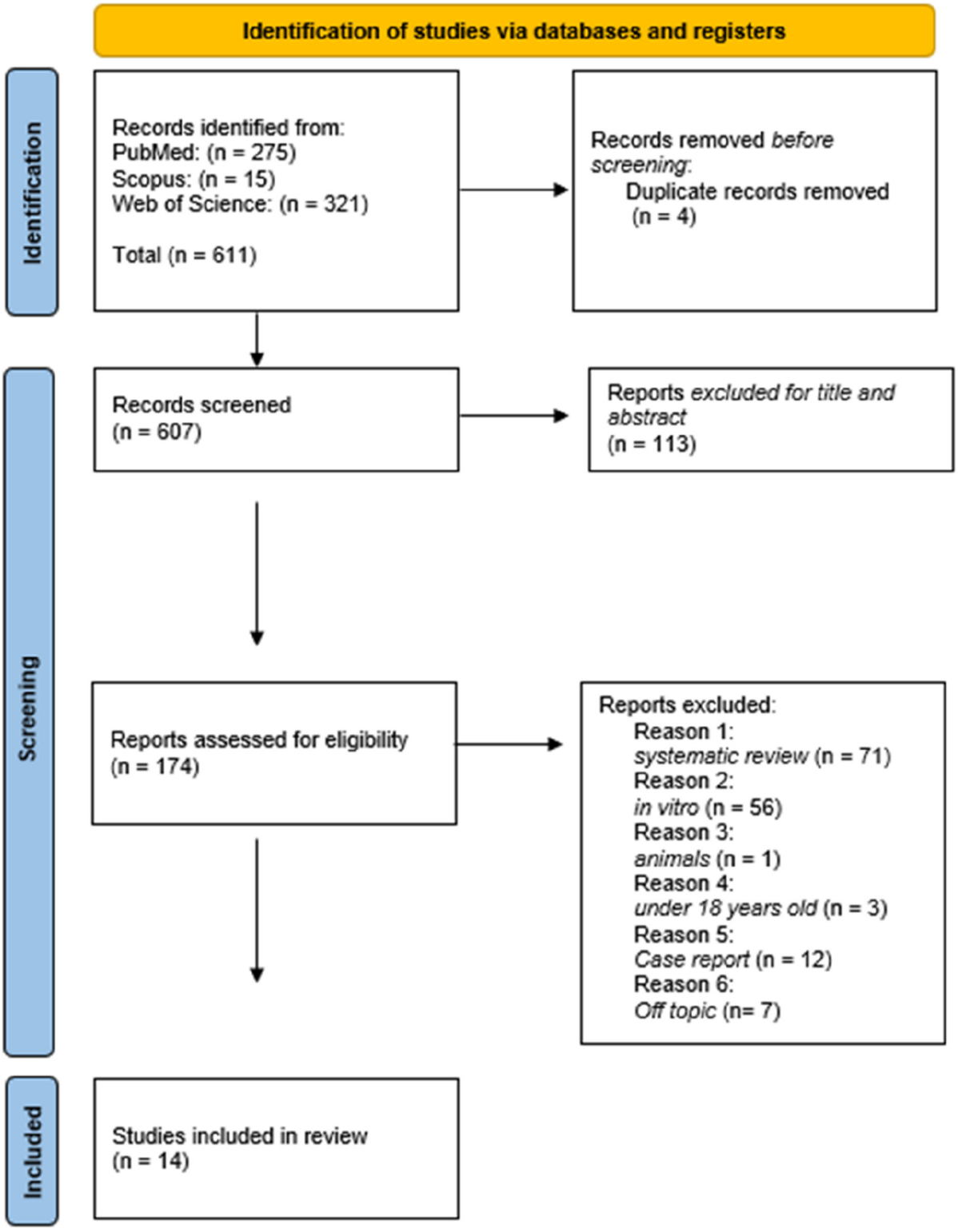

FIGURE 2
PRISMA flow diagram illustrating the study selection process for systematic review. The chart details the number of records identified, screened, assessed for eligibility, and included in the final analysis, along with reasons for exclusion at each stage.

TABLE 2 **Summary table of included studies.**

Authors, year	Country/ Setting	Study design	Aim/ Objective	Materials and methods	Results	Conclusions
Sgaramella et al., 2015 (152)	Italy	Retrospective cohort	Assess HPV16, p16, syndecan-1 in tongue SCC	109 TSCC cases; ISH for HPV16; IHC for p16, syndecan-1	HPV16 absent; p16+ in 33%; syndecan-1 widely expressed; p16 loss linked to worse prognosis in young patients	HPV16 not involved in TSCC; p16 not surrogate for HPV but prognostic
Chen et al., 2016 (153)	China	Case-control	Investigate HPV16/ 18 in OSCC and OPMD	99 patients; PCR and sequencing	No HPV16/18 detected; false positives excluded	HPV uncommon in OSCC/OPMD; PCR + sequencing reliable for detection
de Abreu et al., 2018 (154)	Brazil	Cohort study	Assess HPV prevalence in oral cavity SCC	101 patients; PCR with consensus primers; sequencing	HPV detected in 3/90 (3.3%), all HPV16; no associations with clinicopathological features	HPV not implicated in oral cavity SCC in Brazil
Nopmaneepaisarn et al., 2019 (155)	Thailand	Retrospective	Determine HPV prevalence in HNSCC	504 cases; p16 IHC + ISH ± PCR	HPV in 14.5% OPSCC; 1.5% OSCC/LSCC; HPV + linked to better OPSCC survival	HPV rare outside OPSCC; p16 unreliable; regional differences key
Tokuzen et al., 2021 (156)	Japan	Retrospective cohort	Evaluate HPV16 and p16 in OSCC	100 OSCC; RT-qPCR for HPV16 E6 mRNA; IHC for p16	HPV16 mRNA in 1 case (1%); p16+ in 10%; poor concordance	HPV16 rare in OSCC Japan; p16 unreliable surrogate
Li et al., 2021 (157)	China	Retrospective cohort	Assess prognostic role of nodal status by p16	674 OSCC surgical pts; survival analysis	p16+ in 12.6%; prognosis worsened with more positive nodes regardless of p16	Nodal burden is strong prognostic factor, independent of p16
Arsa et al., 2021 (30)	Thailand	Retrospective	Assess p16, HPV, outcomes in HNSCC	662 pts; p16 IHC; PCR subset	p16 in 10.9%; HPV DNA in 4%; p16+ linked to better OS but poor HPV concordance	p16 prognostic but poor HPV surrogate in low-prevalence regions
Sri et al., 2021 (158)	India	Comparative study	Prevalence HPV16/ 18 in OSCC and PMD	40 archival samples; PCR	HPV16 in 35% OSCC, 5% PMD; no HPV18 detected	HPV16 may play oncogenic role esp. in well-diff. OSCC
Silveira et al., 2022 (159)	Brazil	Cohort study	HR/LR HPV prevalence and prognosis in OSCC/ OPSCC	235 pts; ISH for HPV and EBV; IHC biomarkers	HPV in 25% OPSCC, 11% OSCC; co-infection linked to worse survival	HPV co-infection defines adverse subgroup
Satgunaseelan et al., 2021 (12)	Australia	Comparative genomic/ transcriptomic study	Identify molecular alterations specific to young (<50 years) OSCC patients	Cohort: 26 patients <50 years (17 from Sydney, 9 from TCGA) vs. 11 patients ≥50 years (TCGA)	Young OSCC patients had lower mutation burden than older ones EGFR-amplified cell lines showed active signaling and strong sensitivity to EGFR inhibitors. Genomic differences were not fully explained by smoking	EGFR amplification is a key, actionable biomarker in young OSCC. Routine testing could enable personalized therapy. EGFR inhibitors, especially afatinib, may improve outcomes in this group

(*Continued*)

TABLE 2 Continued

Authors, year	Country/ Setting	Study design	Aim/ Objective	Materials and methods	Results	Conclusions
Petrović et al., 2023 (160)	Serbia	Cross-sectional pilot	Prevalence HR-HPV in OSCC/OPMD/ controls	90 subjects; oral swabs; real-time PCR	HPV in 16.7% OSCC, 6.7% OPMD, 0% controls; non-16/18 types	HPV may play role in OSCC; broader genotype spectrum
Anwar et al., 2024 (29)	Pakistan	Cross-sectional	HR-HPV prevalence and link with p16, habits	186 OSCC biopsies; PCR for HPV16/18; IHC p16	HPV in 3.8% OSCC; weak correlation with p16; no link with chewing habits	HR-HPV marginal in OSCC; tobacco main driver
Tangthongkum et al., 2024 (161)	Thailand	Retrospective cohort	Impact of HPV on OSCC survival	454 OSCC; multiplex PCR; survival analysis	HPV+ in 10.2%; no survival advantage; stage and treatment were main prognostic factors	HPV status not prognostic in OSCC
Becker et al., 2024 (162)	Thailand	Retrospective cohort	HPV infection and OSCC prognosis	454 OSCC; PCR and survival analysis	HPV+ in 10.2%; no survival difference; outcomes linked to stage, ECOG, treatment	HPV not prognostic in OSCC; other risk factors dominant

Absence of HPV infection.

O (Outcome)

Differences in HPV prevalence, etiological involvement, and clinicopathological/prognostic characteristics in OSCC and OVC.

2.5 Data processing

Five independent reviewers (L.C., I.T., L.F., G.M.,M.F. and F.I.) assessed the methodological quality and risk of bias of the included studies using the ROBINS-I. The tool evaluates key domains such as selection, measurement validity, confounding, and data analysis. Discrepancies in scoring were resolved through discussion and consensus, with support from additional reviewers (L.L., A.D.I., F.I., G.F., A.M.I., and G.D.) when needed. The reviewers screened all retrieved records based on predefined inclusion and exclusion criteria. After screening, a total of 611 articles were imported into Zotero (version 6.0.36) for organization and full-text analysis.

3 Results

3.1 Selected studies and their characteristics

This PRISMA (Preferred Reporting Items for SR and Meta-Analyses) flow diagram (Figure 2) outlines the rigorous and systematic process used to select studies for the final review. The systematic review process was conducted according to the PRISMA guidelines. A comprehensive search across PubMed (n = 275), Scopus (n = 15), and Web of Science (n = 321) identified a total of 611 records. After the removal of 4 duplicates, 607 articles were screened by title and abstract, leading to the exclusion of 113 records. A total of 174 full-text articles were evaluated for eligibility. Of these, 159 were excluded for the following reasons: systematic review (n = 71), *in vitro* study (n = 56), animal study (n = 1), participants under 18 years old (n = 3), case report (n = 12), and off-topic articles (n = 7). Ultimately, 14 studies met all inclusion criteria and were included in the systematic review (Table 2).

3.2 Quality and risk of bias assessment for the included articles

The methodological quality and risk of bias of the fourteen included studies were assessed using the ROBINS I Tool for observational studies (Table 3). Each study was independently evaluated by four reviewers (L.C., I.T., L.F.,M.F., and F.I.). The ROBINS I risk of bias tool included seven dominies. Disagreements between reviewers were resolved through discussion and consensus, with the involvement of additional researchers (G.D., F.I., G.M., G.F., L.L., A.D.I., and A.M.I.) as needed. A summary of the item-by-item assessment for each study is provided in Table 2. The methodological quality and potential risk of bias of the studies included in this review were carefully evaluated using the ROBINS-I tool, which is specifically designed for non-randomized observational studies. This tool examines seven key domains, including participant selection, classification of interventions, deviations from intended interventions, handling of missing data, and outcome measurement. Each study was independently assessed by a panel of four reviewers to ensure objectivity and consistency in the evaluation process. Whenever disagreements arose, they were discussed and resolved by consensus, with additional researchers contributing when necessary. This collaborative approach strengthened the reliability of the assessments.

Overall, the risk of bias varied across studies, reflecting differences in study design, reporting quality, and methodological rigor. While some studies demonstrated low risk in several domains, others raised concerns, particularly in participant selection and intervention classification. The detailed results of this assessment are presented in tabular form (Table 3), providing a transparent overview of the strengths and limitations of each included study. This evaluation is essential for interpreting the findings of the

TABLE 3 A tabular summary of the risk of bias assessment for 14 studies, evaluated across the seven domains of ROBINS I.

Authors and year	D1	D2	D3	D4	D5	D6	D7	Overall risk of bias
Sgaramella et al 2005	-	+	+	+	+	-	-	-
Chen et al 2016	-	+	+	+	+	-	-	-
de Abreu et al 2018	-	+	+	+	+	-	-	-
Rodríguez -Carunchio L, et al.2018	-	+	+	+	+	-	-	-
Tokunzen et al 2021	-	+	+	+	+	-	+	-
Li et al 2021	-	+	+	+	+	-	+	-
Arsa et al 2021	-	+	+	+	+	-	+	-
Sri et al 2021	-	+	+	+	+	-	-	-
Satgunaseelan et al 2021	-	+	+	+	+	-	-	-
Silveira et al 2021	-	+	+	+	+	-	+	-
Petrović et al 2023	-	+	+	+	+	-	+	-
Anwar et al 2024	-	+	+	+	+	-	+	-
Tangthongkum et al 2024	-	+	+	+	+	-	+	-
Becker et al 2024	-	+	+	+	-	-	+	-

Domains	Judgement	
D1: Bias arising from the randomization process		
D2: Selection of participants	High	X
D3: Classification of interventions	Some concerns	-
D4: Deviations from intended interventions	Low	+
D5: Missing data		
D6: Measurement of outcomes		
D7: Measurement of outcomes		

systematic review, as it highlights both the robustness and the potential weaknesses of the available evidence.

4 Cases series

These two clinical cases, treated at the Department of Interdisciplinary Medicine, University of Bari 'Aldo Moro,' exemplify the heterogeneity of OSCC in terms of etiology, presentation, and biological behavior. The first case highlights the importance of early diagnosis and the effectiveness of minimally invasive diode laser excision in achieving complete disease control with excellent functional and aesthetic outcomes. Conversely, the second case underscores the emerging role of HPV infection in specific histological variants such as verrucous carcinoma, suggesting that viral status may influence both pathogenesis and prognosis. Taken together, these cases emphasize the need for a multidisciplinary diagnostic approach that combines clinical evaluation, imaging, histopathology, and, when appropriate, molecular testing. Such integration is essential not only to optimize patient outcomes but also to deepen our understanding of the different pathways driving oral carcinogenesis. In both presented cases, HPV16 positivity and p16 overexpression were associated with well-differentiated morphology and a non-keratinizing pattern, consistent with the biological behavior described for HPV-related squamous cell carcinomas. However, given the limited number of cases, no definitive conclusion can be drawn regarding the impact of HPV16 infection on the clinical and pathological features of oral cancer.

4.1 Case report 1

A 69-year-old male, with no history of tobacco or alcohol consumption, presented with a nodular ulcerated lesion on the right margin of the tongue, accompanied by pain and occasional bleeding. High-definition intraoral ultrasonography revealed a well-

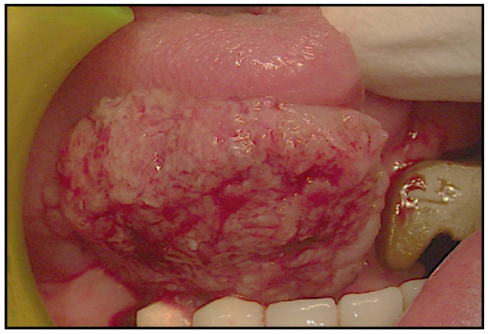

FIGURE 3
Clinical appearance of a nodular ulcerated lesion localized to the right tongue margin, also with pain and bleeding.

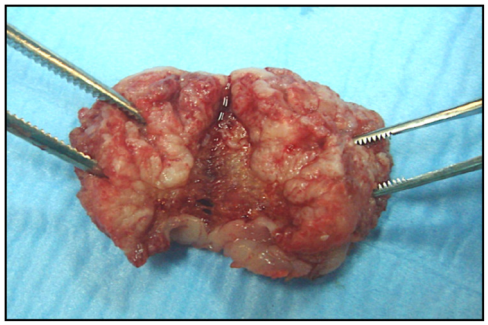

FIGURE 4
Macroscopy of the excised specimen, performed with a Diode Laser set at 3, 5–4 W in continuous wave mode.

defined hypoechoic lesion measuring 8.6 mm in tumor thickness and 3.9 mm in depth. The patient underwent surgical therapy for early OC through 3D laser-guided excision. After topical staining with Lugol's iodine and Toluidine Blue to better delineate the extension, the lesion was excised using a diode laser set at 3.5–4 W in continuous wave mode, followed by primary closure with sutures. Histopathological analysis confirmed the diagnosis of squamous cell carcinoma with keratin islands, an p16 immunohistochemistry performed to detect HPV resulted positive, also with positivity for genotype 16 HPV DNA. The postoperative course was uneventful, with complete healing observed. At 12-month follow-up, there was no evidence of recurrence or residual disease, highlighting the effectiveness of laser-guided excision in early OC (Figures 3–7).

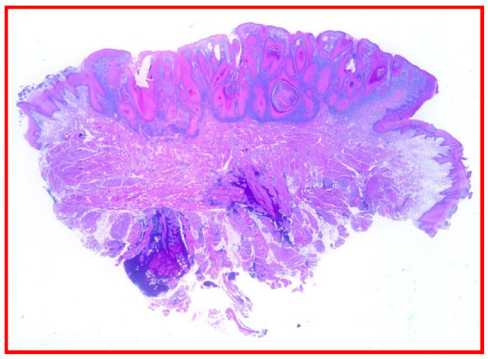

FIGURE 5
Histopathological analysis of the excised lesion confirming the diagnosis of squamous cell carcinoma (H&E).

4.2 Case report 2

A 54-year-old female, non-smoker and non-drinker, presented with a slowly enlarging verrucous lesion of the buccal mucosa, characterized clinically by thick hyperkeratosis and a warty surface. The lesion had been present for more than 6 months and was refractory to conservative management. Histopathological examination revealed a well-differentiated squamous epithelium with minimal cytological atypia, elongated rete ridges, and keratin plugs, consistent with verrucous carcinoma. HPV DNA testing was positive for genotype 16; p16 immunohistochemistry testing was positive for HPV, confirming viral involvement. The patient underwent surgical therapy for early OC through 3D laser-guided excision. The lesion was surgically excised with safety margins, and the postoperative course was uneventful. At 6-month follow-up, the patient showed no evidence of recurrence. This case illustrates the potential oncogenic role of HPV in non-conventional variants of oral squamous carcinoma and supports the importance of molecular testing in selected clinical presentations (Figures 8–13).

5 Discussion

5.1 Evidence from included studies

This systematic review integrates the findings of fifteen studies that investigated the role of HPV infection, p16 expression, and molecular alterations in OSCC across different geographic and clinical contexts. Together, these works provide a complex and sometimes contradictory picture, underscoring that the etiological and prognostic relevance of HPV in oral cavity cancer remains unsettled. Unlike in oropharyngeal squamous cell carcinoma, where HPV-driven oncogenesis is well established, the available evidence suggests that HPV plays at most a limited or context-dependent role in OSCC. A considerable group of studies strongly argued against a major contribution of HPV to oral carcinogenesis. Sgaramella et al. (2015), working in Italy, analyzed 109 cases of tongue squamous cell carcinoma and found no transcriptionally active HPV infection (152). Instead, they observed that p16 negativity was common in younger patients and associated with poorer prognosis, suggesting that p16 has prognostic significance independent of viral infection. Similarly, Chen et al. (2016) in China, examining 99 patients with OSCC and oral potentially malignant disorders, showed that many apparent HPV16/18 positive cases were in fact false positives when confirmatory sequencing was applied, reinforcing the rarity of biologically relevant HPV infection in this population (153). Marinho de Abreu et al. (2018) extended this conclusion to a Brazilian cohort, detecting HPV16 DNA in only 3.3% of OSCC samples and noting that positivity rates were similar to

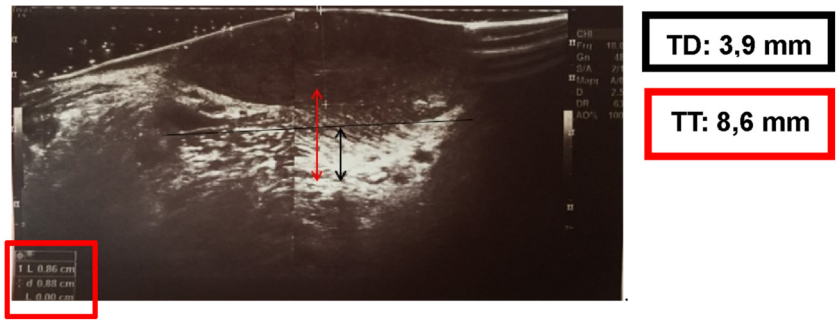

FIGURE 6
Intraoral High Definition Ultrasonography examination of the lesion appeared as a well-defined hypoechoic area measuring 8, 6 mm in Tumor Thickness and 3, 9 mm in Tumor Depth.

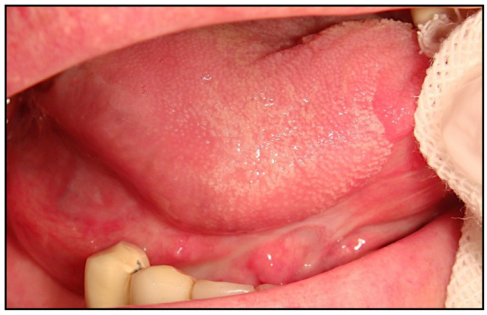

FIGURE 7
One year follow up showed complete healing of the site and absence of recurrences.

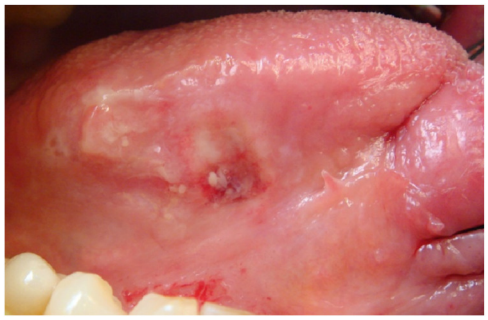

FIGURE 8
Clinical evidence of an ulcerated lesion of the right tongue margin persistent for over months.

background prevalence in healthy individuals (154). In Japan, Tokuzen et al. (2021) identified transcriptionally active HPV16 in just one out of 100 OSCC cases and cautioned against the overuse of p16 immunohistochemistry, citing its poor specificity in this setting (156). More recently, Anwar et al. (2024) in Pakistan confirmed that HPV16/18 were present in only 3.8% of cases and highlighted the discordance between HPV DNA and p16 expression, with the latter frequently positive even in HPV-negative tumors (29). Petrović et al. (2023) in Serbia contributed a further nuance by reporting HPV DNA in 16.7% of cases, but involving non-classical high-risk genotypes (HPV33, HPV39, HPV51, HPV52, HPV59) rather than HPV16/18, suggesting that the oncogenic spectrum of HPV in OSCC, if relevant, may differ from that seen in oropharyngeal cancers. Finally, large cohort studies in Thailand by Tangthongkum et al. (2024) and Becker (2024) found HPV positivity in around 10% of OSCC but observed no prognostic correlation, reinforcing the conclusion that HPV has limited clinical significance in oral cavity cancers. In contrast, a smaller group of investigations suggested that HPV might play a more prominent role in a subset of OSCC cases (161,162). Sathya Sri et al. (2021) in India reported HPV16 positivity in as many as 35% of tumors, particularly in verrucous and well-differentiated carcinomas, arguing for a possible oncogenic role of HPV in specific histological subtypes (158). Silveira et al. (2021/2022) in Brazil found high-risk HPV in 11% of OSCC samples and noted that co-infections correlated with worse prognosis, raising the possibility that HPV could act as a modifier of tumor biology rather than as a primary etiological factor (159). Arsa et al. (2021) in Thailand added further complexity, showing that while HPV DNA was rare (4%), p16 expression correlated with better survival outcomes even outside the oropharynx. This implies that p16, despite its unreliability as a surrogate for HPV infection, may still capture biologically meaningful features of OSCC. Other studies expanded the discussion beyond HPV, emphasizing alternative prognostic and molecular biomarkers (30). Li et al. (2021), in a large Chinese cohort of 674 surgically treated OSCC patients, showed that the number of metastatic lymph nodes was the strongest independent predictor of survival, overshadowing p16 status (157). Finally, Satgunaseelan et al. (2021) highlighted the importance of non-viral molecular drivers by identifying EGFR amplification in young OSCC patients, a feature that conferred marked sensitivity to EGFR inhibitors such as afatinib (12). This study opened the way to considering precision oncology approaches targeting actionable genomic alterations rather than focusing solely on viral status.

Taken together, the fifteen studies provide a heterogeneous but informative picture. On one hand, the weight of evidence from multiple regions, including Italy, China, Brazil, Japan, Pakistan, Serbia, and Thailand, suggests that high-risk HPV16/

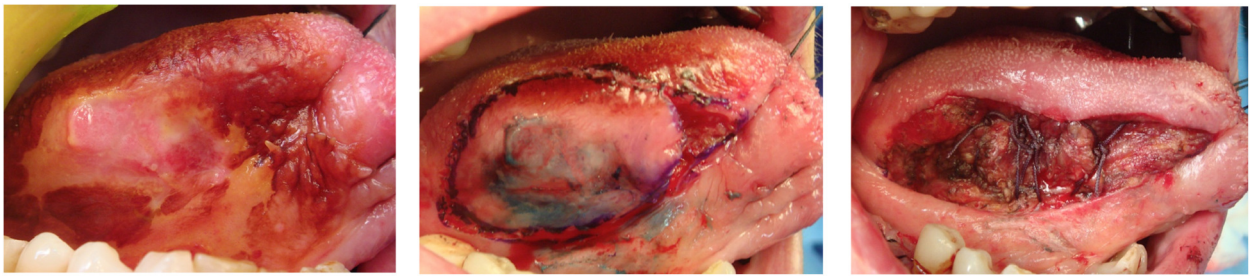

FIGURE 9
Direct application of Lugol and Toluidine Blue solution better evidenced the clinical extension of the lesion which was surgically excised with a Diode Laser (3, 5–4 W in continuous wave modality) and closure obtained with stitches.

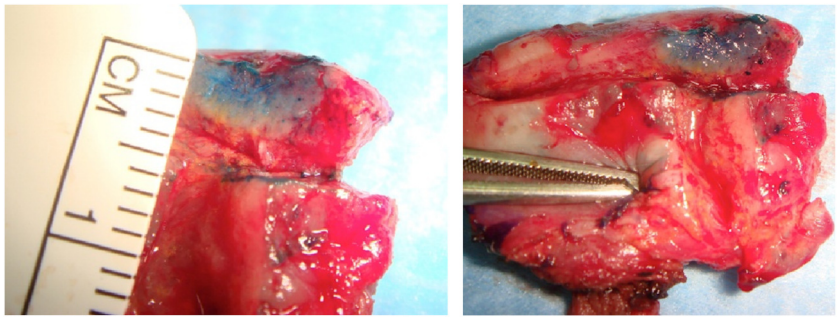

FIGURE 10
Macroscopy detail of the excised lesion which was sent for the histopathological analysis.

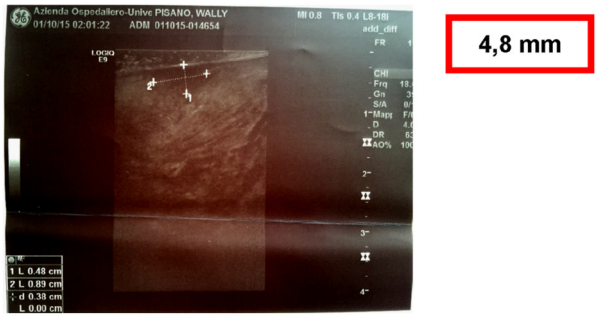

FIGURE 11
Intraoral high definition ultrasonography examination of the lesion showed an hypoechoic lesion measuring 4, 8 mm × 8.9 mm.

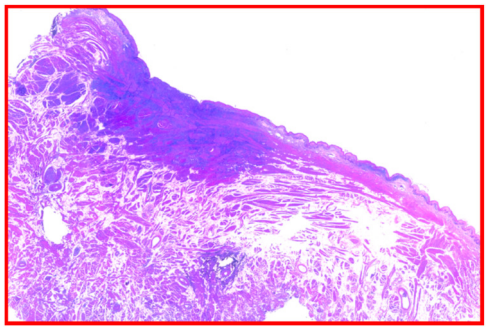

FIGURE 12
Histopathological analysis showed squamous cells patterns also with keratin islands consistent with diagnosis squamous cell carcinoma (H&E).

18 are rarely detected in OSCC and often lack transcriptional activity. On the other hand, a subset of studies, particularly from India and Brazil, indicate that HPV16 may contribute to a proportion of OSCC cases, especially in specific histological contexts. Moreover, the inconsistent prognostic impact of p16 and the emergence of alternative molecular drivers such as EGFR amplification underline that OSCC should not be reduced to a binary classification of HPV-positive versus HPV-negative but instead understood within a multifactorial etiological framework.

5.2 Sources of heterogeneity, strengths and limitations

The heterogeneity across the fifteen studies explains much of the conflicting evidence on HPV in OSCC. Methodological variability is central: Chen et al. (2016) and Tokuzen et al. (2021) demonstrated how false positives arise without confirmatory assays, while other works (e.g., Sathya Sri 2021, Petrović 2023) used DNA detection without RNA validation, leaving uncertainty about transcriptional

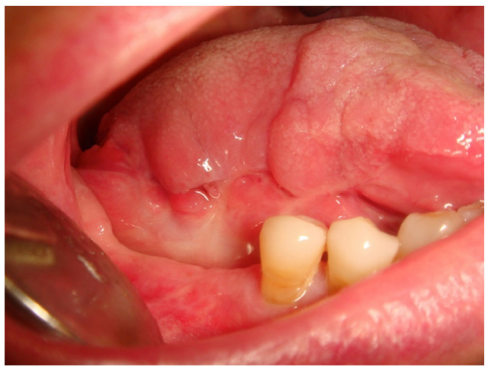

FIGURE 13
Three months follow up showed no recurrences and healing of the treated site.

activity. Several groups, including Silveira (2021) and Arsa (2021), combined HPV typing with p16 immunohistochemistry but reported variable concordance (30, 159).

Geographical differences further shaped findings. While studies in China, Japan, Pakistan, and Thailand generally reported very low HPV prevalence, India (Sathya Sri 2021) and Brazil (Silveira 2021) showed higher detection rates in certain histological subtypes. Serbia (Petrović 2023) uniquely highlighted non-16/18 genotypes. These variations suggest the influence of regional viral ecology, cultural practices, and behavioral exposures (158–160). Indeed, Nopmaneepaisarn (2019), Tangthongkum (2024) and Anwar (2024) all emphasized the dominant role of betel quid, smokeless tobacco, and gutka in OSCC burden (29, 155, 161).

Strengths across the studies include large cohorts (Li 2021, Becker 2024, Tangthongkum 2024), and innovative molecular analyses (Satgunaseelan 2021). Limitations, however, are frequent: small sample sizes (Sathya Sri 2021), retrospective single-center designs, lack of functional assays, and over-reliance on p16 IHC without molecular confirmation (12, 161, 162). Importantly, no included study directly evaluated the effect of HPV vaccination on OSCC incidence, leaving a key gap.

5.3 Clinical and research implications

Collectively, the evidence suggests that HPV is not a major etiological driver of OSCC, unlike in oropharyngeal squamous cell carcinoma. Studies from Italy (Sgaramella 2015), China (Chen 2016), Brazil (Marinho de Abreu 2018), Japan (Tokuzen 2021), and Pakistan (Anwar 2024) all converge on very low HPV16/18 prevalence, supporting the conclusion that routine HPV or p16 testing in OSCC has limited diagnostic or prognostic utility. While p16 may carry prognostic value in some contexts (Arsa 2021), survival is more strongly determined by nodal burden (Li 2021).

Regional and behavioral contexts are critical: betel quid and tobacco use dominate in South and Southeast Asia (Nopmaneepaisarn 2019; Tangthongkum 2024; Anwar 2024), while HPV prevalence is somewhat higher in Indian and Brazilian subsets (Sathya Sri 2021; Silveira 2021). Petrović (2023) highlighted the possible oncogenic role of non-16/18 genotypes, raising questions for future surveillance.

Finally, new molecular insights highlight alternative targets for precision oncology. Satgunaseelan et al. (2021) demonstrated EGFR amplification as a therapeutically actionable driver in young patients, and Silveira et al. (2021) linked HPV co-infection to worse outcomes. These findings underscore that OSCC is primarily driven by traditional carcinogens and molecular alterations, not by HPV. Future research should prioritize standardized HPV testing, prospective multicenter cohorts, and exploration of non-viral molecular drivers, while clinical practice should focus on prevention of established risk factors and integration of actionable biomarkers.

6 Conclusion

Unlike oropharyngeal squamous cell carcinoma, HPV has a limited and inconsistent etiological involvement in OSCC and its verrucous variation. The high-risk HPV genotypes, specifically HPV16 and HPV18, are quite uncommon, and transcriptionally active infections are still in a somewhat unique form. This suggests that HPV is not the only contributing factor in the development of OC, but rather one among multiple etiological determinants. The primary risk factors are traditional ones, such as alcohol and tobacco use, as well as local customs like gutka and betel quid. However, information from particular geographical areas (like Brazil and India) and histological subtypes (such VC and well-differentiated OSCC) indicates that HPV might be involved in a portion of cases. The interpretation is further complicated by the potential participation of non-16/18 genotypes. Crucially, prognostic analyses consistently show that molecular changes, including EGFR amplification, clinical stage, and nodal burden are considerably more important for patient outcomes than p16 or HPV status. Even though p16 immunohistochemistry can sometimes predict outcomes, it is not a trustworthy indicator of HPV infection. All things considered, OSCC is a complex illness in which HPV plays, at most, a supporting or modifying function.

7 Future perspective and limitations

In order to validate transcriptionally active infections and prevent false positives, future research should place a high priority on methodological uniformity and use assays based on both DNA and RNA. To ascertain whether there is a unique subset of HPV-related OSCC and to ascertain its clinical and biological significance, prospective multicenter cohorts are required.

It is necessary to investigate regional variations in HPV prevalence and genotype distribution, especially in relation to non-16/18 high-risk forms. Clinically speaking, combining viral status with non-viral molecular indicators like co-infection patterns or EGFR amplification may improve prognosis models and direct precision treatment. Long-term epidemiological studies comparing vaccinated and unvaccinated cohorts are necessary to evaluate the possible effect of HPV vaccination on OSCC incidence at the population level, as this effect is still unknown. Lastly, in order to create more efficient, customized treatment plans, therapeutic research should go beyond HPV and concentrate on modifiable genetic changes.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

LL: Writing – original draft, Writing – review and editing. ADI: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. GM: Visualization, Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review and editing. FI: Writing – original draft, Writing – review and editing. GF: Data curation, Investigation, Software, Formal Analysis, Funding acquisition, Project administration, Resources, Validation, Visualization, Writing – original draft. LC: Data curation, Methodology, Supervision, Conceptualization, Formal Analysis, Funding acquisition, Investigation, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. IT: Formal Analysis, Project administration, Data curation, Funding acquisition, Resources, Validation, Visualization, Writing – original draft. LF: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft. MF: Resources, Data curation, Formal Analysis, Funding acquisition, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft. AMI: Visualization, Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review and editing. GD: Writing – original draft, Writing – review and editing.

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Appendix A

Pub Med Query:

("oral carcinoma" [Title/Abstract] OR "oral squamous cell carcinoma" [Title/Abstract] OR "oral verrucous carcinoma" [Title/Abstract]) AND ("human papillomavirus" [Title/Abstract] OR HPV [Title/Abstract])

Scopus query:

("oral carcinoma" [Title/Abstract] OR "oral squamous cell carcino-ma" [Title/Abstract] OR "oral verrucous carcinoma" [Title/Abstract]) AND ("human papillomavirus" [Title/Abstract] OR HPV [Title/Abstract]);

Web of Science query:

TS = ("oral carcinoma" OR "oral squamous cell carcinoma" OR "oral verrucous carcinoma") AND TS = ("human papillomavirus" OR HPV).