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REVIEW ARTICLE

Human papillomavirus infection and non-oropharyngeal head and neck cancers: an umbrella review of meta-analysis

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Abstract

Objective The causative and prognostic roles of human papillomavirus (HPV) in non-oropharyngeal squamous cell carcinoma of the head and neck are uncertain. This umbrella review assessed the strength and quality of evidence and graded the evidence derived from published meta-analyses on this subject.

Data sources: MEDLINE, Embase, and the Cochrane Library were searched. Meta-analyses of observational studies and randomized trials were included.

Review methods: Evidence of association was graded according to the established criteria: strong, highly suggestive, suggestive, weak, or not significant.

Results 15 meta-analyses were evaluated. The association with HPV was highly suggestive of oral (OR = 2.40, [1.87–3.07], $P < 0.00001$) and nasopharyngeal cancers (OR = 17.82 [11.20–28.35], $P < 0.00001$). Improved survival emerged only in hypopharyngeal carcinoma and was confirmed in studies in which only p16 + cancers were considered.

Conclusion HPV infection may increase the risk of oral cavity and nasopharyngeal cancer. However, the prognosis was not influenced, except in hypopharyngeal carcinoma.

Keywords Cancer · Head and neck · HPV · Non-oropharyngeal · Meta-analysis · Umbrella review

Introduction

The role of the human papillomavirus (HPV) in the pathogenesis and prognosis of oropharyngeal squamous cell cancer (OPSCC) is widely renowned [1]. More than 15 HPV types are considered to have oncogenic potential, but the majority (> 90%) of HPV-associated head and neck cancers are caused by HPV-16, the same virus frequently involved in anogenital tumors [2]. Searching for HPV presence in OPSCCs or cervical nodal metastases from cancers of unknown primary is part of daily practice, and HPV-positive (HPV +) OPSCC has been recognized as an independent entity in the eighth edition of the American Joint Committee on Cancer tumor node metastasis staging system [3]. HPV + OPSCCs have a better prognosis than their HPV-negative (HPV-) counterparts. This evidence has led to several trials exploring de-escalation treatment protocols to reduce toxicity without affecting outcomes [4].

The causative and prognostic roles of HPV in non-OPSCC are unclear. Infection from HPV seems to be an independent risk factor for a subset of upper aerodigestive

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tract cancers [5], with an estimated prevalence ranging 7–33% according to the involved subsite [6, 7]. For what concerns oncological outcomes of HPV + non-OPSCCs, current research shows more controversial results: if various retrospective studies report favorable outcomes for larynx, oral cavity, hypopharynx, and nasopharynx [8], other works display similar survival rates between HPV + and HPV- non-OPSCCs [9–11] or even worst trends in the presence of HPV infection [12–14].

Thus, we performed an umbrella review of available meta-analyses to clarify the oncological risk and prognostic role of HPV infection in patients with non-OPSCC. Umbrella reviews include systematic reviews and meta-analyses. These provide an overall picture of a broad research field and highlight whether the evidence base is consistent or contradictory [15].

Material and methods

Literature search and eligibility criteria

We searched PubMed, EMBASE, and the Cochrane database of systematic reviews from inception to July 2, 2022, for systematic reviews and meta-analyses of observational studies that investigated the association between HPV infection, risk of non-OPSCC of the head and neck, and death (Supporting Information). We used the terms *("Hpv" or "human papillomavirus" or "p16") and meta-analysis and (oral or mouth or tongue or larynx or laryngeal or hypopharynx or hypopharyngeal or rhinopharynx or nasopharynx or rhinopharyngeal or nasopharyngeal*). We manually searched the citations of the retrieved eligible papers to identify additional publications that may have been missed during the initial search. In this umbrella review, the primary analysis focused mainly on cohort or case–control studies.

Inclusion and exclusion criteria

We included systematic reviews and meta-analyses of human observational epidemiological studies that assessed the incidence or mortality of HPV infection and non-OPSCC. We excluded studies on non-squamous histology and sinonasal cancers. We further excluded narrative reviews and meta-analyses that had only one study or did not report the necessary study-specific data, including the relative risk (RR), hazard ratio (HR), odds ratio (OR), 95% confidence intervals (CI), number of cancer cases and controls, or total population.

Data extraction

Two authors separately extracted the data from the included studies. For each eligible meta-analysis, we extracted the following information: the first author, publication year, study design, number of participants and trials, type of disease and endpoints, HPV detection methods and subtypes, crude or adjusted summary risk estimates, corresponding 95% CIs (ORs, RRs, or HRs), *P* values of pooled effects, Egger's test measurement, and I^2 with *P* for significance. Discrepancies were resolved through discussion. Then, we recalculated the pooled risk estimates (represented as RR, HR, or OR) for the events of each association using random-effects models. Because the absolute risks of the studied outcomes are expected to be low in the general population, the three measures of association (OR, RR, and HR) are also expected to produce comparable estimates. Therefore, for simplicity, all risk estimates were interpreted as ORs. The HPV assessment method (p16 immunohistochemistry [IHC] or HPV DNA in situ hybridization and DNA by polymerase chain reaction [PCR] or real-time PCR) was performed, and a subgroup analysis was performed for meta-analysis of studies where only p16 + cancers were included.

Evaluating the strength of evidence by grading criteria

The association between HPV infection and non-OPSCC was graded as strong, highly suggestive, suggestive, or weak. To be included in the strong evidence group, the meta-analysis had to present a *p*-value of the random effects model smaller than 10^{-6}, including more than 1000 cancer cases, an I^2 for heterogeneity of less than 50%, 95% prediction intervals excluding the null value, and no indication of small study effects (significant *p* with Egger's test) or excess significance bias. Similarly, to satisfy the criteria for inclusion in the highly suggestive group, meta-analyses needed a random effects *p*-value smaller than 10^{-6}, more than 1000 cases, and a nominally statistically significant largest study (i.e., $P < 0.05$) in the meta-analysis. A suggestive association met the following criteria: random effects, $P < 10^{-3}$, and more than 1000 cases. Any remaining meta-analyses for which the *p*-value of the random-effects model was nominally statistically significant were considered to present weak evidence.

Evaluation of the quality of included meta-analyses

We assessed the strength and quality of all included meta-analyses using the AMSTAR tool, which uses 11 criterion items to measure the methodological quality of systematic

reviews [1]. If the specific criterion was met. The overall score relating to review quality was calculated using the sum of the individual scores. A review scoring above 8 was considered high quality, 4–7 as moderate quality, and below 4 as low or critically low quality. All statistical analyses were performed using RevMan 5.4.1 software (Review Manager [Computer program], Version 5.4, The Cochrane Collaboration, 2020), and all p values were two-tailed.

Results

Characteristics of meta-analyses

Among the 305 screened publications, we identified 15 eligible meta-analyses including 192 studies (Fig. 1; Table 1) [6, 17–30]. Almost all studies included case–control studies and analyzed the associations of various viral subtypes using different techniques (mainly PCR). The number of patients ranged from 52 to 24,854 (83, 090 patients). In 14 of the 15 meta-analyses included, more than 1000 patients were included. The meta-analysis type of the included studies was not specified for $n=4$. HPV types were 16–18 in only $n=4$ meta-analyses, various in $n=5$ meta-analyses, and not specified in $n=4$ papers.

A total of 7 endpoints were examined in the 15 meta-analyses: risk of nasopharyngeal, oral, and laryngeal cancer in patients with HPV + diseases ($n=1$, $n=5$, and $n=5$ meta-analyses, respectively); OS in patients with HPV + oral ($n=3$ meta-analyses), laryngeal ($n=3$ meta-analyses), nasopharyngeal ($n=3$ meta-analyses), and hypopharyngeal carcinomas ($n=2$ meta-analyses), compared to the HPV- counterpart.

Summary effect size

Eight meta-analyses included data for oral cavity cancer ($n=5$ risk and $n=3$ for outcome), $n=8$ for laryngeal cancer ($n=5$ for risk and $n=3$ for outcome), $n=3$ for nasopharyngeal cancer, and $n=2$ for the outcome of hypopharyngeal carcinoma. Overall, the summary fixed effects estimates were significant for n = 8 papers, and the summary random effect estimates were significant for $n=7$ papers. In 7

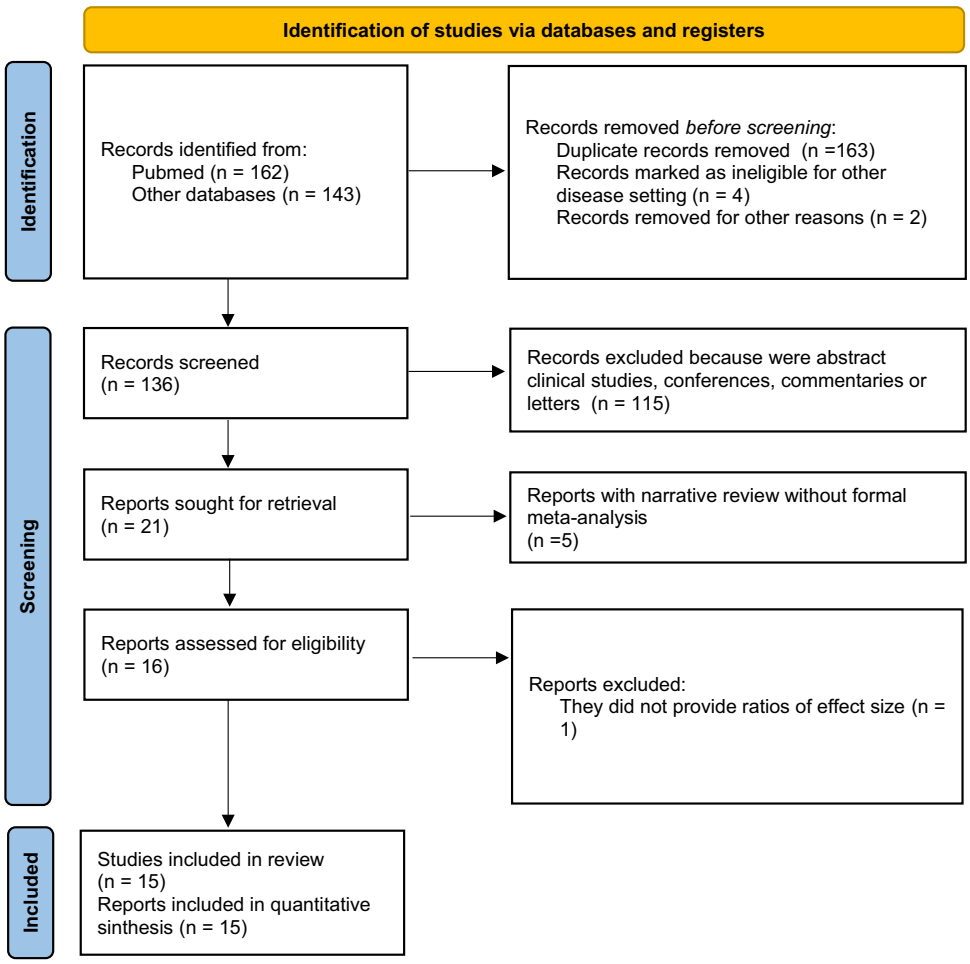

Fig. 1 Flow diagram of included studies

Table 1 Characteristics of included studies

Author/year	No studies/ no patients	Type of studies	Site	HPV types	HPV detection	Type of metric/type of analysis	Publication bias (p Egger test for small studies effect)	Overall quality assessment (AMSTAR2)
Ahmadi/2018	14/2578	Case–control	Larynx	NR	p16 78%, PCR 57%, ISH 14%	OR/UVA	No bias identified (NR)	Moderate
Chaitanya/2016	11/4709	Case–control	Oral cavity	NR	Various	OR/UVA	NR	Critically low
Christianto/2021	13/3065	Cohort	Oral cavity	Various	Various	HR/UVA	NR	Low
Giraldi/2021	5/4829	Case–control	Oral cavity	16–18	Positive for either mRNA of E6 or E7	OR/MVA	NR	Low
Hobbs/2006	11/7578	Case–control	Oral cavity, larynx	16	Various	OR/UVA	NR	Critically low
Li/2013	12/1057	Case–control	Larynx	Various	PCR 97%, ISH or IHC 7%	OR/UVA	No bias identified (* not significant)	High
Liu/2013	44/9970	Case–control	Oral cavity, larynx	NR	Various	OR/UVA	NR	Critically low
O'Rorke/2012	2/52	–	Oral cavity	16	PCR or ISH HPV DNA 100%	HR/UVA	No bias identified (*p = 0.78)	Moderate
Sahovaler/2020	19/24854	17 observational 2 RCT	Oral cavity, larynx, hypopharynx, rhinopharynx	Various	p16/HPV DNA (oral cavity), various (nasopharynx), p16/HPV DNA (larynx)	HR/MVA	No bias identified (NR)	High
Saulle/2015	8/9149	Case–control	Oral cavity, larynx	Various	NR	OR/UVA	NR	Low
Shi/2022	11/6903	–	Hypopharynx	Various	p16 100%	HR/UVA	Bias identified (*p = 0.023^; *p = 0.039^)	Moderate
Sun/2019	28/2612	Case–control	Rhinopharynx	NR	p16 100%	OR/UVA	No bias identified (p = 0.62)	Moderate
Tham/2018	5/2517	Retrospective cohort	Rhinopharynx	16–18	p16 and HPV DNA 100%	HR/MVA	No bias identified (p = 0.991)	High
Wang/2019	8/1442	–	Larynx	NR	PCR 90%, ISH 18%	HR/UVA	Bias identified (*p = 0.018)	Moderate
Zhang/2016	12/1775	Case–control	Larynx	16–18	PCR 100%	OR/UVA	No bias identidfied (*p = 0.21)	High

OR, odds ratio; RR, risk ratio; MVA, multivariate analysis; UVA, univariate analysis; RCT, randomized controlled trial; Case–control, case–control study; ISH, in-situ hybridization; IHC, immunohistochemistry; *, Egger's test; ^, p for bias in HPV DNA and p16 analysis; NR, not reported; No, number of

meta-analyses, the final effect estimates were not significant. The *P*-value was not reported for the $n = 7$ endpoints.

Heterogeneity

The *Q* test for heterogeneity was significant at $p \leq 0.10$ in 6 out of 15 meta-analyses (40%). Very high heterogeneity ($I^2 > 75\%$) was found only in the meta-analysis by Liu et al., who evaluated the risk of oral and laryngeal cancer

in HPV + patients. High heterogeneity was found in $n = 3$ papers that explored 3 other endpoints. In $n = 2$ meta-analyses, heterogeneity was not reported in either meta-analysis.

Publication bias and small studies effect

A small study effect (significance of Egger's test was found in 2 studies). In 5 studies, Egger's test was not significant. In $n = 8$ meta-analyses, it was not reported in eight meta-analyses. Overall, publication bias in the funnel plot was observed in only 2 studies; it was not reported in 6 studies, and there was no evidence of publication bias in 7 studies.

Quality assessment

In total, $n = 6$ meta-analyses (40%) were scored as low or critically low according to the AMSTAR tool. In addition, five meta-analyses scored moderate quality and only $n = 4$ of high quality.

The grading of the evidence (Table 2; Figs. 2, 3; Suppl. Figure 1–4)

Risk of oral cavity cancer: risk of oral cancer was reported in $n = 5$ meta-analyses. Overall, the association between HPV and oral cancer was highly suggestive, because none of the included meta-analyses reported a risk of bias or the Egger test. Overall, the estimated pooled OR was 2.40 (1.87–3.07), $P < 0.00001$.

Risk of laryngeal cancer: The risk of laryngeal cancer was reported in 5 meta-analyses. Overall, the strength of association between HPV and larynx cancer was suggestive because $n = 3$ of the included meta-analyses did not report the risk of bias or the Egger test. Overall, the estimated pooled OR was 3.51 (1.57–7.86), $P = 0.002$.

Risk of nasopharyngeal cancer: risk of nasopharyngeal cancer was reported in $n = 1$ meta-analysis. The association between HPV and nasopharyngeal cancer was highly suggestive because no risk of bias or significant Egger test was reported (in Sahovaler et al., the Egger test was not reported), and P was $< 10^{-6}$. Overall, the estimated pooled OR was 17.82 (11.20–28.35), $P < 0.00001$.

Overall survival in HPV + oral cancers: The OS of patients with HPV + oral cancer was similar to that of HPV- cancers (HR = 0.89 [0.47–1.68[). Data were reported in 3 meta-analyses. However, this association was not statistically significant. There was high heterogeneity in the pooled estimates.

Overall survival in HPV + laryngeal cancers: The OS of patients with HPV + laryngeal cancer was similar to that of patients with HPV-cancers (HR = 0.86 [0.61–1.21], $P = 0.39$). Data were reported in 3 meta-analyses. However, this association was not statistically significant. Heterogeneity was not observed in the pooled estimates.

Overall survival in HPV + hypopharyngeal cancers: OS of patients with HPV + hypopharyngeal cancer was better than that of patients with HPV- cancers (HR = 0.62 [0.52–0.75], $P < 0.00001$). Data were reported in 2 meta-analyses. This association was highly suggestive. There was no heterogeneity in the pooled estimate, but $n = 1$ study reported evidence of publication bias.

Overall survival in HPV + nasopharyngeal cancers: The OS of patients with HPV + nasopharyngeal cancer was similar to that of HPV-cancers (HR = 0.78 [0.59–1.04], $P = 0.09$). Data were reported in 3 meta-analyses. However, this association was not statistically significant. Heterogeneity was not observed in the pooled estimates.

Re-analysis after exclusion of low-quality meta-analyses: Six meta-analyses addressing the HPV-related risk of oral cancers were of low quality. Therefore, a subanalysis that excludes low-quality studies is not possible. After the exclusion of the remaining 2 low-quality meta-analyses assessing the HPV-related risk of laryngeal cancer, the final OR was 6.83 (95% CI 4.63–10.0). Thus, this association remains suggestive.

Subgroup analysis of p16 + studies

Five meta-analyses that analyzed OS in HPV + cancers included studies that evaluated the HPV status using p16 IHC. All studies included in the main analysis for the prognosis of hypopharyngeal and rhinopharyngeal cancers had tumors analyzed with p16 IHC to confirm the favorable prognosis of the first subgroup and the lack of association for the second subgroup. One and two meta-analyses had data for OS in p16 + oral cavity and laryngeal cancers, respectively. No association between HPV status and OS was observed in these studies.

Discussion

Our umbrella review found that HPV infection is a risk factor for squamous cell cancer in the oral cavity, nasopharynx, larynx, and hypopharynx, with a greater pooled OR for nasopharyngeal cancer than for the other analyzed sites. In addition, our analysis showed that HPV infection was associated with a more favorable prognosis for hypopharyngeal HPV + carcinomas, but not for the other evaluated head and neck organs.

The role of HPV carcinogenesis in epithelial cancers, especially at the oropharyngeal site, is widely known. HPV integration into the host cell DNA leads to the expression of multiple oncogenes, which are known to have primary roles in carcinogenesis. Particularly, E6, which inhibits the

Table 2 Description of 15 meta-analyses investigating risk of nonoropharyngeal cancer and related outcome in HPV + patients

Author, year	N[a] studies	Endpoint	Summary odds ratio (95% CI)			Fixed P-value	Random P-value	Heterogeneity I^2 (p)
			Fixed effects	Random effects	Largest study			
ORAL CANCER								
Chaitanya 2016	11	Risk of cancer	2.82 (1.28–6.21)	–	NR	< 0.01	–	0% (0.81)
Giraldi 2021	5	Risk of cancer	1.85 (1.14–3)	–	NR	0.01	–	NR
Hobbs 2006	8	Risk of cancer	2 (1.2–3.4)	–	1.5 (1.2–2)	0.008	–	61.7% (0.01)
Liu 2013	30	Risk of cancer	–	2.79 (1.81–4.29)	0.55 (0.34–0.9)	–	< 0.00001	87% (< 0.00001)
Saulle 2015	5	Risk of cancer	–	4.4 (1.75–11.06)	NR	–	Statistically significant	NR
O'Rorke 2012	2	OS	*0.32 (0.16–0.68)	–	*0.34 (0.14–0.83)	NR	–	0% (0.88)
Sahovaler 2020	13	OS	–	*1.16 (0.83–1.61)	*0.76 (0.66–0.88)	–	0.39	71% (< 0.001)
Christianto 2021	13	OS	–	*1.45 (1.1–1.43)	0.92 (0.54–1.57)	–	0.01	55% (0.008)
Pooled estimate		Risk of cancer: highly suggestive evidence		2.40 (1.87–3.07)			< 0.00001	0% (0.42)
Pooled estimate		OS: not significant		*0.89 (0.47–1.68)			0.72	87% (0.0004)
LARINX CANCER								
Hobbs 2006	8	Risk of cancer	2 (1–4.2)	–	1.1 (0.6–2.2)	0.008	–	47% (0.07)
Li 2013	12	Risk of cancer	5.39 (3.32–8.73)	–	NR	NR	–	1.9 (0.43)
Liu 2013	14	Risk of cancer	–	2.73 (1.61–4.63)	1.39 (0.78–2.48)	–	0.0002	84% (0.0002)
Saulle 2015	3	Risk of cancer	1.60 (0.97–2.65)	–	NR	NR	–	NR
Zhang 2016	12	Risk of cancer	8.07 (5.67–11.48)	–	*5.5 (3.4–8.8)	< 0.01	–	27% (0.18)
Ahmadi 2018	14	OS	–	1.01 (0.58–1.74)	0.83 (0.42–1.61)	–	0.98	66% (0.0007)
Sahovaler 2020	9	OS	–	*0.71 (0.54–0.92)	*0.71 (0.59–0.85)	–	0.009	38% (0.12)
Wang 2019	8	OS	*1.33 (0.6–3)	–	0.91 (0.28–3.2)	NR	–	0% (1)
Pooled estimate		Risk of cancer: suggestive evidence		3.51 (1.57–7.86)			0.002	91% (< 0.00001)
Pooled estimate		OS: not significant		*0.86 (0.61–1.21)			0.39	33% (0.23)
HYPOPHARYNX CANCER								
Sahovaler 2020	3	OS	–	*0.60 (0.47–0.76)	*0.59 (0.45–0.77)	–	< 0.0001	0% (0.48)
Shi 2022	10	OS°	*0.66 (0.49–0.89)	–	*0.71 (0.59–0.84)	0.007	–	0% (0.76)
Pooled estimate		OS: highly suggestive evidence		*0.62 (0.52–0.75)			< 0.00001	0% (0.63)
NASOPHARYNX CANCER								
Sahovaler 2020	5	OS	*0.82 (0.49–1.38)	–	*0.45 (0.21–0.96)	0.22	–	46% (0.12)
Sun 2019	25	Risk of cancer		17.82 (11.20–28.35)	15.9 (7.4–34.2)	–	< 0.00001	47.9% (0.004)
Sun 2019	3	OS	*0.65 (0.06–1.23)	–	0.64 (0.27–1.52)	NR	–	0% (0.9)

Table 2 (continued)

Author, year	N[a] studies	Endpoint	Summary odds ratio (95% CI)			Fixed P-value	Random P-value	Heterogeneity I^2 (p)
			Fixed effects	Random effects	Largest study			
Tham 2018	5	OS	–	0.77 (0.55–1.09)	0.69 (0.38–1.25)	–	0.14	4% (0.38)
Pooled estimate		OS: not significant		0.78 (0.59–1.04)			0.09	0% (0.97)
Pooled estimate		Risk of cancer: highly suggestive		17.82 (11.20–28.35)			< 0.00001	47.9% (0.004)

Abbreviations: *, hazard ratio; °, p16 positive cancers only

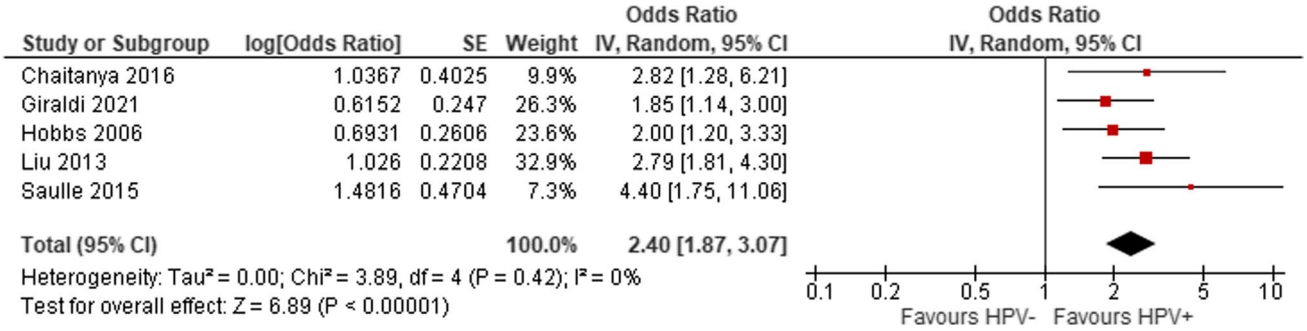

Fig. 2 Forest plot showing results for the association of HPV and oral cancer risk

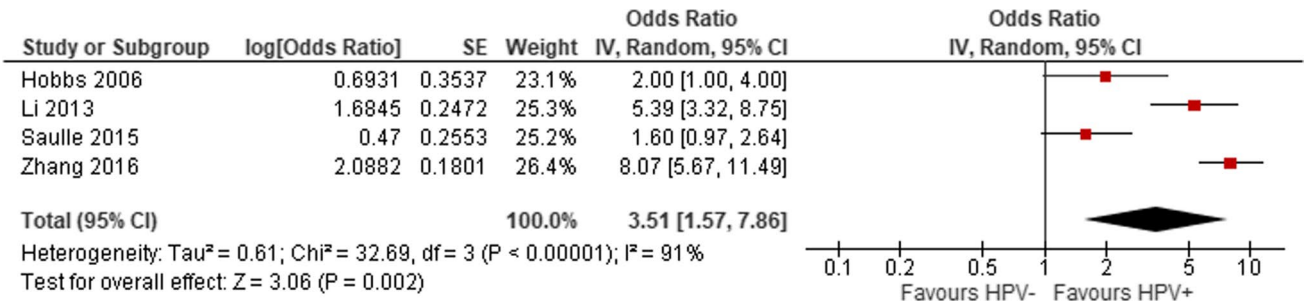

Fig. 3 Forest plot showing results for the association of HPV and laryngeal cancer risk

p53 cascade and E7 binding pRb result in the deregulation of cell cycles and cell degeneration. Those mechanisms lead to p16 overexpression, which is used as a surrogate marker of transcriptionally active infection [31]. It is reasonable to accept that HPV infection leads to similar modifications in cells of different head and neck sites other than the oropharynx, thus having a role in carcinogenesis in all the subsites, as seen in our data. However, the sole contribution of HPV infection with respect to other risk factors for cancer (such as alcohol and tobacco) cannot be inferred from our study because specific data were unavailable and subgroup analysis was not possible.

An unexpected result from this review is the very high pooled-OR of HPV infection for nasopharyngeal cancer risk, which appears 5 to 7 times greater than laryngeal and oral cavity regions, respectively. A possible explanation could be the role of the epithelium and lymphoid tissue interface in HPV-driven carcinogenesis, which is possibly similar to that of the nasopharynx and oropharynx. In fact, the nasopharynx, which contains the pharyngeal and tubal tonsils, forms the "Waldeyer's ring" in conjunction with the palatine and lingual tonsils in the oropharynx. Waldeyer's ring is one of the first interfaces between the host and external infective agents such as HPV. The nasopharyngeal, the palatine, and

lingual tonsils share common structural and functional similarities, with crypts characterized by a thin epithelial layer and lack of basement membrane in some regions, permitting rapid transportation and presentation of exogenous antigens to the underlying lymphoid cells [32]. Current research has hypothesized a crucial role in host–virus immunological and inflammatory interaction at the oropharyngeal level to explain tumorigenesis in this specific area [33]. We surmise that the same interplay could sustain carcinogenesis in HPV infection of the nasopharynx.

With regard to the prognostic role of HPV in non-OPSCC, HPV + cancers showed a highly suggestive better OS than HPV- tumors only in the hypopharynx. No effects were recorded in the nasopharynx, oral cavity, or larynx. Furthermore, the same effect was observed in all studies analyzed (independent of the methods used to detect HPV status) and in studies where p16 IHC was used.

This difference in behavior could be related to the greater radiosensitivity of HPV-associated cancers and different treatment modalities for each organ. HPV-driven head and neck cancers respond better to chemoradiation treatments than HPV-negative diseases. This is related to a compromised host DNA damage-response system, which does not allow the cancer cells to deal with the DNA double-strand breaks, partial TP53 inactivation (induction of apoptosis, which could be activated by radiation, leading to cell death), and stronger immune response due to the presence of E6 and E7 viral proteins, which contribute to improved tumor clearance [34]. Furthermore, the immune microenvironment seems to play a major role in the enhanced HPV-associated response to radiation [34].

The preferred treatment modality for oral cavity cancer is surgery, possibly followed by adjuvant radiotherapy with or without chemotherapy [35]. For laryngeal cancers, the development of transoral laser surgery and open partial laryngectomies has offered a surgical alternative to chemoradiation treatment to achieve organ preservation, extending the surgical indications [36–38]. The scenario for hypopharyngeal cancer is radically different because these tumors present more frequently at advanced stages, and concurrent chemoradiotherapy is the most commonly administered treatment [39]. Thus, the greater radiosensitivity of HPV-related cancers and a more frequent indication of chemoradiotherapy for hypopharyngeal cancers, rather than oral cavity and laryngeal cancers, could justify the difference in OS observed in our work. Further analyses considering disease-free and disease-specific survival and treatment modalities are encouraged to clarify this aspect. In addition, hypopharyngeal cancers show the worst prognosis among head and neck carcinomas [40]. Hence, even a slight improvement in survival may be significant.

HPV infection has not been shown to significantly affect OS in nasopharyngeal cancer. If HPV + head and neck cancers are chemo- and radiosensitive, this is also true for EBV-related nasopharyngeal cancer. In fact, EBV is the main risk factor for nasopharyngeal carcinoma, with chemoradiotherapy as the principal treatment option and a favourable outcome [41]. Hypothesizing that most of the HPV-nasopharynx cancers included in our review could be driven by EBV infection and that both respond well to chemoradiotherapy, which could justify the lack of effect of HPV infection on OS. A similar portrait has been described in studies considering the prognostic role of HPV and EBV in nasopharyngeal cancer, where HPV and EBV infection appeared to be mutually exclusive and with a comparable prognosis [42].

The possible impact of surgery rather than chemoradiation on OS in HPV + oral cavity and laryngeal cancers has already been discussed above. Moreover, results regarding the contribution of HPV to oral cavity tumorigenesis and response to therapies could have been severely biased by the detection method used in various studies. P16 overexpression seems to be an unreliable surrogate for HPV's carcinogenic role of HPV in this organ [43]. Besides, and numerous HPV testing techniques on tissue or saliva in development present a wide range of specificity and sensibility for each organ, which could be helpful in the identification of HPV-induced tumors [44]. More data on HPV testing are needed to formulate further assumptions about HPV's prognostic role of HPV in oral cavity cancers. Furthermore, the included meta-analyses addressing the prognostic role of HPV in the oral cavity and laryngeal cancers show contradictory results [6, 17, 22, 24, 28]. The absence of a significant effect of HPV on OS could be attributed to the mutual nullification of the different results from each study.

Finally, other detrimental prognostic factors in HPV-related non-OPSCC, such as smoking, could have played a role in the outcomes, altering inferences on HPV's sole contribution of HPV to OS. Smoking appears to worsen the prognosis of HPV-driven head and neck SCC [45]. The possible advantages of OS noted in some HPV-associated cancers could have been jeopardized by coexisting smoking habits.

To the best of our knowledge, this is the first review to examine the incidence and mortality rates of HPV infection and non-OPSCC. Additionally, we analyzed all included meta-analyses using objective criteria (AMSTAR-2), publication bias, and small-study effects. With the exception of laryngeal cancer, all cancer risk results were robust and highly suggestive. Despite only two meta-analyses reporting this, the prognostic outcomes were not significant for all sites, except for hypopharyngeal cancer.

However, our umbrella review has some limitations. Different detection methods for HPV testing were used in the included meta-analysis, and patients of different races were enrolled, as well as inclusion/exclusion criteria for the

control cases. As a result, the pooled estimates may suffer from heterogeneity and selection bias. Moreover, the included studies in the various meta-analyses had different follow-up periods and likely included patients treated with different modalities, which may have influenced the results. In addition, according to the AMSTAR 2 criteria, 40% of the meta-analyses included in this umbrella analysis had "low or critically low" methodological quality. The critical flaws considered were the absence of a registered protocol, the absence of the risk of bias in the considered investigations, and the absence of consideration of the risk of bias in the included investigations when interpreting or discussing the outcomes of each study. However, these studies mainly affected the results for oral cancer and HPV status. The exclusion of these studies did not substantially influence the other analyses. Finally, the ORs are primarily crude estimates and have not been adjusted for clinical features (smoking, status, and alcohol consumption) that may increase cancer risk.

Conclusions

HPV could play a role in the tumorigenesis of non-OPSCC, especially in the nasopharynx. HPV + hypopharyngeal cancers seem to have better OS than their HPV counterparts. HPV status does not seem to have a prognostic impact on nasopharyngeal, oral cavity, or laryngeal cancers. Further studies with reliable HPV detection methods are needed to clarify the role of treatment modalities and concurrent clinical features in HPV + non-OPSCC compared to HPV- non-OPSCC.

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Declarations

Conflict of interest None.

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