Kurdistan Journal of Applied Research (KJAR)
Print-ISSN: 2411-7684 | Electronic-ISSN: 2411-7706

Review Article

HPV-Positive Oropharyngeal Cancer: An Umbrella Review of Global Prevalence and Survival Outcomes

Mohammed Khalid Mahmood [a]*, Balen Hamid Qadir [b], Balkees Taha Garib [c], Yad Mariwan Mohammed Amin [d], Ariwan Othman Saeed [e, f], Herve Tassery [a], Delphine Tardivo [a], Romain Lan [a]

[a] Faculty of Medical and Paramedical Sciences, Aix-Marseille University, French National Center of Scientific Research (CNRS), French Blood Establishment (EFS), Bio-Cultural Anthropology, Law, Ethics and Health Laboratory (ADES), Marseille, France.
[b] Department of Dentistry, Komar University of Science and Technology, Sulaymaniyah, Iraq.
[c] College of Dentistry, University of Sulaimani, Sulaymaniyah, Iraq.
[d] Department of Dentistry, Tishk International University, Sulaymaniyah, Iraq.
[e] Zhianawa Cancer Center, Sulaymaniyah, Iraq.
[f] College of Medicine, University of Sulaimani, Sulaymaniyah, Iraq.

Submitted: 04 April 2026
Revised: 16 June 2026
Accepted: 23 June 2026

*** Corresponding Author**: mohammed-khalid.mahmood@etu.univ-amu.fr

Keywords: Human papillomavirus, Oropharyngeal cancer, Prevalence, Survival, Systematic review.

How to cite this paper: M. K. Mahmood, B. H. Qadir, B. T. Garib. Y. M. M. Amin, A. O. Saeed, H. Tassery, D. Tardivo, R. Lan, "HPV-Positive Oropharyngeal Cancer: An Umbrella Review of Global Prevalence and Survival Outcomes", KJAR, vol. 11, no. 1, pp: 222-241 Jun 2026, doi: 10.24017/science.2026.1.15

Abstract: Human papillomavirus (HPV) has transformed oropharyngeal cancer (OPC) epidemiology, creating distinct disease entities. This umbrella reviews synthesized evidence on HPV-positive OPC prevalence and survival. Four databases were searched for systematic reviews (SRs) examining HPV prevalence and survival in OPC. Meta-analysis was performed using random effects methodology. Quality was assessed using A Measurement Tool to Assess systematic Reviews 2 (AMSTAR 2) and evidence certainty was rated by utilizing Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool. A Corrected Covered Area (CCA) analysis was conducted to measure the degree of overlapping literature among the included SRs. Twenty-four SRs encompassing 783 primary studies and 146,218 OPC patients were included. Overall HPV prevalence was 43% (95% CI: 41-46%). HPV-16 predominated (79%), with highest prevalence in tonsils (60%), followed by base of tongue (43%). The pooled prevalence of HPV in soft palate was 8%. Males showed higher prevalence than females (47% vs. 35%). North America had the highest regional prevalence (59%), followed by Oceanica (49%), Europe (44%), and Asia (37%). The comparison of the meta-analyses (MAs) before and after 2020 showed a reduction in prevalence from 48% to 41%, although the difference was not statistically significant. For the virus detection method, p16 and in situ hybridization positivity resulted in higher prevalences compared to Polymerase Chain Reaction (PCR) alone. Significant presence of heterogeneity and publication bias, large CIs and the observational nature of the included study designs led to "low" evaluation of all the pooled analyses assessed by GRADE. HPV-positive patients demonstrated superior survival outcomes, though HPV-non16 subtypes showed poorer prognosis. In conclusion, HPV affects nearly half of OPC cases globally, with significant anatomical, demographic, and geographic variations. These findings support individualized treatment approaches beyond binary HPV status classification.

1. Introduction

Since the discovery of the human papillomavirus (HPV) as a risk factor agent, the epidemiological landscape of oropharyngeal cancer (OPC) has changed dramatically during the last thirty years. Because of this change, HPV-positive and HPV-negative OPCs are now two separate disease entities, each with unique patient demographics, biological traits, and clinical outcomes [1, 2].

In the past, alcohol and tobacco use were the main causes of OPC cases, which usually affected elderly individuals with a bad prognosis. Nonetheless, epidemiological research has shown a startling rise in the incidence of OPC among younger, nonsmoking populations in developed countries since the 1990s [3, 4]. As a result, HPV, especially HPV-16, was found to be a primary cause of oropharyngeal carcinogenesis [5].

When compared to HPV-negative tumors, HPV-positive OPCs exhibit noticeably better treatment responses and survival outcomes, which has resulted in significant modifications to staging schemes and therapeutic approaches [5]. Since HPV status is now a main factor in the 8th edition of the AJCC staging system, research on therapeutic de-escalation techniques for patients with HPV has increased due to its better prognosis [6, 7]. Given that therapy de-escalation trials are currently in progress yet ideal patient selection criteria have not yet been established [8, 9].

Viral oncoproteins E6 and E7 target tumor suppressor pathways as part of the biological mechanisms, which results in tumors that have higher immunogenicity, improved radiosensitivity, and intact wild-type p53 activity [10, 11]. The distinct susceptibility of crypt epithelium to viral infection is reflected in the anatomical preference for tonsillar and base of tongue locations [12]. The tonsillar crypt's permeable basement membrane allows HPV to easily access basal epithelial cells without creating micro abrasions, unlike other oral and head and neck locations where HPV needs tissue damage to reach vulnerable cells [12, 13]. The tonsillar crypts are lined with specialized reticular crypt epithelium with a disrupted basement membrane and basal cell layer [14], and the existence of several branching crypts enhances the surface area for antigen processing by over 700 times [15].

Although the body of research on HPV-positive OPC is expanding, there is still a great deal of variation among studies in terms of patient demographics, outcome measures, and detection techniques. The prevalence of HPV subtypes, anatomical subsite variations, temporal trends, demographic disparities, and geographic variations are among the significant clinical problems that are still not fully addressed. Since new data indicates that not all HPV-positive cancers show comparable results [16, 17], a more comprehensive investigation of the survival benefits linked to HPV positivity is also necessary. The best methodology for answering these concerns in-depth is an umbrella review strategy, which combines data from several SRs to get reliable estimates and pinpoint sources of heterogeneity.

This is the first systematic umbrella review that collects and evaluates all previous systematic reviews (SRs) and meta-analyses (MAs) on the prevalence and survival of HPV-related OPC, to the best of our knowledge and according to the literature search. Its objectives are to clarify the literature, provide an overview of the state of the field, pinpoint knowledge gaps, and pave the way for future studies to concentrate on better solutions. Therefore, the aim of this systematic umbrella review was to provide a thorough evidence synthesis on the prevalence and survival outcomes of HPV-positive OPCs, and to investigate the differences by HPV subtype, anatomical subsite, temporal trends, demographic factors, geographic regions, and detection methodologies.

2. Materials and Methods

2.1. Protocol Registration

The PRISMA criteria [18] were followed in conducting this umbrella review. Under the registration number CRD420251104214, the protocol for this study was prospectively registered in the PROSPERO (https://www.crd.york.ac.uk/PROSPERO/view/CRD420251104214).

2.2. Eligibility Criteria

In accordance with the PECOS/T guideline, the following research questions were developed for this review: (P) Problem: How common is HPV among OPC patients? How does this prevalence vary by time, sex, location, HPV subtype, cancer subsite, and detection technique? What impact does HPV infection have on OPC survival? (P) Population: OPC patients, whether infected with HPV or not. (E) Exposure: HPV positivity or negativity. (C) Comparison: Comparison between baseline and follow-up, or comparison between cases and controls. (O) Result: Survival and prevalence. (S) Study design: All English-language published SRs and meta-analyses (MAs) that have reported their pooled analysis in

percentages or the number of positive instances from the sample under study. (T) Time: SRs and MAs published prior to July 2025 in the mentioned databases.

Redefining variables such as OPC (and its subgroups), HPV positive (and its subgroups), prevalence, and survival measures was not necessary because the included SRs had previously established these classifications when choosing which main studies to include. As a result, all the variable categories were simply gathered together.

Included were all MAs that reported the aforementioned association and reported their findings as a percentage. Due to their lack of comparability, the few MAs that displayed their results in odds ratios (OR) were disqualified. Additionally, all MAs from *in vitro*, animal, and preclinical research were disqualified.

Excluded were non-systematic reviews (narrative, scoping, etc.), those that reported their findings in a statistical method and unit that were not comparable, and those that looked at one of the OPC or HPV factors without examining the other.

SRs without MAs were also included in the evidence synthesis of survival outcome as a pooled analysis for the survival outcome was not possible because of the lack of comparability.

2.3. Search Strategy

To find all the records published prior to July 2025, the electronic databases PubMed, MEDLINE, Scopus, and Embase were searched.

The MeSH phrases and keywords associated with OPC (and its subtypes), HPV (and its subtypes), and systematic review/meta-analysis formed the basis of the search technique. Table S1 provides a complete list of search phrases and combinations. Dates of publication were not restricted.

2.4. Study Selection

Initially, duplicates were eliminated once the gathered records were entered into reference management software. Two independent reviewers (M. M. and B. Q.) carried out the study selection process in two phases. Titles and abstracts were screened for potentially relevant studies based on eligibility criteria in Part 1 of the selection procedure. The full-text publications were then thoroughly examined for eligibility in Part 2. MAs and SRs who satisfied all qualifying requirements were chosen to be included. The two reviewers discussed and worked out any disagreements that arose during the screening process. A third reviewer (Y. A.) made the final decision in cases when no consensus could be obtained.

2.5. Data Extraction

Two reviewers (M. M. and B. Q.) independently extracted the data. When agreement could not be reached, a third reviewer (M. A.) was consulted in order to reconcile the conflicting data extraction.

Worksheets for general prevalence, HPV subtypes, cancer subsites, sex, time, and detection techniques were created within an Excel file to offer an organized gathering of data by clinical variables/parameters.

The following research characteristics were extracted: sample size, demographic characteristics, year of publication, number of primary studies included in the quantitative and qualitative analysis, study design of the primary studies, first author's surname, and their key findings.

The number of HPV-positive cases and the total number of OPC cases were extracted for the pooled analysis because prevalence and proportion were the primary effect sizes in this review. The number of HPV-positive cases is estimated using the point estimate for studies that only provided the prevalence in percentage and 95% CIs, omitting the total number of OPC tests and HPV-positive cases.

2.6. Quality Evaluation of the Included Studies

The included studies were evaluated for methodological quality using the AMSTAR 2 tool [19]. Each review is given a quality grade of high, moderate, poor, or severely low using the AMSTAR 2 tool. The seven domains designated as "critical" by AMSTAR 2 are given particular attention. Each

evaluation was completed independently by two reviewers (M. M. and B. Q.), and disagreements were resolved by discussion or, if necessary, the participation of a third reviewer (Y. A.).

2.7. Synthesis and Analysis of Data

The DerSimonian and Laird random-effects model [20] was employed to guarantee methodological consistency among the included studies. The number of cases and the sample size were taken and reanalyzed because all of the results were expressed as percentages.

The I2 statistical test was used to evaluate study heterogeneity. For heterogeneity, a p-value of less than 0.10 was deemed statistically significant. The Cochrane Handbook for Systematic Reviews' recommendation that values 0% and 40% as possibly unimportant, 30% to 60% as indicative of moderate heterogeneity, 50% to 90% as substantial, and 75% to 100% as indicative of considerable heterogeneity was followed when interpreting the I^2 values [21].

Additionally, statistical techniques were used to evaluate the existence of publication bias. To find small-study effects, Egger's regression test was used; a p-value of less than 0.05 suggested possible bias [22]. Cochrane's RevMan program, which can be accessible online, was used for all statistical analyses in this umbrella review [23].

2.8. Assessment of Evidence Certainity

The degree of certainty in the evidence supporting the results in this study was evaluated using the GRADE framework [24].

2.9. Overlap Analysis

A Corrected Covered Area (CCA) analysis was conducted to measure the number of repeated primary studies in the included SRs to see the degree of overlapping literature [25].

3. Results

3.1. Selection of Included Studies

A comprehensive search of PubMed, MEDLINE, Scopus, and Embase yielded 639 records. Forty eight records were left for full-text screening after 584 out-of-scope, duplicate records and non-SRs were eliminated. Additionally, 21 more articles were eliminated because they had insufficient data (n = 2), duplicates (n = 1), or no data pertinent to the study's declared scope (n = 18). Moreover, three reviews that were very close to be included, were excluded because one only reported the measurement of OR without sufficient data on the HPV prevalence [26]. Another one reported prevalence and survival analysis for head and neck cancers without specific data for OPC [27]. The third one focused on treatment modalities rather than survival measurement [17]. In the final phase, 24 distinct SRs satisfied the requirements for inclusion; 18 of these were included in the prevalence's quantitative synthesis, while 8 were included in the survival's qualitative analysis. Prevalence and survival data were included in two reviews. Figure 1 depicts the study selection procedure.

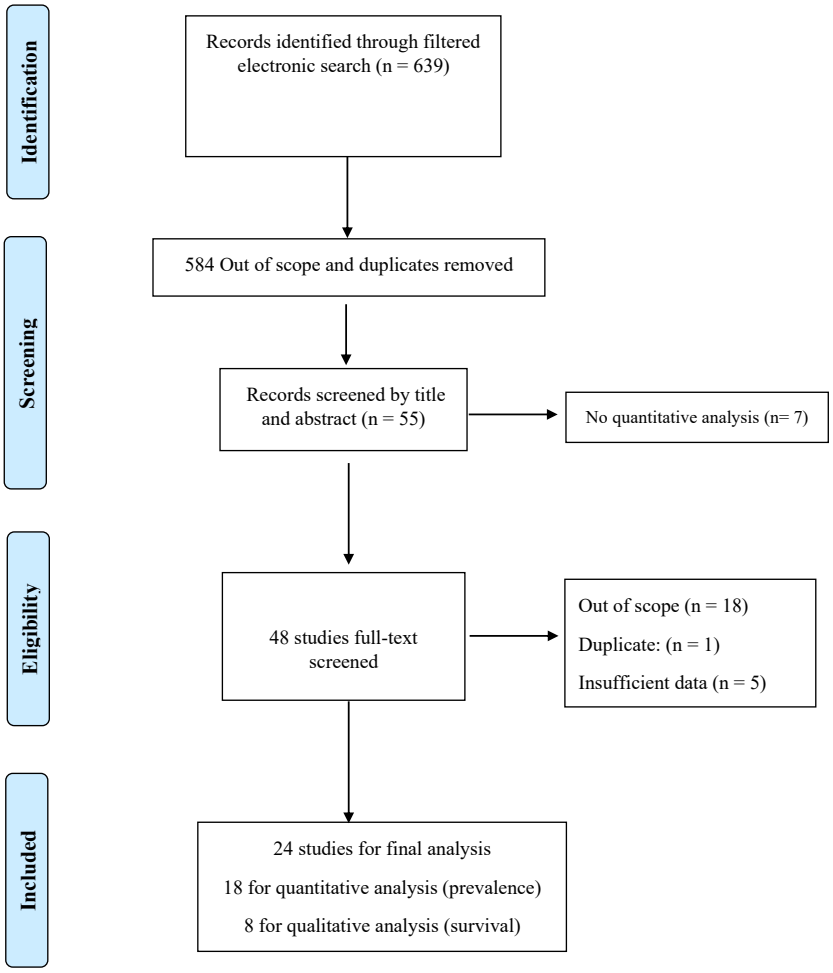

Figure 1: Study selection process.

3.2. Characteristics of the Included Studies

The frequency of HPV-related OPCs was investigated by 18 MAs [28-45]. The main categories of HPV were positivity or negativity, HPV subtype and viral detection method. Whereas the chief categories of OPC were cancer subsite such as the base of tongue, tonsils, soft palate and other sites. The essential clinical and demographical variables were prevalence in percentage of number of positive cases out of the sample, time, sex and geography.

The SRs came out between 2012 and 2025. Only cross-sectional or case-control observational studies were present in all of the included MAs. With a minimum of 8 and a maximum of 134 original studies, the meta-analyses included a wide spectrum of primary research.

In total, 783 primary studies were included in all the MAs. The MAs covered 146,218 OPC patients. Most of the included MAs contained global data, while few studies only focused on patients from specific continents or countries. Among the MAs that were included, the most adjusted factors were age, sex, smoking, region, education, comorbidities, lifestyle, and socioeconomic status. The study design of the primary studies were mostly cross-sectional and retrospective cohorts for the prevalence outcome. Table 1 presents the key characteristics of the studies.

Concerning the survival studies, 8 SRs were included that examined the survival of HPV-related OPC [29, 32, 46-51]. The main outcomes were overall survival, 5-years survival, disease-specific survival, disease-free survival and recurrence. The exposure was OPC with or without HPV infection. The number of included primary studies ranged from a minimum of 5 to a maximum of 77 studies in a total of 203 primary studies. These studies included ~65 thousand patients. Due to the vast heterogeneity among the exposures and outcomes of the studies pooled analyses couldn't be performed. The study design of the primary studies were mostly cross-sectional, retrospective and prospective cohorts for the survival outcome. Table 2 presents the key characteristics of these studies.

Table 1: Key characteristics of the included studies for prevalence.

Study	No. of included studies	Sample size	Population	HPV Prevalence	Subgroup findings
[28]	14	894	Europe	41.3% (31.8,50.7)	Tonsils: 66.4%; Pharynx: 15.3%
[29]	20	6,442	Global	Oropharynx (other than base of tongue and tonsils): 20% (13,30%)	---
[30]	71	10,908	Global	44.2%	HPV16: 37.2%; HPV33: 2.4%; HPV18: 1.6%; HPV35: 1.53%; HPV58: 0.89%. North America: 66.8%; Oceania: 43%; Europe: 41.4%; Africa: 4.89%. Females: 43.1%; Males: 34.5%. Tonsil: 45.7%; Base of tongue: 36.6%.
[31]	55	11,469	Global	42% (36,49%)	HPV16: 89%; Tonsils (highest): 63%
[32]	80	12,662	Global	49% (11,51%)	Base of tongue: 48%; Tonsils: 55%
[33]	8	514	China	HPV-16 only: 31.6% (21.7,41.5%)	---
[34]	58	5,433	Global	43.2%	Tonsils: 56% (54,58%); Base of tongue: 40% (38,43%); Soft palate: 12% (9,15%); Posterior wall: 19% (16,22%)
[35]	47	60,912	Global	50.8% (41.6,59.9%)	North America (highest): 60.2%; Asia-Pacific (lowest): 34.2%
[36]	134	12,139	Global	48.1% (43,53%)	North America (highest): 72.6% (63.8,80.6%). p16INK4a positivity in HPV+ cases: 87.2% (81.6,91.2%)
[37]	15	6,009	Global	44.8% (36.4,53.5%)	Male: 45.7% (36.5,55%); Female: 42.2% (34.3,50.5%). p16: 49.4% (38.2,60.5%); p16+ISH/PCR: 44.7% (33.5,56.2%)
[38]	102	5,398	Global	47.7% (42.9,52.5%)	Before 2000: 40.5% (35.1,46.1); 2000,2004: 64.3% (56.7,71.3); 2005,2009: 72.2% (52.9,85.7)
[39]	54	3,946	Global	45.8% (38.9,52.9%)	p16INK4a positivity in HPV+ cases: 86.7% (79.2,92.9%). E6/E7 mRNA positivity in HPV+ cases: 86.9% (73.2,96.8%)
[40]	14	1,145	South America	17.9% (7.6,31.4%)	---
[41]	25	1,815	Global	49% (46,51%)	HPV16/18 highest in Whites (61.1%), followed by Blacks (58.0%) and Asians (25.2%) (P<0.0001)
[42]	10	873	Global (only men)	45% (24,66%)	---
[43]	26	2,768	Asia Pacific	40.53% (38.71,42.35%)	HPV prevalence in OPC vs. oral cavity cancer (OR: 14.66; 6.09,35.26) and laryngeal cancer (OR: 4.06; 3.05,5.39 & OR: 3.23; 1.37,7.61) respectively
[44]	30	2,099	United States	Pre-1990: 20.9% (11.8,37.0); 1990,1999: 51.4% (45.4,58); 2000,2014: 65.4% (60,70.7)	---
[45]	30	455	India	22% (13,34%)	HPV attributable fraction (E6/E7 mRNA): 12.54%; (p16 positivity): 9.68%

HPV: human papillomavirus; OPC: oropharyngeal cancer; NA: not available.

Table 2: Key characteristics of the included studies for survival.

Ref	No. of included studies	Study focus	Total patients	Outcome	Key findings
[29]	42	HPV prevalence and survival in other OPC sites (excluding tonsils/base of tongue)	6,442	5-year overall survival	HPV prevalence 20% (95% CI 13,30%); No significant survival difference between HPV+ and HPV− (p=0.43)
[47]	10	Association of smoking and outcomes in HPV-positive OPC	2,321	Overall survival, disease-specific survival, disease-free survival, locoregional recurrence	8/10 studies showed significant effect of smoking on increasing recurrence and mortality
[32]	77	Survival of OPC patients	12,662	Overall survival	HPV+ OPC: HR 0.31 (95% CI 0.27,0.36)
[48]	5	Racial disparities and HPV status in OPC	1,153	Overall survival by race adjusted for HPV	HR 1.45 (95% CI 0.87,2.40) for black vs white patients
[49]	24	Sex differences in HPV-associated OPC	101,574	Overall survival by sex	No significant difference between male and female patients (aHR 0.98, 95% CI 0.93,1.04)
[50]	31	HPV-related OPC	NA	Disease-specific, overall, progression-free, disease-free survival	Pooled HR for tonsillar cancer: 0.50 (95% CI 0.33,0.77); OPC: 0.47 (95% CI 0.35,0.62)
[51]	9	HPV16 vs HPV-non16 subtypes in OPC	1,529 (1,310 HPV16; 219 HPV-non16)	Overall survival, recurrence-free survival, p16 positivity	HPV16: 5-year OS 83.4% (95% CI 77.8,89.0%); HPV-non16: 69.3% (95% CI 58.5,80.1%); HPV-non16 had significantly worse OS (log OR −0.54, p=0.008)
[46]	5	Racial disparities by HPV status in OPC	HPV+: 23,608; HPV−: 12,112	Overall survival by race, stratified by HPV status	HPV+ OPC: HR 1.10 (95% CI 0.96,1.23) black vs white (nonsignificant); HPV− OPC: HR 1.50 (95% CI 1.12,1.88) black vs white (significant)

HPV: human papillomavirus; HR: hazard ratio; NA: not available; OPC: oropharyngeal cancer; OS: overall survival; aHR: adjusted hazard ratio.

3.3. Quality of the Included Studies

The AMSTAR 2 instrument was utilized to evaluate the methodological quality of the SRs included. Out of the 25 included SRs, 13 were of "moderate" quality, 7 scored "low" or "critically low" quality, while only 4 studies scored a "high" quality assessment.

Just one research listed the studies that were excluded and explained why (Q7). The funding sources for the included studies were not disclosed by any of the SRs (Q10). Only eight of the research had previously registered their protocols in databases (Q2). When evaluating and explaining the review's findings, several research either ignored or only partially took the risk of bias in individual studies into account (Q13). Once more, a large number of review authors either failed to conduct a sufficient examination into publication bias or just partially did so (Q15). For every included SR, a complete itemized AMSTAR 2 rating is presented table S2.

3.4. Overlap Analysis

The CCA measurement showed that out of the total 783 studies, 631 records were unique, resulting in a CCA value of 2.22% which is categorized as "slight overlap. Details of the analysis are presented in table S3.

3.5. *Meta-analyses Results*

A total of ten pooled analyses were conducted as presented in table 3.

Table 3: Umbrella meta-analysis results.

Variables	Sample size	No. of included estimates	Effect size (95% CI)	p-value	I^2, p heterogeneity	Egger's test (Publication bias)	GRADE
Overall prevalence	147,447	20	0.43 (0.41,0.46)		99%, p<0.0001	0.01	Low
Sample size							
>1000	139,652	11	0.46 (0.43,0.48)	Intergroup difference: 0.18	98.6%, p<0.0001		
<1000	7,795	9	0.39 (0.29,0.49)		98.8%, p<0.0001		
Study quality							
Moderate-High quality	110,120	10	0.44 (0.41,0.47)	Intergroup difference: 0.54	98.7%, p<0.0001		
Low-Critically low quality	37,327	10	0.42 (0.37,0.47)		98.9%, p<0.0001		
HPV subtypes	82,367	24			100%, p=0	0.83	Low
HPV-16	20,504	6	0.79 (0.69,0.88)		99.6%, p<0.0001		
HPV-18	20,565	7	0.02 (0.01,0.03)		95.9%, p<0.0001		
HPV-33	15,883	4	0.03 (0.01,0.06)		98.5%, p<0.0001		
HPV-35	9,719	3	0.02 (0.01,0.05)		97.8%, p<0.0001		
Other than HPV-16 and 18	15,696	4	0.14 (0.09,0.19)		98.9%, p<0.0001		
Cancer subsite	28,465	15			99.5%, p=0	0.27	Low
Tonsils	13,498	5	0.60 (0.55,0.66)		97.5%, p<0.0001		
Base of tongue	6,543	5	0.43 (0.34,0.51)		97.8%, p<0.0001		
Soft palate	1,323	3	0.08 (0.04,0.14)		87.1%, p=0.0004		
Other	7,101	2	0.27 (0.11,0.47)		99%, p<0.0001		
Time	138,657	19					
Before 2020	34,747	11	0.48 (0.41,0.54)	Intergroup difference: 0.09	99.2%, p<0.0001	0.23	Low
After 2020	103,910	8	0.41 (0.38,0.45)		99%, p<0.0001		
Before 2015	15,103	7	0.46 (0.40,0.52)	Intergroup difference: 0.82	97.8%, p<0.0001	0.23	Low

Table 3: continue.

After 2015	123,554	12	0.45 (0.41,0.49)		99.4%, p=0		
Sex		8			99.8%, p=0	0.11	Low
Male	25,792	4	0.47 (0.33,0.61)	Intergroup difference: 0.32	99.8%, p<0.0001		
Female	7,518	4	0.35 (0.17,0.55)		99.6%, p<0.0001		
Region	47,760	25			99.3%, p=0	0.045	Very low
Europe	18,580	5	0.44 (0.41,0.46)		93.6%, p<0.0001		
Asia	10,037	6	0.37 (0.34,0.40)		90.1%, p<0.0001		
Africa	447	2	0.15 (0.00,0.45)		98.1%, p<0.0001		
South America	2,361	3	0.23 (0.21,0.27)		64.2%, p=0.06		
North America	14,717	7	0.59 (0.53,0.64)		97.9%, p<0.0001		
Oceanica	1,618	2	0.49 (0.38,0.60)		94.9%, p<0.0001		
Detection methods	27,237					0.60	Low
PCR	18,516	7	0.44 (0.29,0.59)		99.7%, p=0		
p16	4,390	4	0.63 (0.37,0.86)		99.6%, p<0.0001		
In situ hybridization (ISH)	1,972	2	0.61 (0.56,0.65)		76.5%, p=0.039		
PCR + ISH	20,488	9	0.48 (0.35,0.60)	Intergroup diff between (PCR+ISH) and (p16+E6/E7 mRNA): 0.12	99.6%, p=0	0.48	
p16 + E6/E7 mRNA	4,617	5	0.68 (0.45,0.87)		99.6%, p<0.0001		

CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; PCR: polymerase chain reaction; ISH: in situ hybridization.

The overall prevalence of HPV was 43% (41-46%) among OPC cases. Twenty estimates from 18 MAs contributed to this pooled analysis. Although this result was statistically significant, both the heterogeneity and publication bias were significant also (Table 3, Figure 2 and 3).

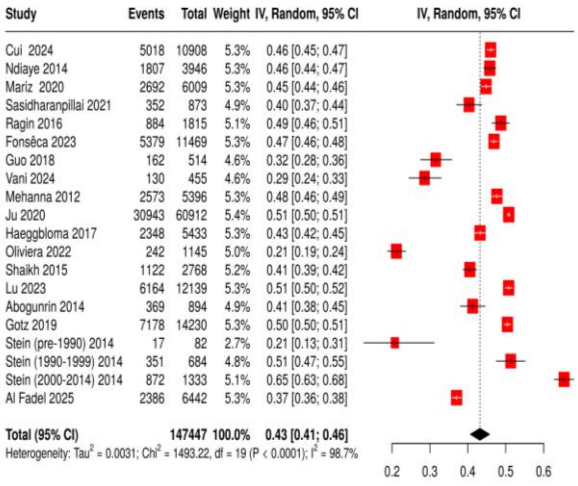

Figure 2: Forest plot of the prevalence of HPV-positive oropharyngeal cancers.

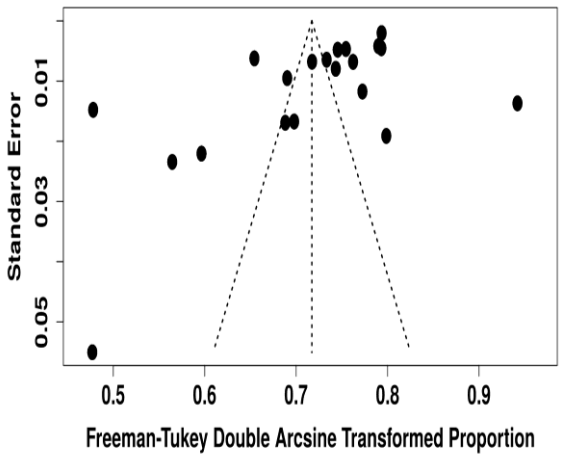

Figure 3: Funnel plot of the prevalence of HPV-positive oropharyngeal cancers showing proof of publication bias (Egger's test: p = 0.01).

A sensitivity analysis was conducted by comparing studies with a sample size of more than 1000 cases with those of less than 1000 cases. Even though large sample studies gave a higher prevalence (46% vs. 39%), the difference was not significant (p = 0.18). Moreover, comparison between the moderate/high quality studies with the low/critically low-quality studies showed no significant difference (Table 3, figure S1 and S2).

HPV-16 constituted most of the subtypes (79%), while the prevalence of HPV other than 16 and 18 was 14% (Table 3, Figure 4). Regarding the cancer subsite, prevalence was 60% in the tonsils, followed by 43% and 8% in the bases of the tongue and soft palate respectively (Table 3, Figure 5).

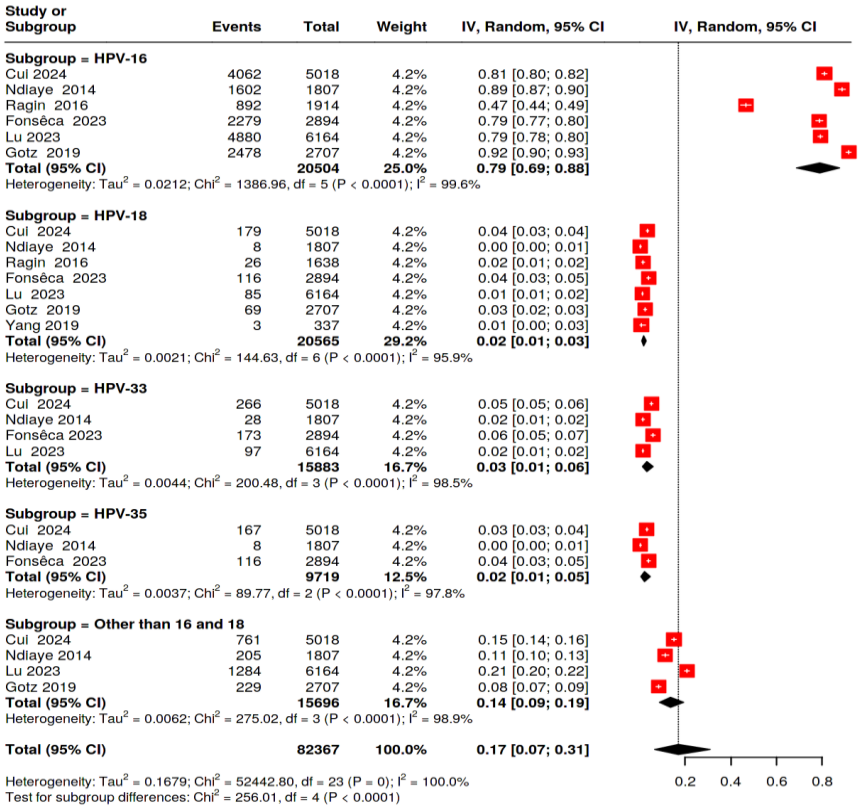

Figure 4: Forest plot of the prevalence of HPV-positive oropharyngeal cancer cases stratified according to the viral subtypes.

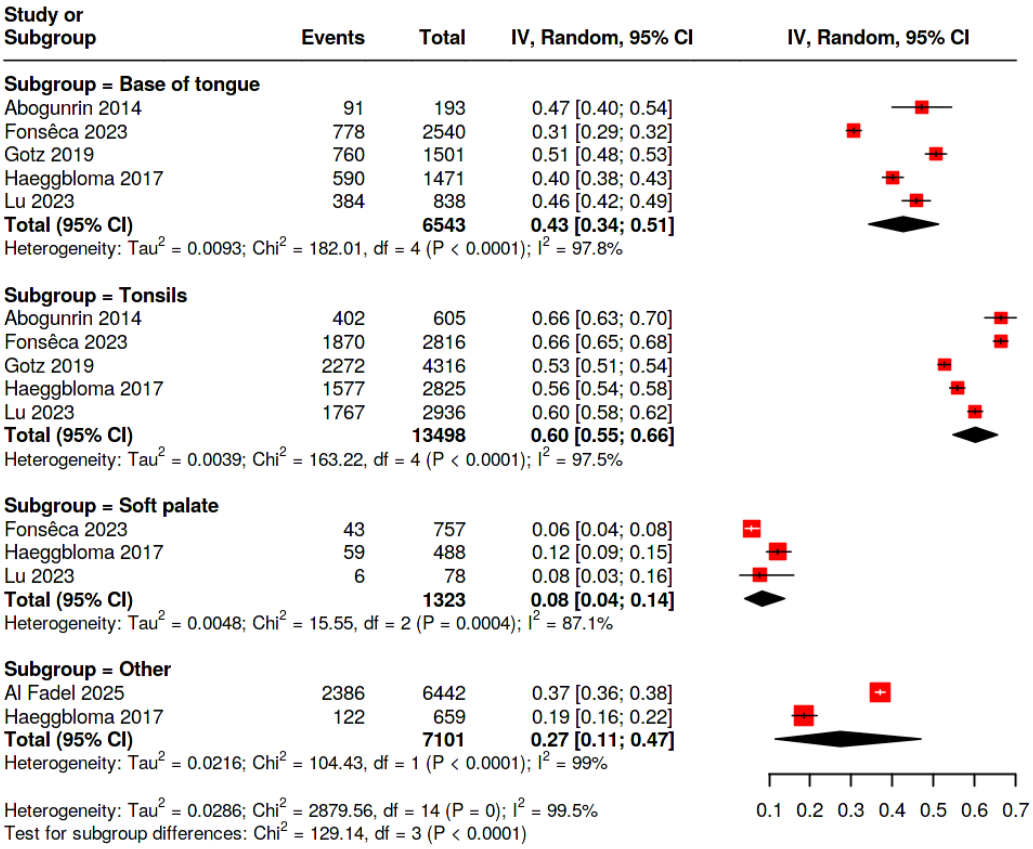

Figure 5: Forest plot of the prevalence of HPV-positive oropharyngeal cancers stratified according to subsites.

Time-wise analysis of the comparison before and after 2015, revealed approximately the same prevalence results. However, the comparison of the MAs before and after 2020 showed a reduction in prevalence from 48% to 41%, although the difference was not statistically significant (p = 0.09) (Table 3, Figures S4 and S5). Male OPC patients had higher HPV prevalence compared to females (47% vs. 35%, p = 0.32) (Table 3, Figure 6). North America had the highest prevalence (59%), followed by 49% for Oceanica, 44% for Europe and 37% for Asia (Table 3, Figure S5).

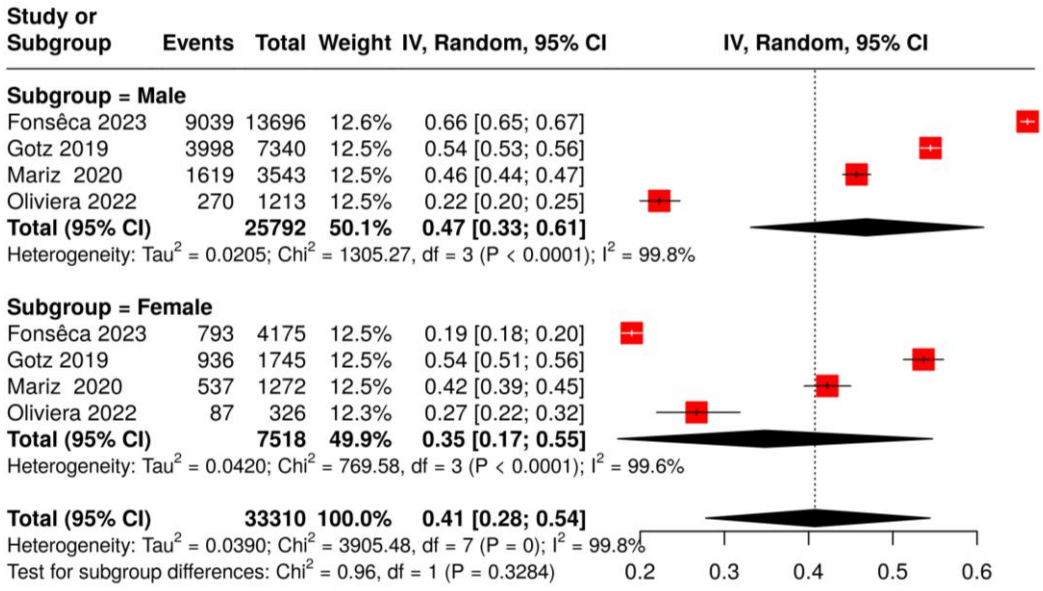

Figure 6: Forest plot of the prevalence of HPV-positive oropharyngeal cancers comparing the sexes.

For the virus detection method, pooled analysis for prevalence based on PCR was 0.44 (0.29-0.59). p16 and in situ hybridization (ISH) positivity resulted in higher prevalences of 0.63 (0.37-0.86) and 0.61 (0.56-0.65) respectively (Table 3, Figure 7). The PCR+ISH was compared as direct viral detection methods with a category of p16 + E6/E7 mRNA which represent markers of viral activity. Although the latter group gave a higher pooled prevalence PCR+ISH group (68% vs. 48%), the difference didn't reach statistical significance (p = 0.12) (Table 3, Figure S6).

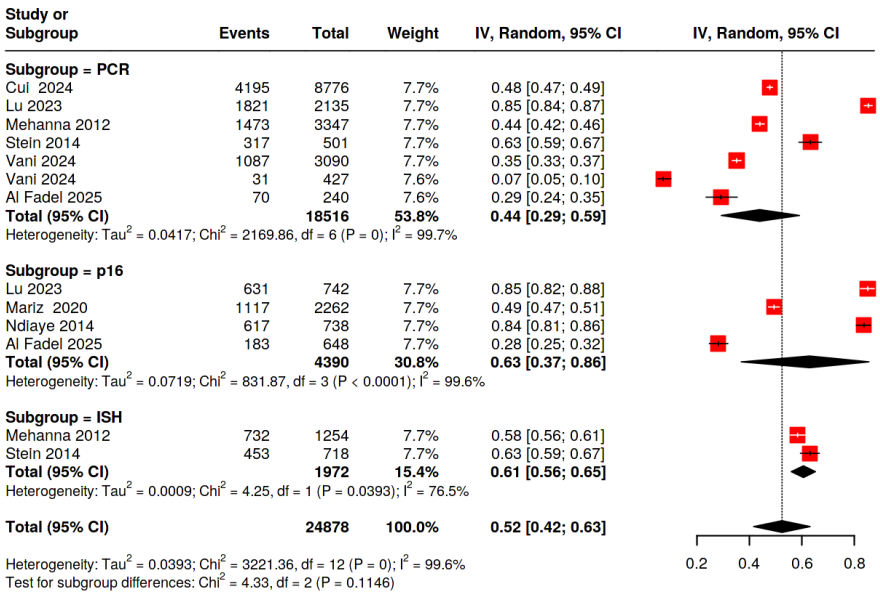

Figure 7: Forest plot of the prevalence of HPV-positive oropharyngeal cases stratified by detection methods.

Significant presence of heterogeneity and publication bias, large CIs and the observational nature of the included study designs led to "low" evaluation of all the pooled analyses assessed by GRADE tool.

4. Discussion

To the best of our knowledge and as far as the literature search indicates, this is the first systematic umbrella review to gather and analyze all the prior SR and MAs on the prevalence and survival of HPV-related OPC. Its goals are to shed light on the literature, take a snapshot of the field's current state, identify knowledge gaps, and open the door for future research to focus on higher-quality interventions.

4.1. Prevalence

An overall prevalence of 43% (95% CI: 41%-46%) was found from a sample of 147,447 OPC cases. The population attributable fraction (PAF) is estimated to be 63,402 cases (95% CI: 60,453-67,826) that can be attributed to HPV. This means HPV is responsible for approximately 4 out of every 10 OPC cases globally

The comparison between moderate/high and low/critically low quality studies revealed comparable pooled prevalence, indicating that paper quality was not the source of heterogeneity. Studies with large sample size resulted in a higher pooled prevalence compared to the smaller sample size studies (46% vs. 39%). However, the intergroup difference was not significant. The reason for this could be the better ability of viral detection in large sample size studies, while the smaller sample size studies might have led to some false negative results.

HPV-16 was the most frequent subtype with the pooled prevalence of 79%. This was followed by %3 for HPV-33 and 2% for both HPV-18 and HPV-35. The same predominance of HPV-16 was reported in head and neck cancers [52], cervical cancer [53], anogenital [54] and penile cancers [55].

Tonsils and base of the tongue had the highest pooled prevalence of HPV with 0.60 (0.55-0.66) and 0.43 (0.34-0.51) respectively. The pooled prevalence of HPV in soft palate was 0.08 (0.04-0.14). Some

studies collected the other sites beside tonsils, base of the tongue and soft palate (like the posterior and lateral walls of the pharynx) under the category of "other". The pooled analysis HPV in "other" sites was 0.27 (0.11-0.47).

Because of their distinct anatomical vulnerabilities, the tonsils and base of the tongue have the highest and second-highest HPV prevalences among OPC cases [56]. In contrast to other oral and head & neck regions where HPV requires tissue damage to reach vulnerable cells, the tonsillar crypt's permeable basement membrane makes it simple for HPV to reach basal epithelial cells without causing micro abrasions. Specialized reticular crypt epithelium with a disturbed basement membrane and basal cell layer lines the tonsillar crypts, and the presence of many branching crypts increases the surface area for antigen processing by more than 700 times [57]. Due to the localized expression of immune checkpoint programmed death ligand, the tonsillar crypt may provide a favorable immunological milieu for HPV infection, but the multilayered epithelium at other oropharyngeal locations protects the stem cell population [56]. The second-highest HPV prevalence is found at the base of the tongue, which has identical lingual tonsillar tissue with comparable vulnerabilities. Tonsillar anatomy plays a crucial role in HPV-related carcinogenesis, as evidenced by the fact that only 3% of oropharyngeal malignancies originating from non-tonsillar locations had high-risk HPV, compared to 92% from tonsillar sites [58].

The time-wise analysis of the comparison before and after 2015 revealed approximately the same prevalence. However, the comparison of the MAs before and after 2020 showed a reduction in prevalence from 48% to 41%, although the difference was not statistically significant ($p = 0.09$). This could be attributed to the effect of recent vaccination strategies both among healthy and cancer populations. For instance, in the United States, infections with the four HPV strains that Gardasil prevents fell 88% among females aged 14–19 and 81% among those aged 20–24 within 12 years of the vaccine's introduction [59]. In comparison to unvaccinated males, vaccinated males were less likely to develop head and neck cancers and all HPV-related cancers [60]. Moreover, vaccinated individuals had an 80% lower incidence of oral HPV-16 infection, according to a meta-analysis of 4 studies and 13,285 participants [61].

Male OPC patients had higher pooled prevalence of HPV (47% vs. 35%) compared to females ($p = 0.32$). This difference may stem from several factors. Males with OPC have a greater HPV prevalence than females, which is indicative of basic variations in immunological response and sexual behavior [62]. Early in their sexual encounters, females who engage in conventional genital sex contract an infection. Within a small number of partners, they quickly seroconvert the infection into a systemic antibody that provides lifelong protection. Men have longer durations of susceptibility before generating protective antibodies because they require a significantly higher number of sexual partners to seroconvert an infection into a protective antibody [63]. Men usually need more sexual exposures than women to acquire protective antibodies, and the lifetime number of oral sex partners is the main factor influencing the risk of HPV-positive OPC, with an overall risk of 5.7 for ≥6 lifetime oral sex partners [64, 65]. Women also typically have stronger and faster immune responses to HPV infections, possibly due to hormonal protection from estrogen, which aids in the more efficient removal of viruses. This pattern is consistent with a larger epidemiological trend that indicates OPC is primarily a male disease, with the majority of OPC cases now being HPV-positive, with the increase observed primarily in young males in industrialized countries [66, 67].

The regional differences in HPV pooled prevalence in OPCs, with North America showing the highest prevalence (59%) followed by Europe (44%), Asia (37%), South America (23%), and Africa (15%), reflect distinct epidemiological, behavioral, and healthcare system factors. Recent decades have seen substantial changes in sexual behavior in North America and Europe, such as a rise in oral sex practices and modifications to partnership patterns, which make it easier for HPV to spread to the oropharynx [68]. The rise is primarily observed in young men in industrialized nations , and since oral sex is more common among younger people, disparities in oral sexual behaviors account for age- and race-related prevalence [69]. Higher identification rates of HPV-positive cases are also a result of these areas' more developed healthcare systems, which include better diagnostic tools and organized HPV testing procedures [69]. Furthermore, the percentage of OPCs driven by HPV has increased relative to those

caused by alcohol and tobacco due to the drop in traditional risk factors including smoking and alcohol usage in North America and Europe [67]. Different sexual behavioral patterns, lower rates of oral sex practices, the continued dominance of alcohol and tobacco as the main risk factors for OPC, and possibly less thorough HPV testing in healthcare systems, which could result in an under-detection of HPV-positive cases, could all be contributing factors to the lower prevalence in Asia, Africa, and South America [38].

The prevalence of HPV varied significantly based on the diagnostic method employed. While p16 immunohistochemistry and in situ hybridization (ISH) showed higher prevalences of 63% (95% CI: 0.37-0.86) and 61% (95% CI: 0.56-0.65), respectively, PCR-based detection produced a pooled prevalence of 44% (95% CI: 0.29-0.59) which is closer to the overall pooled prevalence of this review (43%). Comparison between viral activity markers (p16 + E6/E7 mRNA) and direct viral detection techniques (PCR + ISH), the latter group exhibited a greater pooled prevalence (68% vs. 48%), although this difference was not statistically significant ($p = 0.12$).

HPV DNA detection by PCR identifies viral presence but not transcriptional activity. Therefore, it is prone to false positives from non-oncogenic transient infection [70]. p16 is a surrogate marker for high-risk HPV-mediated E7 oncoprotein activity and it is highly sensitive but less specific, as p16 can be overexpressed in HPV-negative tumors [71]. Moreover, E6/E7 mRNA is the most specific marker of transcriptionally active, oncogenic HPV infection, but it is technically demanding and not universally available [72]. Lastly, combined testing (p16 + HPV DNA or mRNA) is currently recommended by ASCO guidelines for definitive HPV attribution in clinical trials [73]. The analysis of this review shows a higher pooled prevalence with combined markers (68%), likely reflecting improved sensitivity.

These results imply that detection techniques that focus on viral activity markers may be able to detect a wider range of HPV-associated infections. The variation in detection rates highlights the potential clinical utility of combining multiple detection approaches for a more thorough evaluation of HPV status in patients with OPC, as well as the significance of taking the diagnostic method into account when interpreting HPV prevalence data. Clinically, the choice of detection method directly impacts reported prevalence and patient stratification, and standardization is urgently needed for de-escalation trial eligibility.

4.2. Survival

Eight SR and MAs were included that focused on the survival of HPV related OPCs. Several important conclusions may be drawn from the combined data of these reviews.

Not all HPV-positive OPC patients have the same prognosis, as Shenker *et al.*'s [51] important finding shows. Compared to patients with HPV-16, those with HPV-non16 OPC may have a worse overall survival (OS) and a lower likelihood of becoming p16 positive. According to the meta-analysis, HPV-non16 subtypes had a considerably worse 5-year OS than HPV-16, and their OS at 5 years was significantly worse than HPV-16's. Furthermore, there was a lower likelihood of p16 positivity by IHC in individuals with HPV-non16 infection, which may indicate variations in host response and viral biology. A clinically relevant grouping, the 14.3% frequency of HPV-non16 subtypes may necessitate distinct prognostic considerations and possible exclusion from de-escalation treatments.

Al Fadel *et al.*'s MA [29] showed that the prognostic benefit and HPV prevalence vary among oropharyngeal subsites. The distinctive survival benefit linked to HPV positivity is absent from other oropharyngeal sites, such as the soft palate, uvula, and pharyngeal walls, while HPV-positive tonsil and base of tongue tumors demonstrate well-established survival advantages. The HPV prevalence at these sites is much lower (20% vs. 50–55%). This implies that anatomical subsite should be a crucial factor in prognostic classification, challenging the approach of treating all OPC equally based on HPV status.

Important evidence that HPV status modifies racial disparities in OPC survival may be drawn in the Stein *et al.*'s SR [46]. For patients who were HPV-positive and HPV-negative, the pooled HR related to black race was 1.10 and 1.50, respectively. Importantly, the racial difference in OPC survival was nonsignificant for HPV-positive and remains for HPV-negative. This review implies that although being HPV-positive offers a survival advantage that seems to cut across racial lines, ongoing inequalities in HPV-negative could be caused by variations in tumor biology, socioeconomic position, or access to

care. The need for better healthcare delivery in disadvantaged groups is highlighted by the finding that unmeasured variations in socioeconomic status and access to care may be a contributing factor in this gap.

O'Rorke *et al.*'s MA [50], which included 42 studies and more than 1,500 patients, offers strong evidence of the HPV survival advantage. Overall survival was 54% higher for patients with HPV-positive in head and neck squamous cell carcinoma (HNSCC) than for those with HPV-negative HNSCC (HR 0.46). The pooled HR for tonsillar carcinoma and OPC was 0.50 and HR 0.47, respectively. The pooled HR for disease-specific survival was 0.28, which indicates a significant improvement in outcomes specific to cancer. Crucially, these advantages were constant irrespective of confounder, HPV detection technique, or geographic location adjustments, offering compelling proof of the HPV prognostic effect's resilience.

Chen *et al.*'s SR [47] offers proof that smoking considerably reduces the survival benefit of OPC with HPV. Smoking stands out as one of the most significant modifiable prognostic variables in this population, with 80% of studies demonstrating statistically significant connections between smoking and worse outcomes and adjusted hazard ratios ranged from 1.3 to 7.2 for various survival endpoints.

Götz *et al.*'s [32] review reveals important methodological problems that could account for discrepancies in the literature. The significant heterogeneity (I^2 = 97%) in HPV prevalence across studies (0% to 61.2%) indicates that detection methodology, study population characteristics, and geographic factors significantly impact reported outcomes, even though they did not find any significant differences between detection methods in their comparison. Shenker *et al.*'s [51] finding that HPV-non16 subtypes have a lower probability of being p16-positive complicates HPV detection methods even further. The need for standardized HPV testing procedures that take into consideration both HPV subtype and p16 status is highlighted by this diversity, which advices more precaution when selecting de-escalation treatment techniques.

According to the Marrero-Gonzalez *et al*. MA [49], there were notable sex-based differences that vary by region, with US research showing no significant difference and international studies favoring female patients (aHR = 0.68). These differences may demonstrate the intricate relationship that exists between host variables, healthcare access, and viral oncogenesis.

These results point to the need for significant improvement in the "HPV-positive OPC" diagnosis, even though it is prognostically relevant. De-escalation trials for current treatments should consider:

- HPV subtype stratification: Patients with a poorer prognosis (14% prevalence of HPV-non16 subtypes) may need to be excluded from de-escalation programs or require other treatment modalities.
- Anatomical subsite considerations: HPV positivity may not have the same predictive effect on non-tonsillar, non-base of tongue, oropharyngeal sites.
- Integration of smoking status: Because smoking consistently has negative effects, it may be a relative contraindication for treatment de-escalation to continue smoking.
- Improved HPV testing procedures: p16 immunohistochemistry and HPV subtyping together may yield more precise prognostic data than each test alone.
- Aspects related to health equity: Equal access to HPV testing and specialist care is still crucial, even though having an HPV-positive status seems to lessen racial inequities.

Standardized methods and more accurate classification techniques are needed, as evidenced by the significant methodological variation found among studies. Instead of depending only on binary HPV status for treatment decisions, future research should concentrate on creating complete prognostic models that incorporate HPV subtype, anatomical location, smoking status, and demographic characteristics.

4.3. Oncogenic Role of HPV in OPC

HPV plays an oncogenic role in OPC through multiple molecular and biological mechanisms. By expressing oncoproteins E6 and E7, which target and deactivate important tumor suppressor pathways—E6 deactivates p53, while E7 targets pRb—the virus starts carcinogenesis [74]. This results in

unchecked cell division and genomic instability. The tonsillar crypts are lined with a porous basement membrane that allows HPV easy access to basal epithelial cells without micro-abrasions. Viral particles are deposited across the basement membrane and disrupted basal cell layer, which makes it easier to infect basal cells without the necessary trauma seen in cervical cancer [75]. When HPV integrates into the host genome, it interferes with regular apoptotic and cell cycle regulation processes and fosters an immune-permissive milieu that permits ongoing infection [76]. Due to the increased radiosensitivity and immunogenicity of HPV-driven tumors, HPV-positive OPC has one of the fastest-rising incidences of any cancer in high-income countries [7].

Several theories have been put forward to explain why the HPV-positive OPC has a higher chance of survival compared to HPV-negative OPC. Younger patients who have had less exposure to alcohol and smoke tend to have HPV-positive malignancies, which improves their general health and treatment tolerance [7]. Furthermore, unlike cancers linked to tobacco or alcohol, which frequently have p53 mutations [77], HPV-driven malignancies are biologically unique in that they retain wild-type p53 function, which makes them more susceptible to DNA-damaging therapies like chemotherapy and radiation [78]. These malignancies are caused by viral oncoproteins E6 and E7, which produce weaknesses that increase the tumor cells' vulnerability to treatment-induced cell death. Better results are also frequently achieved by HPV-positive patients because they frequently have stronger immune responses against the viral antigens [79].

4.4. Strength and Limitations

This review has several methodological strengths that fortify the validity of its conclusions, such as thorough search approach across several databases, using random-effects model, utilizing AMSTAR 2 and the GRADE tools for evaluating study qualities and evidence certainty respectively. With 24 SRs that included 783 primary studies covering more than 146 thousand OPC patients, it has a very broad scope, making it one of the largest syntheses of evidence on the prevalence and survival of HPV-related OPC. Numerous clinically significant subcategories, such as HPV subtypes, cancer subsites, temporal trends, sex differences, geographic variations, and detection techniques, were methodically investigated in this study.

On the other hand, some limitations should also be noted. One was the incredibly high heterogeneity found in all pooled analyses, which restricted the pooled results' interpretability and generalizability of some of the analyses. Because of the observational nature of the included studies, considerable heterogeneity, and publication bias, the GRADE assessment yielded “low” certainty of evidence for all outcomes. According to AMSTAR 2, only four out of twenty-five studies received "high" quality ratings. Moreover, some studies only provided HPV percentage without the actual number of positive cases out of the total sample. This conversion might have caused some measurement imprecisions. Extreme variability prevented quantitative synthesis limited the study to qualitative description for survival analysis. Important confounding factors such alcohol use, smoking status, and treatment regimens may not have been sufficiently controlled for in the analyses of all the included SRs. Lastly, only one included SR specifically addressed HPV-non16 survival outcomes, and data on non-16 subtypes were insufficient across most included reviews to allow subgroup pooling. This limits the ability to draw definitive conclusions regarding the prognostic impact of non-16 subtypes and their suitability for treatment de-escalation strategies.

5. Conclusions

This extensive umbrella review, which shows an overall HPV prevalence of 43% among OPC patients worldwide, offers crucial insights into the epidemiology and prognosis of HPV-related OPC. Significant differences in prevalence were found across several dimensions: HPV-16 was the most common subtype (79%), tonsils were the most common cancer subsite (60%) followed by base of tongue (43%), males had higher HPV prevalent OPCs than females (47% vs. 35%), and there were notable regional differences, with North America having the highest rates (59%). Despite methodological heterogeneity, the survival evidence synthesis consistently showed superior outcomes for HPV-positive patients, with significant prognostic nuances such as poorer outcomes for HPV-non16 subtypes, smoking-related

survival detriment, and anatomical subsite-specific variations. Clinically, these findings affect the risk stratification, therapy de-escalation considerations, and the creation of more accurate prognostic models that consider anatomical location, smoking status, and HPV subtype rather than just binary HPV status. To increase the accuracy of future evidence synthesis, standardized HPV detection procedures, harmonized outcome criteria, and high-quality prospective studies are vital. While the growing impact of HPV vaccination programs indicates the need for ongoing surveillance to track shifting epidemiological patterns in the post-vaccination era, the significant geographic and demographic variations noted underscore the significance of region-specific epidemiological data for guiding local prevention strategies and clinical guidelines.

Author contributions: Mohammed Khalid Mahmood: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Balen Hamid Qadir:** Conceptualization, Data curation, Investigation, Methodology, Project administration. **Balkees Taha Garib:** Writing – original draft, Writing – review & editing. **Yad Mariwan Mohammed Ali:** Conceptualization, Data curation, Formal Analysis. **Herve Tassery:** Supervision, Validation, Project administration, Writing – original draft, Writing – review & editing. **Delphine Tardivo:** Supervision, Validation, Project administration, Writing – original draft, Writing – review & editing. **Romain Lan:** Supervision, Validation, Project administration, Writing – original draft, Writing – review & editing.

Data availability: Data supporting this article is presented in the supplementary materials.

Conflicts of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding: The authors did not receive support from any organization for the conducting of the study.

References

[1] A. F. Carlander *et al.*, "A contemporary systematic review on repartition of HPV-positivity in oropharyngeal cancer worldwide," *Viruses*, vol. 13, no. 7, p. 1326, 2021, doi: https://doi.org/10.3390/v13071326.

[2] M. Zamani *et al.*, "The current epidemic of HPV-associated oropharyngeal cancer: an 18-year Danish population-based study with 2,169 patients," *European Journal of Cancer*, vol. 134, pp. 52–59, 2020, doi: https://doi.org/10.1038/s41388-023-02819-y.

[3] T. Guo, S. Y. Kang, and E. E. Cohen, "Current perspectives on recurrent HPV-mediated oropharyngeal cancer," *Frontiers in Oncology*, vol. 12, p. 966899, 2022, doi: https://doi.org/10.3389/fonc.2022.966899.

[4] M. Lechner, J. Liu, L. Masterson, and T. R. Fenton, "HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management," *Nattional Reviews in Clinical Oncology*, vol. 19, no. 5, pp. 306–327, 2022, doi: 10.1038/s41571-022-00603-7.

[5] C. T. Allen, J. S. Lewis, S. K. El-Mofty, B. H. Haughey, and B. Nussenbaum, "Human papillomavirus and oropharynx cancer: Biology, detection and clinical implications," *The Laryngoscope*, vol. 120, no. 9, pp. 1756–1772, Sep. 2010, doi: 10.1002/lary.20936.

[6] D. R. Lowy and K. Munger, "Prognostic implications of HPV in oropharyngeal cancer," *New England Journal of Medicine*, vol. 363, no. 1, pp. 82–4, 2010, https://hpvinfo.com.br/artigos/HPV-Orofaringe2.pdf.

[7] K. K. Ang *et al.*, "Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer," *New England Journal of Medicine*, vol. 363, no. 1, pp. 24–35, Jul. 2010, doi: 10.1056/NEJMoa0912217.

[8] H. Mirghani *et al.*, "Treatment de-escalation in HPV-positive oropharyngeal carcinoma: Ongoing trials, critical issues and perspectives," *International Journal of Cancer*, vol. 136, no. 7, pp. 1494–1503, Apr. 2015, doi: 10.1002/ijc.28847.

[9] J. J. Kang *et al.*, "Consensuses, controversies, and future directions in treatment deintensification for human papillomavirus-associated oropharyngeal cancer," *CA. A Cancer Journal for Clinicians*, vol. 73, no. 2, pp. 164–197, Mar. 2023, doi: 10.3322/caac.21758.

[10] W. Borena *et al.*, "HPV-induced oropharyngeal cancer and the role of the E7 oncoprotein detection via brush test," *Cancers*, vol. 12, no. 9, p. 2388, 2020, doi: https://doi.org/10.3390/cancers12092388.

[11] L. Oton-Gonzalez *et al.*, "Serum HPV16 E7 oncoprotein is a recurrence marker of oropharyngeal squamous cell carcinomas," *Cancers*, vol. 13, no. 13, p. 3370, 2021, doi: https://doi.org/10.3390/cancers13133370.

[12] C. C. Fossum, A. V. Chintakuntlawar, D. L. Price, and J. J. Garcia, "Characterization of the oropharynx: anatomy, histology, immunology, squamous cell carcinoma and surgical resection," *Histopathology*, vol. 70, no. 7, pp. 1021–1029, 2017, doi: https://doi.org/10.1111/his.13140.

[13] L. B. Campos *et al.*, "Oncoviruses in the oral cavity: recent advances in understanding viral infections and tumorigenesis," *Internationl Journal of Molecular Science*, vol. 26, no. 14, p. 6721, 2025, doi: https://doi.org/10.3390/ijms26146721.

[14] H. Miniggio, "Biological significance of palatine tonsillar epithelium: microstructure and disease," *South African Dental Journal*, vol. 71, no. 10, pp. 496–499, 2016, https://hdl.handle.net/10520/EJC-7c1a621c0.

[15] J. D. Howard and C. H. Chung, "Biology of human papillomavirus–related oropharyngeal cancer," in *Seminars in Radiation Oncology*, Elsevier, 2012, pp. 187–193. Accessed: Jun. 14, 2026. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1053429612000215

[16] A. M. Evans, M. Salnikov, S. F. Gameiro, S. Maleki Vareki, and J. S. Mymryk, "HPV-positive and-negative cervical cancers are immunologically distinct," *Journal of Clinical Medicine*, vol. 11, no. 16, p. 4825, 2022, doi: https://doi.org/10.3390/jcm11164825.

[17] M. B. Wang, I. Y. Liu, J. A. Gornbein, and C. T. Nguyen, "HPV-Positive Oropharyngeal Carcinoma: A Systematic Review of Treatment and Prognosis," *Otolaryngology and Neck Surgery*, vol. 153, no. 5, pp. 758–769, Nov. 2015, doi: 10.1177/0194599815592157.

[18] M. J. Page *et al.*, "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews," *bmj*, vol. 372, 2021, Accessed: Jun. 14, 2026, doi: doi: 10.1136/bmj.n71.

[19] B. J. Shea *et al.*, "AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both," *bmj*, vol. 358, 2017, Accessed: Jun. 14, 2026, doi: doi: 10.1136/bmj.j4008.

[20] R. DerSimonian and N. Laird, "Meta-analysis in clinical trials," *Controlled Clinical Trials*, vol. 7, no. 3, pp. 177–188, 1986, doi: 10.1016/0197-2456(86)90046-2.

[21] H. Jpt, "Cochrane handbook for systematic reviews of interventions," *Httpwww Cochrane-Handb. Org*, 2008, Accessed: Jun. 14, 2026. [Online]. Available: https://cir.nii.ac.jp/crid/1571980075694747776

[22] M. Egger, G. D. Smith, M. Schneider, and C. Minder, "Bias in meta-analysis detected by a simple, graphical test," *bmj*, vol. 315, no. 7109, pp. 629–634, 1997, doi: doi: 10.1136/bmj.315.7109.629.

[23] J. T. Fekete and B. Gy\Horffy, "MetaAnalysisOnline. com: web-based tool for the rapid meta-analysis of clinical and epidemiological studies," *Journal of Medical Internet Research*, vol. 27, p. e64016, 2025, doi: https://doi.org/10.2196/64016.

[24] G. H. Guyatt *et al.*, "GRADE: an emerging consensus on rating quality of evidence and strength of recommendations," *Bmj*, vol. 336, no. 7650, pp. 924–926, 2008, https://cir.nii.ac.jp/crid/1370853567793495940.

[25] D. Pieper, S.-L. Antoine, T. Mathes, E. A. Neugebauer, and M. Eikermann, "Systematic review finds overlapping reviews were not mentioned in every other overview," *Journal of Clinical Epidemiology*, vol. 67, no. 4, pp. 368–375, 2014, https://doi.org/10.1016/j.jclinepi.2013.11.007.

[26] C. G. L. Hobbs, J. A. C. Sterne, M. Bailey, R. S. Heyderman, M. A. Birchall, and S. J. Thomas, "Human papillomavirus and head and neck cancer: a systematic review and meta-analysis.," *Clinical Otolaryngology*, vol. 31, no. 4, 2006, Accessed: Jun. 14, 2026. [Online]. Available: http://www.drchrishobbs.com/uploads/8/2/1/2/8212308/hpv__hnscc.pdf

[27] F. Dayyani, C. J. Etzel, M. Liu, C.-H. Ho, S. M. Lippman, and A. S. Tsao, "Meta-analysis of the impact of human papillomavirus (HPV) on cancer risk and overall survival in head and neck squamous cell carcinomas (HNSCC)," *Head and Neck Oncology*, vol. 2, no. 1, p. 15, Dec. 2010, doi: 10.1186/1758-3284-2-15.

[28] S. Abogunrin, G. L. Di Tanna, S. Keeping, S. Carroll, and I. Iheanacho, "Prevalence of human papillomavirus in head and neck cancers in European populations: a meta-analysis," *BMC Cancer*, vol. 14, no. 1, p. 968, Dec. 2014, doi: 10.1186/1471-2407-14-968.

[29] A. M. Al Fadel, K. K. Jakobsen, L. H. Jensen, A.-L. F. Carlander, C. Grønhøj, and C. von Buchwald, "The epidemiological trends and survival of HPV-related oropharyngeal cancer other than tonsils and base of tongue- a systematic review and meta-analysis," *Oral Oncology*, vol. 165, p. 107311, 2025, doi: 10.1016/j.oraloncology.2025.107311.

[30] M. Cui *et al.*, "Characteristics of human papillomavirus infection among oropharyngeal cancer patients: A systematic review and meta-analysis," *Archives of Oral Biology*, vol. 157, p. 105830, 2024, doi: 10.1016/j.archoralbio.2023.105830.

[31] T. C. Fonsêca *et al.*, "Global prevalence of human papillomavirus-related oral and oropharyngeal squamous cell carcinomas: a systematic review and meta-analysis," *Clinical Oral Investigations*, vol. 28, no. 1, p. 62, Dec. 2023, doi: 10.1007/s00784-023-05425-0.

[32] C. Gotz, C. Bischof, K.-D. Wolff, and A. Kolk, "Detection of HPV infection in head and neck cancers: Promise and pitfalls in the last ten years: A meta-analysis," *Molecualr and Clinical Oncology*, Oct. 2018, doi: 10.3892/mco.2018.1749.

[33] L. Guo *et al.*, "Prevalence of human papillomavirus type-16 in head and neck cancer among the Chinese population: a meta-analysis," *Frontiers in Oncology*, vol. 8, p. 619, 2018, doi: 10.3389/fonc.2018.00619.

[34] L. Haeggblom, T. Ramqvist, M. Tommasino, T. Dalianis, and A. Näsman, "Time to change perspectives on HPV in oropharyngeal cancer. A systematic review of HPV prevalence per oropharyngeal sub-site the last 3 years," *Papillomavirus Research*, vol. 4, pp. 1–11, 2017, doi: https://doi.org/10.1016/j.pvr.2017.05.002.

[35] X. Ju *et al.*, "High-Risk Human Papillomavirus–Related Oropharyngeal Squamous Cell Carcinoma Among Non-Indigenous and Indigenous Populations: A Systematic Review," *Otolaryngology and Neck Surgery*, vol. 165, no. 1, pp. 23–32, Jul. 2021, doi: 10.1177/0194599820975042.

[36] Y. Lu *et al.*, "Human papillomavirus and $p16^{INK4A}$ in oropharyngeal squamous cell carcinomas: A systematic review and meta-analysis," *Internation Journal of Cancer*, vol. 154, no. 5, pp. 830–841, Mar. 2024, doi: 10.1002/ijc.34763.

[37] B. A. L. A. Mariz *et al.*, "Global prevalence of human papillomavirus-driven oropharyngeal squamous cell carcinoma following the ASCO guidelines: A systematic review and meta-analysis," *Critical Reviews in Oncology and Hematology*, vol. 156, p. 103116, 2020, doi: 10.1016/j.critrevonc.2020.103116.

[38] H. Mehanna *et al.*, "Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer—systematic review and meta-analysis of trends by time and region," *Head & Neck*, vol. 35, no. 5, pp. 747–755, May 2013, doi: 10.1002/hed.22015.

[39] C. Ndiaye *et al.*, "HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis," *Lancet Oncology*, vol. 15, no. 12, pp. 1319–1331, 2014, doi: 10.1016/S1470-2045(14)70471-1.

[40] A. C. Oliveira, I. C. Cavalcanti De Lima, V. M. Frez Marques, W. H. Alves De Araújo, and C. De Campos Ferreira, "Human papillomavirus prevalence in oral and oropharyngeal squamous cell carcinoma in South America: A systematic review and meta-analysis," *Oncology Review*, vol. 16, no. 1, Mar. 2022, doi: 10.4081/oncol.2022.552.

[41] C. Ragin *et al.*, "Prevalence of HPV infection in racial–ethnic subgroups of head and neck cancer patients," *Carcinogenesis*, vol. 38, no. 2, pp. 218–229, 2017, doi: 10.1093/carcin/bgw203.

[42] S. Sasidharanpillai, N. Ravishankar, V. Kamath, P. V. Bhat, P. Bhatt, and G. Arunkumar, "Prevalence of human papillomavirus (HPV) DNA among men with oropharyngeal and anogenital cancers: a systematic review and meta-analysis," *Asian Pacific Journal of Cancer Prevention*, vol. 22, no. 5, p. 1351, 2021, doi: 10.31557/APJCP.2021.22.5.1351.

[43] M. H. Shaikh, N. A. McMillan, and N. W. Johnson, "HPV-associated head and neck cancers in the Asia Pacific: A critical literature review & meta-analysis," *Cancer Epidemiology*, vol. 39, no. 6, pp. 923–938, 2015, doi: 10.1016/j.canep.2015.09.013.

[44] A. P. Stein, S. Saha, M. Yu, R. J. Kimple, and P. F. Lambert, "Prevalence of Human Papillomavirus in Oropharyngeal Squamous Cell Carcinoma in the United States Across Time," *Chemical Research in Toxicology*, vol. 27, no. 4, pp. 462–469, Apr. 2014, doi: 10.1021/tx500034c.

[45] N. V. Vani, R. Rama, R. Madhanagopal, R. Vijayalakshmi, and R. Swaminathan, "Human Papillomavirus–Attributable Head and Neck Cancers in India—A Systematic Review and Meta-Analysis," *JCO Global Oncology*, no. 10, p. e2300464, Mar. 2024, doi: 10.1200/GO.23.00464.

[46] E. Stein, N. R. Lenze, W. G. Yarbrough, D. N. Hayes, A. Mazul, and S. Sheth, "Systematic review and meta-analysis of racial survival disparities among oropharyngeal cancer cases by HPV status," *Head & Neck*, vol. 42, no. 10, pp. 2985–3001, Oct. 2020, doi: 10.1002/hed.26328.

[47] S. Y. Chen *et al.*, "The association of smoking and outcomes in HPV-positive oropharyngeal cancer: A systematic review," *American Journal of Otolaryngology*, vol. 41, no. 5, p. 102592, 2020, doi: 10.1016/j.amjoto.2020.102592.

[48] N. R. Lenze, D. R. Farquhar, A. L. Mazul, M. M. Masood, and J. P. Zevallos, "Racial disparities and human papillomavirus status in oropharyngeal cancer: A systematic review and meta-analysis," *Head & Neck*, vol. 41, no. 1, pp. 256–261, Jan. 2019, doi: 10.1002/hed.25414.

[49] A. R. Marrero-Gonzalez, E. S. Chernov, S. A. Nguyen, B. A. Keith, M. N. Stevens, and A. E. Kejner, "Sex and human papillomavirus in oropharyngeal cancer: A systematic review and meta-analysis," *American Journal of Otolaryngology*, vol. 45, no. 6, p. 104464, 2024, doi: 10.1016/j.amjoto.2024.104464.

[50] M. A. O'Rorke, M. V. Ellison, L. J. Murray, M. Moran, J. James, and L. A. Anderson, "Human papillomavirus related head and neck cancer survival: a systematic review and meta-analysis," *Oral Oncology*, vol. 48, no. 12, pp. 1191–1201, 2012, doi: 10.1016/j.oraloncology.2012.06.019.

[51] R. F. Shenker, N. B. Razavian, R. B. D'Agostino Jr, Y. M. Mowery, D. M. Brizel, and R. T. Hughes, "Clinical outcomes of oropharyngeal squamous cell carcinoma stratified by human papillomavirus subtype: A systematic review and meta-analysis," *Oral Oncology*, vol. 148, p. 106644, 2024, doi: 10.1016/j.oraloncology.2023.106644.

[52] K. Kobayashi, K. Hisamatsu, N. Suzui, A. Hara, H. Tomita, and T. Miyazaki, "A review of HPV-related head and neck cancer," *Journal of Clinical Medicine*, vol. 7, no. 9, p. 241, 2018, doi: 10.3390/jcm7090241.

[53] A. Hammer, A. Rositch, F. Qeadan, P. E. Gravitt, and J. Blaakaer, "Age-specific prevalence of HPV 16/18 genotypes in cervical cancer: A systematic review and meta-analysis," *International Journal of Cancer*, vol. 138, no. 12, pp. 2795–2803, Jun. 2016, doi: 10.1002/ijc.29959.

[54] A.-B. Moscicki *et al.*, "Updating the natural history of human papillomavirus and anogenital cancers," *Vaccine*, vol. 30, pp. F24–F33, 2012, https://doi.org/10.1016/j.vaccine.2012.05.089.

[55] T. B. Olesen *et al.*, "Prevalence of human papillomavirus DNA and p16INK4a in penile cancer and penile intraepithelial neoplasia: a systematic review and meta-analysis," *Lancet Oncology*, vol. 20, no. 1, pp. 145–158, 2019, doi: 10.1016/S1470-2045(18)30682-X.

[56] A. K. Mattox *et al.*, "Myeloid cells are enriched in tonsillar crypts, providing insight into the viral tropism of human papillomavirus," *American Journal of Pathology*, vol. 191, no. 10, pp. 1774–1786, 2021, doi: 10.1016/j.ajpath.2021.06.012.

[57] Y. X. Lim, M. L. Mierzwa, M. A. Sartor, and N. J. D'Silva, "Clinical, morphologic and molecular heterogeneity of HPV-associated oropharyngeal cancer," *Oncogene*, vol. 42, no. 40, pp. 2939–2955, 2023, doi: 10.1038/s41388-023-02819-y.

[58] S. Roberts, D. Evans, H. Mehanna, and J. L. Parish, "Modelling human papillomavirus biology in oropharyngeal keratinocytes," *Philosophical Transactions of the Royal Society B Biology and Science*, vol. 374, no. 1773, 2019, doi: 10.1098/rstb.2018.0289.

[59] M. A. Villarroel, A. M. Galinksy, P.-J. Lu, and C. Pingali, "Human papillomavirus vaccination coverage in children ages 9–17 years: United States, 2022," 2024, Accessed: Jun. 14, 2026. [Online]. Available: https://stacks.cdc.gov/view/cdc/145593

[60] A. Tsentemeidou *et al.*, "Human papillomavirus vaccine to end oropharyngeal cancer. A systematic review and meta-analysis," *Sexually Transmmitted Diseases*, vol. 48, no. 9, pp. 700–707, 2021, doi: 10.1097/OLQ.0000000000001405.

[61] J. Zhang, Z. Qin, C. Lou, J. Huang, and Y. Xiong, "The efficacy of vaccination to prevent human papilloma viruses infection at anal and oral: a systematic review and meta-analysis," *Public Health*, vol. 196, pp. 165–171, 2021, doi: https://doi.org/10.1016/j.puhe.2021.05.012.

[62] P. Garutti, S. Montori, E. Bazzan, and C. Tarabbia, "Gender differences in the epidemiology and prevention of human papillomavirus (HPV) and HPV-related diseases," *Journal of Sex- and Gender-Specific Medicine*, vol. 4, no. 4, p. 152, 2018, doi: 10.1723/3091.30836.

[63] R. M. Lewis, L. E. Markowitz, J. W. Gargano, M. Steinau, and E. R. Unger, "Prevalence of genital human papillomavirus among sexually experienced males and females aged 14–59 years, United States, 2013–2014," *Journal of Infectious Diseases*, vol. 217, no. 6, pp. 869–877, 2018, doi: 10.1093/infdis/jix655.

[64] C. Ragin *et al.*, "Oral HPV infection and sexuality: a cross-sectional study in women," *International Journal of Molecular Science*, vol. 12, no. 6, pp. 3928–3940, 2011, doi: 10.3390/ijms12063928.

[65] G. D'Souza, K. Cullen, J. Bowie, R. Thorpe, and C. Fakhry, "Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection," *PloS One*, vol. 9, no. 1, p. e86023, 2014, doi: 10.1371/journal.pone.0086023.

[66] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA. A Cancer Journal for Clinicians*, vol. 68, no. 6, pp. 394–424, Nov. 2018, doi: 10.3322/caac.21492.

[67] S. Marur, G. D'Souza, W. H. Westra, and A. A. Forastiere, "HPV-associated head and neck cancer: a virus-related cancer epidemic," *Lancet Oncology*, vol. 11, no. 8, pp. 781–789, 2010, https://doi.org/10.1016/S1470-2045(10)70017-6.

[68] G. D'Souza *et al.*, "Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer," *New England Journal of Medicine*, vol. 356, no. 19, pp. 1944–1956, May 2007, doi: 10.1056/NEJMoa065497.

[69] M. L. Gillison *et al.*, "Prevalence of oral HPV infection in the United States, 2009-2010," *Jama*, vol. 307, no. 7, pp. 693–703, 2012, doi:10.1001/jama.2012.101.

[70] P. M. Weinberger *et al.*, "Molecular Classification Identifies a Subset of Human Papillomavirus–Associated Oropharyngeal Cancers With Favorable Prognosis," *Journal of Clinical Oncology*, vol. 24, no. 5, pp. 736–747, Feb. 2006, doi: 10.1200/JCO.2004.00.3335.

[71] J. S. Lewis Jr *et al.*, "Human papillomavirus testing in head and neck carcinomas: guideline from the College of American Pathologists," *Archives of Pathology & Laboratory Medicine*, vol. 142, no. 5, pp. 559–597, 2018, doi: https://doi.org/10.5858/arpa.2017-0286-CP.

[72] H. Mirghani, F. Amen, F. Moreau, and J. L. St Guily, "Do high-risk human papillomaviruses cause oral cavity squamous cell carcinoma?," *Oral Oncology*, vol. 51, no. 3, pp. 229–236, 2015, doi: https://doi.org/10.1016/j.oraloncology.2014.11.011.

[73] C. Fakhry *et al.*, "Human Papillomavirus Testing in Head and Neck Carcinomas: ASCO Clinical Practice Guideline Endorsement of the College of American Pathologists Guideline," *Journal of Clinical Oncology*, vol. 36, no. 31, pp. 3152–3161, Nov. 2018, doi: 10.1200/JCO.18.00684.

[74] B. A. Werness, A. J. Levine, and P. M. Howley, "Association of Human Papillomavirus Types 16 and 18 E6 Proteins with p53," *Science*, vol. 248, no. 4951, pp. 76–79, Apr. 1990, doi: 10.1126/science.2157286.

[75] H. C. Hafkamp *et al.*, "A subset of head and neck squamous cell carcinomas exhibits integration of HPV 16/18 DNA and overexpression of $p16^{INK4A}$ and p53 in the absence of mutations in p53 exons 5–8," *International Journal of Cancer*, vol. 107, no. 3, pp. 394–400, Nov. 2003, doi: 10.1002/ijc.11389.

[76] D. E. Symer *et al.*, "Diverse tumorigenic consequences of human papillomavirus integration in primary oropharyngeal cancers," *Genome Research*, vol. 32, no. 1, p. 55, 2022, doi: https://doi.org/10.1101/gr.275911.121.

[77] N. Stransky *et al.*, "The Mutational Landscape of Head and Neck Squamous Cell Carcinoma," *Science*, vol. 333, no. 6046, pp. 1157–1160, Aug. 2011, doi: 10.1126/science.1208130.

[78] F. P. Worden *et al.*, "Chemoselection As a Strategy for Organ Preservation in Advanced Oropharynx Cancer: Response and Survival Positively Associated With HPV16 Copy Number," *Journal of Clinical Oncology*, vol. 26, no. 19, pp. 3138–3146, Jul. 2008, doi: 10.1200/JCO.2007.12.7597.

[79] S. Lyford-Pike *et al.*, "Evidence for a role of the PD-1: PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma," *Cancer Research*, vol. 73, no. 6, pp. 1733–1741, 2013, doi: https://doi.org/10.1158/0008-5472.CAN-12-2384.