BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 22 N 5

DOI:10.58240/1829006X-2025.22.5-193

REVIEW ARTICLE

HUMAN PAPILLOMAVIRUS-ASSOCIATED OROPHARYNGEAL SQUAMOUS CELL CARCINOMA: A SCOPING REVIEW OF CURRENT EVIDENCE AND FUTURE DIAGNOSTIC PERSPECTIVES

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Received: Jun 25 2026; Accepted: Aug 15. 2026; Published: Aug 20. 2026

ABSTRACT

Background:Human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) represents a rapidly evolving area in head and neck oncology. Although HPV16-driven carcinogenesis, epidemiological trends, vaccination strategies, and diagnostic approaches have been extensively investigated, evidence remains heterogeneous across molecular, clinical, and preventive domains.A comprehensive mapping of current knowledge is required to identify research trends, knowledge gaps, and future priorities.

Objective:To map current evidence regarding epidemiology, molecular mechanisms, prevention strategies, diagnostic approaches, and emerging technologies related to HPV-associated oropharyngeal cancer.

Methods:A scoping review was conducted according to Joanna Briggs Institute (JBI) methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). PubMed, Scopus, Web of Science and Google Scholar databases were searched for studies published from January 2000 to July 2026. Studies investigating HPV-associated oropharyngeal cancer, including epidemiological characteristics, viral mechanisms, diagnostic methods, prevention, and emerging technologies, were included. Data were extracted regarding study characteristics, HPV detection methods, molecular pathways, clinical outcomes, prevention strategies, and future diagnostic approaches.

Results:A total of 40 studies were included in the evidence mapping. Current literature demonstrates that HPV16 is the predominant oncogenic genotype associated with OPSCC. Major research domains included HPV prevalence, viral integration mechanisms involving E6/E7 oncogenic pathways, immune response, vaccination effectiveness, molecular detection techniques, and emerging artificial intelligence-based diagnostic approaches. Evidence gaps were identified regarding standardized screening strategies, global epidemiological variations, and clinical implementation of novel diagnostic technologies.

Conclusion:HPV-associated oropharyngeal cancer represents a multidisciplinary research field integrating virology, oncology, prevention, and precision medicine. Future studies should focus on standardized diagnostic pathways, long-term vaccine effectiveness, biomarker validation, and integration of emerging technologies into clinical practice.

Keywords: Head and neck cancer; human papillomavirus; HPV; oropharyngeal squamous cell carcinoma; carcinogenesis.

INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) is a malignant epithelial tumor arising from the mucosal surfaces of the oropharynx, including the palatine tonsils, tonsillar crypts, base of the tongue, soft palate, and posterior pharyngeal wall. OPSCC represents a major subgroup of head and neck squamous cell carcinomas (HNSCCs) and contributes substantially to global cancer morbidity and mortality [1,2]. Traditionally, tobacco smoking and excessive alcohol consumption have been considered the principal environmental risk factors associated with oral and oropharyngeal malignancies. The synergistic carcinogenic effects of tobacco and alcohol exposure have historically accounted for the majority of cases of head and neck cancer; however, epidemiological patterns have changed considerably during recent decades, with human papillomavirus (HPV) infection emerging as an independent and increasingly important etiological factor, particularly in tumors originating from the tonsillar region and base of the tongue [3,4,7]. According to the World Health Organization (WHO) and the International Agency for

Research on Cancer (IARC), persistent infection with high-risk HPV genotypes is a well-established cause of several malignancies, including cervical, anal, penile, vulvar, vaginal, and head and neck cancers [15,23]. HPV-associated OPSCC has become recognized as a distinct molecular and clinical entity compared with conventional tobacco- and alcohol-related carcinomas. These tumors demonstrate unique biological characteristics, including specific molecular alterations, different patterns of disease progression, improved sensitivity to therapy, and generally more favorable prognosis when compared with HPV-negative OPSCC [7,9].

HPV is a small, non-enveloped, double-stranded DNA virus belonging to the Papillomaviridae family. The viral genome contains early genes responsible for regulation of viral replication and malignant transformation, including the oncogenes E6 and E7, as well as late genes encoding viral structural proteins [7]. Infection occurs primarily through microabrasions of the mucosal epithelium, allowing viral particles to reach basal epithelial cells. Persistent infection with oncogenic HPV types may result in abnormal expression of viral oncoproteins, leading to disruption of essential cellular regulatory mechanisms involved in proliferation, apoptosis, and genomic stability [8,9].

The carcinogenic activity of high-risk HPV is mainly mediated through the E6 and E7 proteins. HPV E6 promotes degradation of the tumor suppressor protein p53, resulting in impaired DNA damage repair and inhibition of apoptosis. HPV E7 interacts with the retinoblastoma (RB) tumor suppressor pathway, causing uncontrolled progression through the cell cycle and promoting cellular immortalization [8,9]. Integration of HPV DNA into the host genome and continuous expression of E6/E7 oncogenes represent critical molecular events in HPV-driven carcinogenesis, contributing to genomic instability, immune escape, and malignant transformation of infected epithelial cells [8,33].

More than 200 HPV genotypes have been identified, with high-risk HPV16 representing the predominant oncogenic subtype associated with OPSCC worldwide. HPV16 accounts for the majority of HPV-positive oropharyngeal tumors and is strongly associated with cancers arising from lymphoid-rich anatomical sites, particularly the tonsillar crypts and base of the tongue [7,12]. The susceptibility of these sites to HPV-mediated carcinogenesis is thought to be related to their specialized reticulated epithelium, which facilitates viral access to basal epithelial cells and persistence of infection [20].

The epidemiology of OPSCC has undergone substantial transformation over the last several decades. While tobacco-related head and neck cancers have declined in many developed countries due to reduced smoking prevalence, HPV-associated OPSCC incidence has continued to increase [12,27]. Current evidence indicates that HPV is detected in approximately 20–90% of OPSCC cases depending on geographic region, population characteristics, and diagnostic methodology used for HPV identification [9,10]. In North America and several European countries, HPV-positive tumors constitute a large proportion of newly diagnosed OPSCC cases, whereas considerable regional differences remain across Asia, Africa, and other regions [10,34].

Unlike traditional head and neck cancers, HPV-associated OPSCC frequently affects younger patients with limited or absent exposure to tobacco and alcohol. A pronounced male predominance has consistently been reported, with epidemiological studies demonstrating substantially higher incidence rates among men compared with women [7,16]. The observed sex differences may be associated with variations in HPV exposure, immune responses, sexual behavior patterns, and differences in the natural history and clearance of oral HPV infection [16].

The acquisition of oral HPV infection is primarily related to sexual exposure. Multiple epidemiological studies have demonstrated associations between oral HPV positivity and sexual behaviors, including oral–genital contact, increased number of sexual partners, early sexual initiation, and other indicators of higher HPV exposure risk [13,17].

HPV is also implicated in a range of other malignancies, highlighting its significant oncogenic potential across multiple anatomical sites (figure 1) [19].

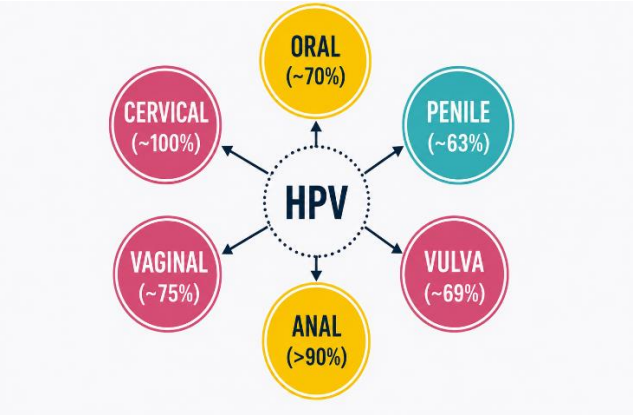

Figure 1.HPV-related malignancies

Studies have reported the HPV status of tumors located in different anatomical subregions of the oral cavity (at the base of the tongue, in the folds of the tonsils, or in the back of the throat) (fig.2)[19].

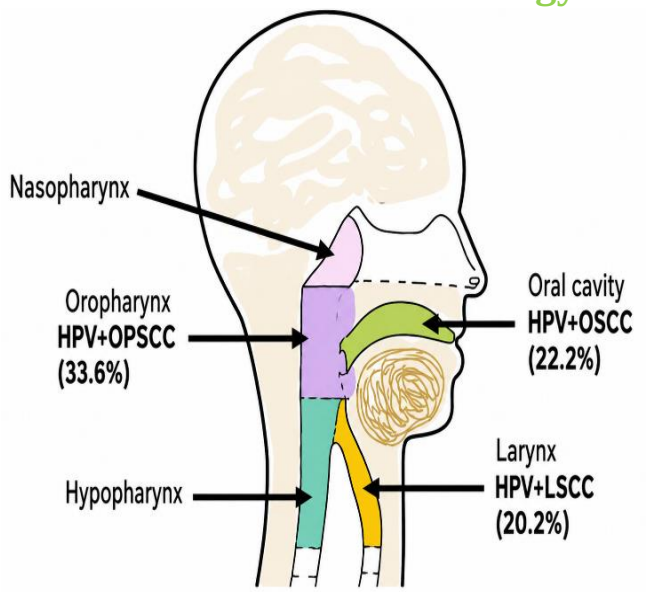

Figure 2. Distribution of human papillomavirus associated head and neck cancers (HPV + HNC) between anatomical sites. HPV is associated with 33.6% of OPSCC (lavender), 22.2% of OSCC (bright green), and 20.2% of LSCC (gold) worldwide

Studies conducted in large population-based cohorts have further demonstrated increased prevalence of oncogenic oral HPV infection among individuals with specific sexual behavior patterns, particularly among men [18]. However, HPV infection is common in sexually active populations, and the majority of infections are transient due to effective host immune clearance.

Persistent infection with high-risk HPV types represents the critical biological event associated with malignant transformation [14,22].

Sexually-transmitted HPV virus is a leading cause of lingual cancer, tonsil cancer, oropharyngeal cancer(fig3,4,5) and it spreads from person to person via oral sex.

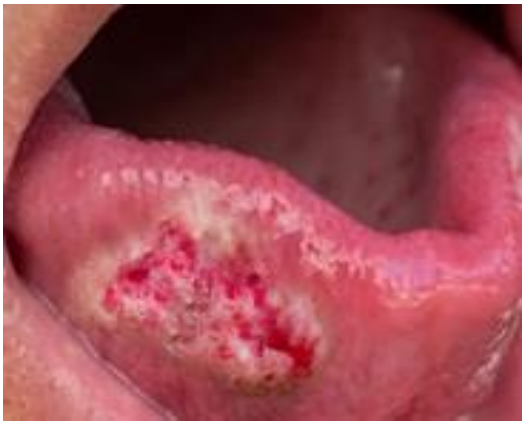

Figure 3. Lingual cancer is caused by HPV

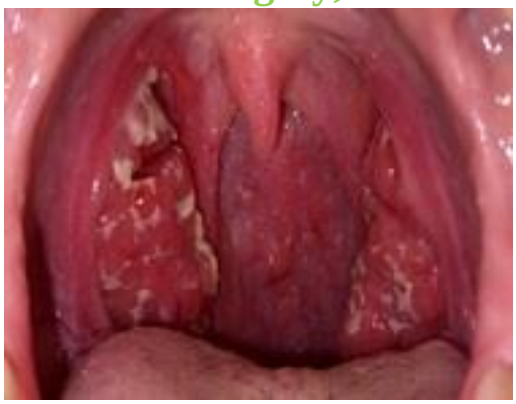

Figure 4 Tonsil cancer is caused by HPV

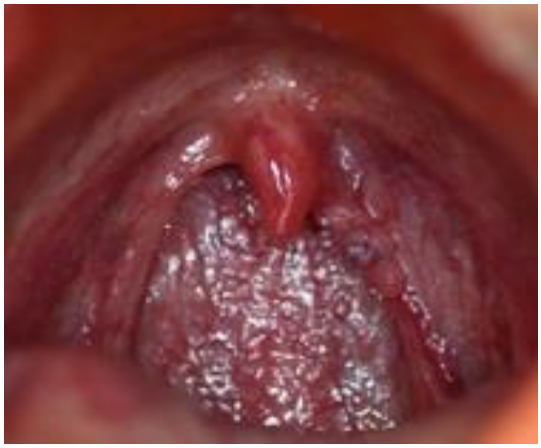

Figure 5. Oropharyngeal cancer is caused by HPV

The natural history of oral HPV infection is influenced by multiple viral, host, and environmental factors. Viral genotype, viral load, immune status, smoking exposure, age, and anatomical location of infection contribute to the probability of viral persistence and progression toward malignancy [14,22]. Most individuals are able to eliminate oral HPV infection spontaneously; however, failure of immune-mediated clearance may lead to prolonged viral persistence, accumulation of molecular abnormalities, and eventual development of invasive carcinoma [22].

From a pathological perspective, malignant transformation represents a multistep process involving epithelial dysplasia, accumulation of genetic alterations, invasion through the basement membrane, and metastatic potential. Oral epithelial dysplasia is characterized by cellular atypia, increased mitotic activity, abnormal maturation, and architectural disturbances that may precede invasive carcinoma [6].

Tumor progression is further regulated by interactions between malignant epithelial cells and the tumor microenvironment, including inflammatory pathways, angiogenesis, immune modulation, and cancer stem cell-related mechanisms that contribute to tumor survival and progression [5,22].

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Clinically, oral and oropharyngeal cancers may demonstrate different morphological patterns, including ulcerative, nodular, and papillary growth characteristics. Ulcerative lesions typically present as persistent non-healing ulcers with progressive enlargement, whereas nodular lesions appear as firm masses with gradual expansion. Papillary lesions demonstrate exophytic growth patterns and may exhibit different biological behavior compared with conventional invasive carcinomas[4]. Early identification of suspicious mucosal lesions remains essential because delayed diagnosis continues to represent a major factor contributing to poor clinical outcomes.

Prevention of HPV-associated OPSCC has become an important global health objective. Prophylactic HPV vaccination provides effective protection against persistent infection with high-risk HPV genotypes and has demonstrated substantial efficacy in preventing HPV-related anogenital cancers [11,23,25]. Although HPV vaccination programs were initially developed primarily for cervical cancer prevention, increasing evidence supports their potential contribution to reducing the future burden of HPV-associated head and neck malignancies [24]. Expanding vaccination coverage among adolescents and eligible adults remains a key strategy for reducing HPV-related cancer incidence worldwide [25].

Advances in diagnostic approaches have significantly improved the detection and characterization of HPV-associated tumors. Current diagnostic strategies include HPV DNA detection, RNA-based assays evaluating transcriptionally active HPV infection, p16 immunohistochemistry as a surrogate marker, and molecular profiling approaches [9,10].

More recently, artificial intelligence (AI)-based technologies have emerged as promising tools in oncology, enabling automated image analysis, molecular classification, early cancer detection, and integration of complex biological datasets for precision medicine applications [31,32].

Despite substantial advances in understanding HPV-driven OPSCC, important challenges remain, including geographic variation in disease prevalence, differences in diagnostic standards, incomplete vaccination coverage, limitations of current screening approaches, and the need for improved personalized treatment strategies. Emerging technologies, including artificial intelligence, machine learning, and computational pathology, may provide new opportunities for improving early diagnosis, risk stratification, and individualized patient management [31,32].

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Therefore, this scoping review aims to systematically map the current evidence regarding HPV-associated oropharyngeal cancer, with particular emphasis on epidemiology, molecular mechanisms of carcinogenesis, transmission and risk factors, preventive strategies, diagnostic approaches, and emerging technologies shaping future clinical practice.

2. MATERIALS AND METHODS

2.1 Study Design and Reporting Framework

This scoping review was conducted using the methodological framework proposed by the Joanna Briggs Institute (JBI) for evidence synthesis and scoping reviews. The reporting of the review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [30,31].

The objective of this review was to map the existing evidence regarding human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC), with particular emphasis on epidemiological characteristics, molecular mechanisms of HPV-driven carcinogenesis, risk factors, prevention strategies, diagnostic approaches, and emerging technologies. A scoping review approach was selected because the available literature includes diverse types of evidence, including epidemiological studies, molecular investigations, clinical studies, diagnostic research, and emerging technology-based approaches. The purpose of this review was to characterize the scope and characteristics of current knowledge, identify major research trends, and highlight existing gaps in the field rather than to estimate pooled treatment effects or perform quantitative meta-analysis.

2.2 Review Question and PCC Framework

The review question was developed according to the Population–Concept–Context (PCC) framework recommended by the Joanna Briggs Institute for scoping reviews [30]. The primary research question was: What is the current evidence regarding the epidemiology, molecular mechanisms, prevention strategies, diagnostic approaches, and emerging technologies associated with HPV-related oropharyngeal squamous cell carcinoma?

The PCC framework was defined as follows:

Population: Patients diagnosed with HPV-associated oropharyngeal cancer or head and neck squamous cell carcinoma, as well as clinically relevant biological samples derived from these populations.

Concept: HPV infection, viral oncogenesis, molecular mechanisms of carcinogenesis, epidemiology, risk factors, prevention strategies, diagnostic methods, and emerging technologies related to HPV-associated OPSCC.

Context: Clinical, epidemiological, molecular, diagnostic, and translational research settings.

2.3 Search Strategy

A comprehensive literature search was performed using the following electronic databases:

- PubMed/MEDLINE;
- Scopus;
- Web of Science;
- Google Scholar.

The search strategy was developed using a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to HPV infection, head and neck cancer, and oropharyngeal malignancies. The following search terms were combined using Boolean operators (AND, OR):

("Human papillomavirus" OR HPV OR HPV16 OR "high-risk HPV")
AND
("oropharyngeal cancer" OR "oropharyngeal squamous cell carcinoma" OR OPSCC OR "head and neck squamous cell carcinoma")
AND
("epidemiology" OR "carcinogenesis" OR "molecular mechanisms" OR E6 OR E7 OR "HPV detection" OR vaccination OR prevention OR diagnosis OR "artificial intelligence").

The search was restricted to publications available in the English language. Studies published between January 2000 and July 2026 were considered eligible to capture contemporary developments in the understanding, diagnosis, prevention, and management of HPV-associated OPSCC. In addition, the reference lists of included studies and relevant publications were manually screened to identify additional potentially eligible studies.

2.4 Eligibility Criteria

Eligibility criteria were defined according to the PCC framework.

Inclusion Criteria

Studies were eligible for inclusion if they fulfilled the following criteria:

- Original clinical, epidemiological, molecular, diagnostic, or translational studies;
- Studies investigating the association between HPV infection and oropharyngeal squamous cell carcinoma or head and neck cancers;
- Studies reporting HPV prevalence, HPV genotypes, molecular mechanisms, clinical characteristics, diagnostic approaches, or prevention strategies;
- Studies involving human participants or clinically relevant human-derived biological samples;
- Publications available in English;
- Studies published within the predefined search period.

Exclusion Criteria

Studies were excluded when they met any of the following criteria:

- Narrative reviews, systematic reviews, meta-analyses, editorials, commentaries, and letters;
- Case reports without relevant HPV-associated findings;
- Animal-only studies;
- Experimental studies without direct clinical relevance;
- Duplicate publications;
- Studies lacking sufficient information related to the objectives of the review.

2.5 Study Selection Process

All identified records were imported into reference management software, and duplicate records were removed before the screening process. Titles and abstracts were independently screened by two reviewers based on predefined eligibility criteria. Articles considered potentially relevant were subsequently evaluated through full-text assessment. Disagreements regarding study eligibility were resolved through discussion and consensus between reviewers. The initial database search identified 84 records. After removal of duplicate records and preliminary screening, potentially eligible studies underwent full-text evaluation. Following application of the predefined inclusion and exclusion criteria, 40 studies were included in the final scoping review. The study selection process followed the PRISMA-ScR reporting framework, and the stages of identification, screening, eligibility assessment, and final inclusion are presented in the PRISMA-ScR flow diagram (Figure **6**).

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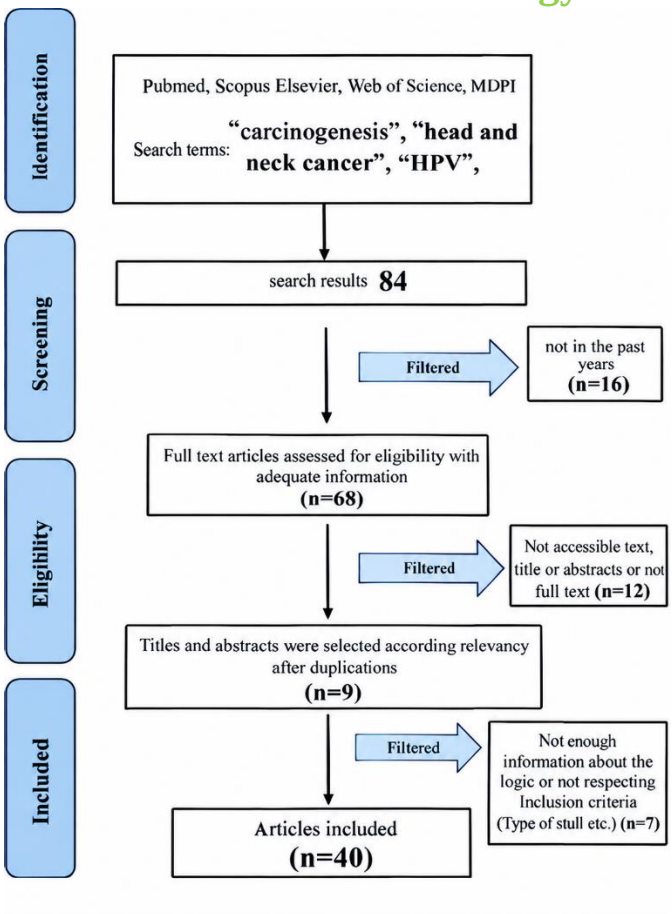

Figure 6. PRISMA-ScR flow diagram of study selection process

2.6 Data Extraction and Charting

Data extraction was performed using a standardized data-charting form developed in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews [30].

The following characteristics were extracted from each included study:

- First author and year of publication;
- Country and geographic region of the study;
- Study design and methodological approach;
- Sample size and participant characteristics;
- Anatomical location of the tumor;
- HPV detection and genotyping methods;
- Distribution of HPV16 and other high-risk HPV genotypes;
- Molecular mechanisms involved in HPV-associated carcinogenesis;
- Clinical characteristics and reported outcomes;
- Prevention strategies, including HPV vaccination approaches;
- Diagnostic methods and biomarker-based approaches;
- Emerging technologies, including artificial intelligence-based diagnostic and analytical methods.

Data extraction was performed independently by two reviewers using the predefined data-charting framework. Any discrepancies identified during the extraction process were resolved through discussion and consensus.

2.7 Data Synthesis

A descriptive qualitative synthesis of the included studies was conducted.

The extracted evidence was organized into the following major thematic domains:

1. Epidemiology and global distribution of HPV-associated OPSCC;
2. HPV transmission pathways and associated risk factors;
3. Molecular mechanisms underlying HPV-mediated carcinogenesis;
4. Clinical characteristics, treatment response, and prognosis;
5. Prevention strategies and HPV vaccination;
6. Diagnostic approaches, HPV detection methods, and biomarker development;
7. Emerging technologies, including artificial intelligence and computational approaches in HPV-associated cancer research.

Because of the considerable heterogeneity among included studies regarding study populations, research designs, HPV detection techniques, diagnostic criteria, and reported outcomes, statistical pooling and quantitative meta-analysis were not considered appropriate.

2.8 Methodological Considerations

According to current Joanna Briggs Institute guidance for scoping reviews, formal methodological quality appraisal and risk-of-bias assessment were not performed [30].

The primary objective of this review was to systematically map the available evidence, describe current research trends, identify methodological differences between studies, and highlight existing knowledge gaps in HPV-associated oropharyngeal cancer research rather than to evaluate intervention effectiveness or generate pooled estimates.

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3. RESULTS

3.1 Study Characteristics and Evidence Mapping

The literature search identified evidence describing multiple aspects of human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC), including epidemiology, viral transmission, molecular mechanisms, clinical characteristics, prevention strategies, diagnostic approaches, and emerging technologies.

The included evidence consisted of epidemiological studies, molecular investigations, clinical studies, diagnostic studies, and translational research.

The reviewed studies demonstrated that HPV-associated OPSCC represents a biologically distinct subgroup of head and neck squamous cell carcinoma (HNSCC), with different etiological factors, molecular alterations, and clinical behavior compared with HPV-negative tumors.

The main characteristics of the included studies, including study focus, methodological approach, and investigated HPV-related factors, are summarized in **Table 1**.

Table 1. Characteristics of Included Evidence on HPV-Associated Oropharyngeal Cancer

Study area	Main evidence identified	Representative references
Epidemiology of oral and oropharyngeal cancer	Global burden of oral cancer and changing epidemiological patterns	[1,2]
Traditional risk factors	Association of tobacco and alcohol exposure with oral and pharyngeal cancer	[3]
HPV-associated head and neck cancer	HPV as an independent etiological factor in OPSCC	[7,12,33]
HPV detection and diagnosis	Molecular detection methods and clinical implications	[9,10]
HPV vaccination and prevention	Vaccine effectiveness and preventive strategies	[11,23,25]
Artificial intelligence and digital diagnostics	AI applications in cancer detection and precision medicine	[31]

3.2 Epidemiology of HPV-Associated Oropharyngeal Cancer

HPV-associated OPSCC has become one of the most rapidly increasing subsets of head and neck malignancies worldwide. Unlike conventional HNSCC, which is strongly associated with tobacco and alcohol exposure, HPV-positive OPSCC represents a distinct disease entity driven primarily by persistent infection with oncogenic HPV types. Current evidence indicates substantial geographic variation in HPV prevalence among OPSCC cases, with reported HPV positivity ranging approximately from 20% to 90%, depending on population characteristics, geographic region, and detection methodology. The highest prevalence rates have been reported in North America and several European countries [9,12,33]

Among oncogenic HPV types, HPV16 is the predominant genotype identified in HPV-associated OPSCC. HPV16 accounts for the majority of HPV-positive tumors, whereas HPV18 and other high-risk genotypes are detected less frequently [7,12].

HPV-positive OPSCC demonstrates characteristic demographic features. The disease predominantly affects middle-aged adults, commonly between 40 and 60 years of age, and shows a marked male predominance. Epidemiological studies have demonstrated substantially higher prevalence among men compared with women, which may reflect differences in HPV exposure, sexual behavior patterns, immune responses, and viral persistence mechanisms [13,16,18]. The epidemiological characteristics of HPV-associated OPSCC are summarized in **Table 2**.

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Table 2. Epidemiological and Clinical Characteristics of HPV-Associated OPSCC

Characteristic	Reported findings	References
HPV contribution to OPSCC	Approximately 20–90% of OPSCC cases depending on region and detection method	[9,12,33]
Predominant HPV genotype	HPV16 is the dominant oncogenic subtype	[7,12]
Age distribution	Most commonly affects individuals aged 40–60 years	[12]
Sex distribution	Strong male predominance reported in epidemiological studies	[16,18]
Main anatomical sites	Tonsillar crypts and base of tongue are predominant locations	[7]
Traditional risk factors	Frequently occurs without heavy tobacco or alcohol exposure	[12,27]

3.3 Transmission and Risk Factors

Oral HPV infection is primarily acquired through sexual exposure, particularly oral–genital contact. Population-based studies have demonstrated significant associations between oral HPV positivity and sexual behavior characteristics, including increased number of sexual partners, early sexual debut, and oral sexual practices [16–18]. However, HPV infection is relatively common among sexually active individuals, and most infections are transient due to effective host immune clearance. Persistent infection with high-risk HPV types represents the critical step associated with malignant transformation [19,22]. Additional factors influencing HPV persistence include immune status, smoking exposure, viral genotype, viral load, and anatomical site of infection. Immunosuppression and coexisting environmental risk factors may facilitate progression from persistent infection to malignant disease [20,22].

3.4 Molecular Mechanisms of HPV-Mediated Carcinogenesis

High-risk HPV-associated carcinogenesis is primarily mediated through continuous expression of viral oncogenes E6 and E7. These viral proteins interfere with essential cellular regulatory pathways by targeting tumor suppressor mechanisms. HPV E6 promotes degradation of p53, resulting in impaired DNA repair mechanisms and inhibition of apoptosis. HPV E7 interacts with the retinoblastoma protein (pRb), leading to uncontrolled cell-cycle progression and cellular immortalization [7,8].

Integration of HPV DNA into the host genome represents an important molecular event associated with malignant transformation. Persistent viral oncogene expression promotes genomic instability, immune escape, and progressive epithelial transformation [8,29].

The major molecular pathways involved in HPV carcinogenesis are summarized in **Table 3**.

Table 3. Molecular Mechanisms, Diagnosis, Prevention and Emerging Technologies

Domain	Main findings	References
Viral oncogenesis	E6-mediated p53 degradation and E7-mediated pRb inhibition	[7,8]
Viral persistence	Failure of immune clearance promotes malignant progression	[21,22]
HPV detection	PCR, molecular assays, p16 immunohistochemistry	[9,28]
Vaccination	Effective prevention against high-risk HPV infection	[11,23,25]
Artificial intelligence	AI-assisted cancer detection and precision oncology applications	[31]

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3.5 Diagnosis, Prevention and Emerging Technologies

Current diagnostic approaches for HPV-associated OPSCC include HPV DNA detection, RNA-based assays, and p16 immunohistochemistry as a surrogate marker of transcriptionally active HPV infection. However, unlike cervical cancer, standardized population-based screening programs for oral HPV infection are currently unavailable [9,28].

Prevention strategies primarily focus on HPV vaccination. Available evidence demonstrates that prophylactic vaccination effectively reduces persistent infection with high-risk HPV genotypes and may contribute to reducing future HPV-associated malignancies [11,23,25].

The orogenital route of transmission has been shown to be the most documented route of oral HPV infection. Prevention of HPV - HNSCC is based on the prevention of oral infection with high-risk HPV types. The strategy for the prevention of HPV-HNSCC involves the education of health workers and public health education about the viral nature of this cancer variant, routes of HPV infection, patterns of corresponding dangerous sexual activity and possibilities of mechanical protection against infection, but the main expectations are associated with the systematic vaccination of the population against HPV, recommended by WHO for the “prevention of cervical cancer, as well as cancer of the vagina, vulva, anus, penis, oropharynx and other HPV-associated diseases” (fig.7).

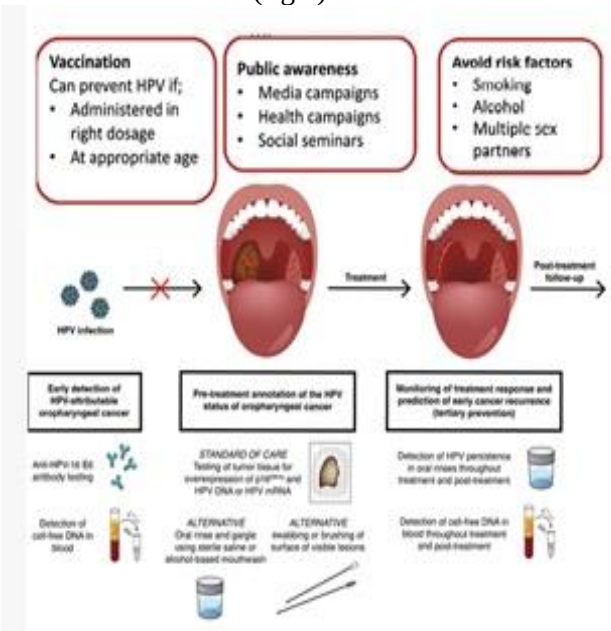

Figure 7. Schematic pictuars prevention of oropharyngeal cancer

Three vaccines containing self-assembling empty "shells" of high-risk HPV L1 capsid proteins have been developed to date: the bivalent vaccine "Cervarix" (licensed in 2007) with L1 types 16 and 18, the tetravalent vaccine "Gardasil-4" (2006) with L1 types 16, 18, 6, 11, and the nonovalent vaccine "Gardasil 9" (2014) with L1 types 16, 18, 6, 11, 31, 33, 45, 52, and 58. The vaccine, administered intramuscularly in two or three doses, provides adaptive immunity to HPV infection of both the anogenital andoral tissues: after the first (and second) vaccine injection, within 4-6 months, memory B cells mature, which, after reactivation by the last injection, differentiate into long-lived plasma cells capable of secreting specific antibodies over the next 10-20 years and maintaining their circulation in the body's biological environments, including in serous exudate in the area of microdamage to the epithelium, effectively blocking the connection of L1 of infectious HPV with epithelial cells of the basal layer preventing infection.

Formation of collective immunity against HPV (significant reduction in virus circulation in the population, including a reduction in the risk of infection of the male population) is expected with regular vaccination of ≥ 80% of girls aged 9–14 years, before the debut of sexual activity (the primary target population group in WHO documents); corresponding state programs operate in 71 countries around the world

HPV can be transmitted by self-vaccination from thegenital area to the mouth area through infected nails. Therefore, HPV in the head and neck is transmitted orally through oral sex, contributing to the majority of HPV transmission/infections associated with the head and neck[30].

Almost all of these cancers are caused by HPV16, a subtype of the HPV virus. Studies show that approximately 70 percent of oropharyngeal cancers are caused by HPV.

Recent advances in artificial intelligence and computational oncology have introduced new possibilities for early cancer detection, automated image interpretation, molecular classification, and personalized clinical decision-making. Although these technologies remain under investigation, they represent promising future approaches for improving diagnosis and risk stratification in HPV-associated cancers [31,].

4. DISCUSSION

4.1 HPV as a Distinct Molecular and Epidemiological Entity in OPSCC

The findings of this scoping review confirm that human papillomavirus, particularly HPV16, represents a major etiological factor in the development of oropharyngeal squamous cell carcinoma. Over recent decades, HPV-positive OPSCC has emerged as a clinically and

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biologically distinct subgroup of head and neck cancer, differing substantially from traditional tobacco- and alcohol-associated malignancies. The increasing incidence of HPV-positive OPSCC, particularly in North America and Europe, contrasts with the declining incidence of tobacco-related head and neck cancers. This epidemiological transition reflects changes in population behavior, reduced tobacco exposure, and increasing recognition of HPV as an independent carcinogenic factor [7,12,33]. Large population-based analyses have demonstrated that HPV-associated tumors account for a growing proportion of OPSCC cases, particularly among younger and middle-aged patients without substantial exposure to conventional carcinogens [27,35].

Unlike HPV-negative OPSCC, HPV-positive tumors frequently demonstrate improved biological behavior and better clinical outcomes. The favorable prognosis is associated with preserved treatment sensitivity, distinct molecular characteristics, and enhanced immune recognition of viral-associated tumor antigens [35].

4.2 Molecular Basis of HPV-Driven Carcinogenesis

The carcinogenic mechanism of HPV-associated OPSCC is primarily mediated by persistent expression of viral oncogenes E6 and E7. These proteins disrupt essential cellular regulatory pathways through inactivation of p53 and retinoblastoma protein (pRb), resulting in impaired apoptosis, uncontrolled cellular proliferation, and genomic instability [7,8].

Integration of HPV DNA into the host genome represents a critical event in malignant transformation. Continuous expression of viral oncogenes contributes to accumulation of molecular alterations and facilitates immune escape, allowing progression from persistent infection to invasive carcinoma [8,29].

Compared with HPV-negative cancers, HPV-positive OPSCC demonstrates different molecular profiles, including increased immune activity and higher levels of viral antigen expression. These characteristics provide a biological explanation for the improved response to treatment and the growing interest in immune-based therapeutic strategies [35,37].

4.3 Transmission, Persistence, and Risk Factors

The reviewed evidence indicates that oral HPV acquisition is strongly associated with sexual exposure, particularly oral–genital contact. Epidemiological studies have consistently demonstrated associations between oral HPV infection and sexual behavior patterns, including increased number of partners and early sexual initiation [16–18].

However, the presence of HPV infection alone is insufficient for carcinogenesis. Most oral HPV infections are transient and are eliminated by host immune mechanisms. Persistent infection with high-risk HPV genotypes represents the essential prerequisite for malignant transformation [20,22].

Several cofactors may influence viral persistence and progression, including smoking, immune suppression, age, viral genotype, and local tissue characteristics. These factors may contribute to differences in disease development among infected individuals [19,22].

4.4 Clinical Implications and Prognostic Differences

HPV-positive OPSCC differs clinically from conventional HNSCC. Patients are often younger, have limited tobacco and alcohol exposure, and frequently present with small primary tumors accompanied by cervical lymph node metastases.

Despite advanced nodal disease at diagnosis, HPV-positive OPSCC generally demonstrates improved survival outcomes compared with HPV-negative disease. The landmark study by Ang et al. demonstrated that HPV status represents one of the strongest prognostic biomarkers in OPSCC, with HPV-positive patients showing significantly improved overall survival [35].

These findings have influenced current treatment strategies and stimulated research into individualized therapeutic approaches aimed at maintaining oncological control while reducing treatment-related morbidity.

4.5 Treatment De-intensification and Modern Therapeutic Strategies

Because HPV-positive OPSCC patients generally have better prognosis, treatment de-intensification has become an important research direction. The objective of these approaches is to reduce long-term complications such as swallowing dysfunction, xerostomia, and speech impairment without compromising tumor control. Clinical studies evaluating reduced-intensity radiotherapy, modified chemotherapy regimens, and response-adapted approaches suggest that selected patients may benefit from less aggressive treatment strategies; however, these approaches require careful patient selection and remain under clinical investigation [36,39].

Immunotherapy represents another important development in HPV-associated head and neck cancer. Immune checkpoint inhibitors targeting PD-1/PD-L1

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pathways, including nivolumab and pembrolizumab, have demonstrated clinical benefit in recurrent or metastatic HNSCC and may be particularly relevant in HPV-positive tumors because of their viral antigen expression and immune activation profile [37,38].

Surgical management has also evolved with the introduction of minimally invasive techniques such as transoral robotic surgery (TORS) and transoral laser microsurgery. These approaches aim to preserve organ function while maintaining oncological safety in selected early-stage patients [40].

4.6 Prevention, Screening Challenges, and Future Perspectives

HPV vaccination remains the most effective preventive strategy against HPV-associated malignancies. Although current vaccination programs were primarily developed for cervical cancer prevention, increasing evidence suggests potential long-term benefits in reducing HPV-related OPSCC incidence [11,23,25]. A major unresolved challenge is the absence of a standardized screening strategy for oral HPV infection. Unlike cervical cancer, where established screening programs allow early detection of precancerous lesions, OPSCC currently lacks validated population-based screening methods [9,28].

Future research should focus on improving early detection through molecular biomarkers, salivary diagnostics, and computational approaches. Artificial intelligence-based technologies may provide additional opportunities for automated image interpretation, risk prediction, and integration of complex clinical and molecular data [31,32].

4.7 Limitations of Current Evidence

Several limitations should be considered when interpreting the available evidence. First, most epidemiological studies originate from North America and Europe, limiting global generalizability. Second, variability in HPV detection methods, including differences between DNA, RNA, and p16-based approaches, contributes to heterogeneity among studies [9,10]. Additionally, although HPV vaccination demonstrates strong efficacy against infection with high-risk HPV genotypes, direct evidence regarding reduction of OPSCC incidence remains limited because of the long latency period between infection and cancer development [23,25].

4.8 Future Research Directions

Future investigations should prioritize the development of standardized oral HPV screening strategies, longitudinal studies evaluating vaccine impact on OPSCC incidence, and personalized treatment approaches integrating molecular biomarkers. The combination of HPV molecular profiling, immunotherapy, minimally invasive surgery, and artificial intelligence-based diagnostic systems may contribute to a more individualized management model for HPV-associated OPSCC.

CONCLUSION

Human papillomavirus, particularly HPV16, is a major etiological factor in oropharyngeal squamous cell carcinoma and represents a distinct molecular and clinical subtype of head and neck cancer. This scoping review highlights the central role of persistent high-risk HPV infection and viral oncogenes E6 and E7 in carcinogenesis, as well as the changing epidemiology of HPV-positive OPSCC, which increasingly affects younger patients without traditional risk factors. HPV vaccination remains the most effective preventive strategy, while the absence of standardized oral HPV screening continues to represent an important clinical challenge. Advances in molecular diagnostics, immunotherapy, minimally invasive surgery, and artificial intelligence-based technologies provide promising opportunities for improving early detection, risk stratification, and personalized management. Future research should focus on establishing effective screening approaches, evaluating the long-term impact of vaccination on OPSCC incidence, and integrating emerging technologies into multidisciplinary care to further improve patient outcomes.

DECLARATION

Acknowledgements
"Not applicable"

Conflict of interest

The author declares that he has no Conflict of interest.

Funding
The work was not funded.

Data Sharing
Not applicable

Ethical Approval
"Not applicable"

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