




REVIEW

Does human papillomavirus modify the risk of oropharyngeal cancer related to smoking and alcohol drinking? A systematic review and meta-analysis

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Abstract

Objective: To synthesize evidence for interactions of traditional oropharyngeal squamous cell carcinoma (OPSCC) risk factors—tobacco smoking and alcohol drinking—with human papillomavirus (HPV).

Data Sources: MEDLINE, Embase, Cochrane Database of Systematic Reviews, ProQuest, and Global Health were searched with no restrictions on language or publication date.

Methods: All case–control studies assessing interactions between these factors in OPSCC were considered. Quality was assessed using the Newcastle–Ottawa Scale for case–control studies. The main outcome was the OR for developing OPSCC for the following interactions: (1) HPV and smoking, (2) HPV and alcohol drinking, and (3) HPV, alcohol drinking, and smoking. Interactions were assessed from stratified analysis (by HPV status) and/or joint effect analysis (synergy index and multiplicative index).

Results: The search provided 3084 relevant studies, of which 9 were included. In the stratified analysis, the OR of developing OPSCC among smokers with HPV was less than that among smokers without HPV. A similar pattern was observed for alcohol drinking. This effect persisted among smokers and heavy alcohol drinkers with HPV compared with those without HPV. Joint effect analysis on the additive scale showed sub-additive antagonistic interactions between HPV and smoking, and between HPV and alcohol. On the multiplicative scale, sub-multiplicative interactions were found between HPV and smoking, and HPV and alcohol.

Conclusions: This meta-analysis suggests a negative directed interaction of HPV and smoking; and HPV and heavy alcohol drinking in the development of primary OPSCC on stratified analysis and joint effect analysis.

Level of Evidence: 3A.

Rawan T. Arif and Meaad A. Mogaddam contributed equally to this work.

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KEYWORDS

alcohol, head and neck squamous cell carcinoma, human papillomavirus, interaction, oropharyngeal cancer

1 | INTRODUCTION

Head and neck cancers (HNCs) represent the sixth most common cancer worldwide. One of the most common HNCs is oropharyngeal squamous cell carcinoma (OPSCC), which includes the posterior and lateral pharyngeal walls, base of tongue, tonsils, and soft palate. The incidence of oropharyngeal cancer worldwide in 2020 was 98,412.¹ The development of OPSCC is linked to three major independent risk factors: tobacco smoking, alcohol drinking, and human papillomavirus (HPV) infection.^{2,3} HPV, especially HPV 16 and 18, is shown to be a strong independent cause of OPSCC. HPV status is also well known to affect a patient's survival, as those with HPV-positive disease have improved cancer-related survival compared to those with HPV-negative disease.^{4,5} Data about the interaction between the three major risk factors in the development of OPSCC are scarce and often conflicting, some studies having observed no interaction⁶ and others having demonstrated an additive or synergistic association.^{5,7-9} Less clear is whether HPV status influences OPSCC risk when associated with alcohol and tobacco use.^{5,9}

Until recently, the main research synthesis was directed toward assessing the relationship between the individual and combined OPSCC risk factors on patients' survival or cancer recurrence.^{10,11} Yet, to the best of our knowledge, no previous systematic review or meta-analysis has thoroughly investigated the interaction between these factors (tobacco smoking and alcohol drinking) and HPV in the development of primary OPSCC. Therefore, the aim of this systematic review was to synthesize the existing evidence on the interaction between tobacco smoking, alcohol drinking, and HPV in the etiology of primary OPSCC.

The specific objectives of this study were as follows:

1. To explore the interaction between smoking and HPV status by examining the effect of smoking on oropharyngeal cancer among HPV-positive patients and, separately, among HPV-negative patients.
2. To explore the interaction between alcohol drinking and HPV status by examining the effect of alcohol drinking on oropharyngeal cancer among HPV-positive patients and, separately, among HPV-negative patients.
3. To explore the interaction between the three risk factors by examining the effect of smoking and alcohol drinking on oropharyngeal cancer among HPV-positive patients and, separately, among HPV-negative patients.
4. To explore the direction of the interaction on additive and multiplicative scales, if evident.

2 | METHODS

In this study, we followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline. To frame the research question, PECOS model was structured (details are available in the Supplemental Online Material). The inclusion criteria were any case-control studies that assessed the interaction between HPV, alcohol drinking, and/or smoking in the etiology of OPSCC. If a study included oral cancer and oropharyngeal cancer, only oropharyngeal cancer data were included. Studies that reported crude estimates in which the interaction results could be inferred from the data were also included. Exclusion criteria were studies that investigated other anatomical sites or premalignant lesions, other risk factors such as genetic factors, and different outcomes (i.e., survival, prediction, prognosis, and/or treatment response). We did not restrict the search to English language or publication date, and no filters were applied to the search.

2.1 | Study selection

All eligible studies were identified by using a two-level search strategy. First, a systematic search was conducted in MEDLINE, Embase, Cochrane Database of Systematic Reviews, ProQuest, and Global Health from the earliest record up to and including May 31, 2021. Second, references of selected articles were reviewed for additional relevant studies. For this purpose, two authors (Meaad A. Mogaddam and Rawan T. Arif) independently conducted the searches, any discrepancies being resolved by consensus. Controlled vocabularies were used to combine all possible terminologies related to the following concepts: "head and neck cancer" and the risk factors "smoking," "alcohol," and "HPV infection" (Detailed Search Strategy in Supplemental Online Material).

Data extraction was done independently by two reviewers (Meaad A. Mogaddam and Rawan T. Arif) and compiled in a spreadsheet. Discrepancies were resolved by consensus, and if they were unresolved, a third reviewer made the decision (Nada J. Farsi and/or Leena A. Merdad).

2.2 | Quality assessment

The Newcastle-Ottawa Scale for case-control studies was used to assess the quality of the studies.¹² This tool is composed of eight items that are categorized into three groups: the selection of the study groups; the comparability of the groups; and finally the ascertainment exposure of interest for case control studies. Stars are awarded for each quality item, such that the highest quality studies are awarded up to nine stars. Because we assessed the interaction of three different exposures (smoking, alcohol drinking, and HPV), we

considered the assessment of smoking and alcohol drinking under a single exposure category, given the similarity of their collection; HPV exposure was considered in a second separate category. Hence, the third domain of the quality assessment scale, ascertainment of exposure, was modified to include two new categories of exposure: smoking and alcohol drinking, and HPV. Instead of allocating one star to questions one and two in the exposure ascertainment section, we allocated a half star to each question for the first exposure, as well as for the second exposure. The total score for quality, however, remained the same.¹² Each reviewer generated a score independently for each article (Meaad A. Mogaddam and Rawan T. Arif), and this value was reviewed. When the two reviewers disagreed regarding a score, they tried to reach a consensus before involving a third reviewer (Nada J. Farsi and/or Leena A. Merdad).

2.3 | Statistical analysis

Analyses included studies with estimates from univariate or multivariate models. For interaction studies, odd ratios (ORs) were pooled by using the inverse variance method. The main outcome was the OR and 95% confidence interval (CI) for developing primary OPSCC in relation to any of the interaction combinations: (1) HPV and smoking, (2) HPV and alcohol drinking, and (3) HPV, alcohol drinking, and smoking. Because the exposure categories of smoking and alcohol drinking varied widely among the different studies, we only included estimates of the two opposite extremes of exposure: the highest and lowest exposure categories of each study.

The interaction between smoking and alcohol drinking with HPV status was assessed in two ways: stratified analysis (by HPV status) or joint effect analysis (additive and multiplicative scales). First, the stratified ORs of having OPSCC that compared HPV-negative patients and HPV-positive patients for each risk factor (smoking and alcohol drinking) were pooled from the studies that reported it. Second, the joint effect interaction between risk factors was also assessed with two scales; (1) additive, by calculating the synergy index, and (2) multiplicative, by calculating the multiplicative index, based on the estimates from joint effect analyses whenever they were presented. The synergy index and the multiplicative index equations were used based on Rothman, and Andersson et al.^{13,14} methods as following:

A-For Smoking and HPV interaction:

$$\text{Synergy index} = \frac{OR_{SMK+HPV+} - OR_{SMK-HPV-}}{OR_{SMK+} + OR_{HPV+} - 2OR_{SMK-HPV-}},$$

$$\text{Multiplicative index} = \frac{OR_{SMK-HPV-} * OR_{SMK+HPV+}}{OR_{SMK+} * OR_{HPV+}},$$

B-For Alcohol and HPV interaction:

$$\text{Synergy index} = \frac{OR_{ALCHL+HPV+} - OR_{ALCL-HPV-}}{OR_{ALCHL+} + OR_{HPV+} - 2OR_{ALCL-HPV-}},$$

$$\text{Multiplicative index} = \frac{OR_{ALCL-HPV-} * OR_{ALCHL+HPV+}}{OR_{ALCHL+} * OR_{HPV+}},$$

The synergy index was expressed as either sub-additive (antagonism), when the synergy index is less than one, or as supra-additive (synergism), when the synergy index is greater than one, or as no interaction, when synergy index is equal to one. The multiplicative index was addressed in a similar fashion; sub-multiplicative, when the multiplicative index is less than one, or as supra-multiplicative, when the multiplicative index is greater than one, or as no interaction, when multiplicative index is equal to one. The overall estimate of the interaction ORs was analyzed on the basis of a random effects model.

To assess and quantify the degree of heterogeneity, we estimated the I^2 statistic. In the current study, any percentage exceeding 50% implied substantial heterogeneity.¹⁵ Forest plots were constructed for all associations of risk factors with the outcome. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled OR estimates for the remaining studies. The meta-analysis was performed by using RevMan software version 5.4 (*Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020*).

2.4 | Assessing the overall certainty of the evidence

Grading of Recommendation, Assessment, Development, and Evaluation system for prognostic factors was followed to assess the overall certainty of the evidence in all included studies in the quantitative synthesis (stratified and joint effect analysis). Eight domains were considered for assessment: risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, dose response, and plausible confounding. The overall assessment of the evidence certainty was categorized into; high, moderate, low, or very low.¹⁶

3 | RESULTS

3.1 | Literature search

Of the 3084 potentially relevant articles initially screened, we identified 53 eligible studies for full-text screening. Of these, nine case-control studies were included for qualitative and quantitative analysis (Figure 1).

3.2 | Qualitative assessment

Table 1 presents the characteristics of the nine included studies. All were case-control studies published between 1998 and 2020, comprising a total of 2191 cases and 7575 controls. Five of the included studies were conducted in the United States^{5,17,19-21} whereas the others were performed in different countries.²²⁻²⁴ In all the studies, investigators assessed their estimates by stratification by HPV status (confirmed by polymerase chain reaction [PCR] and/or enzyme-linked immunosorbent assay [ELISA]) or by joint effect analysis. In only one study were estimates adjusted further

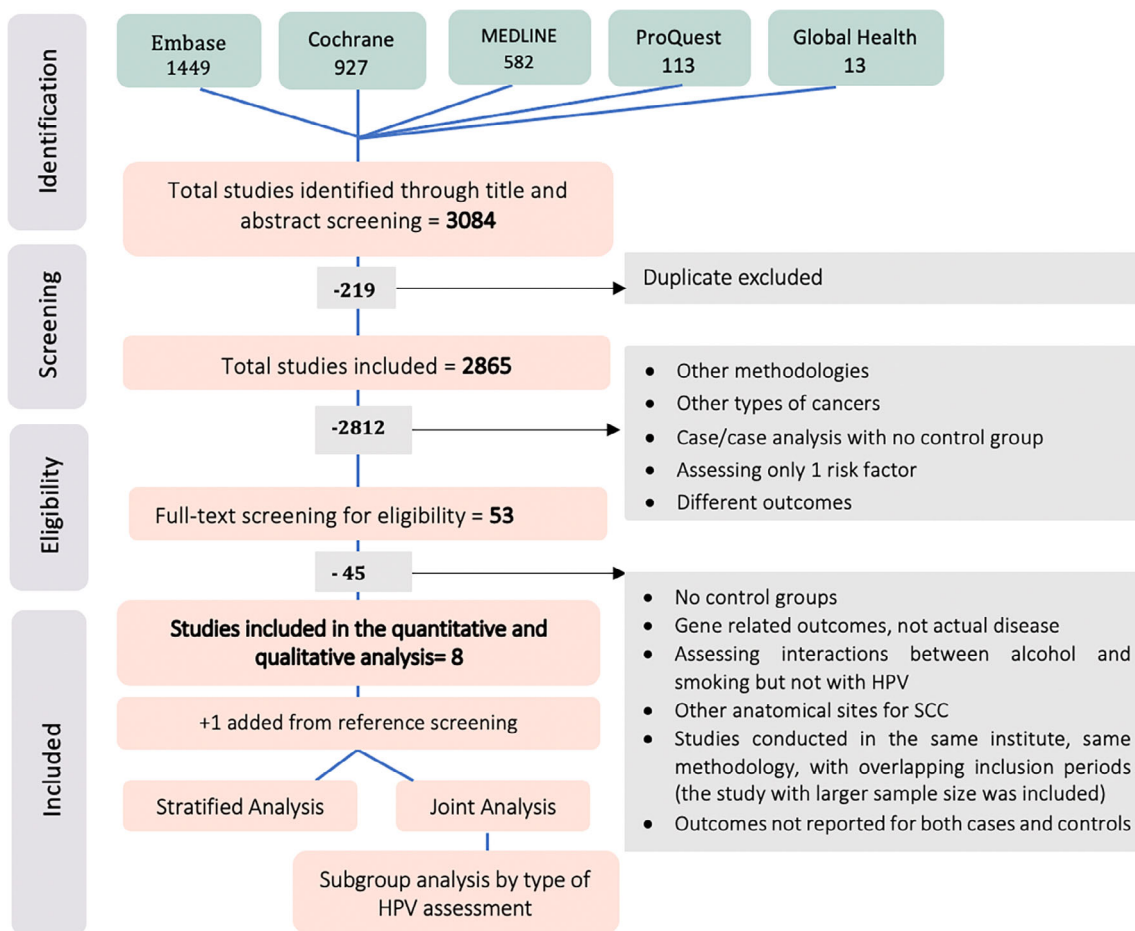


FIGURE 1 Flow diagram of literature search. HPV, human papillomavirus; SCC, squamous cell carcinoma

by regression analysis.⁵ Seven studies reported analyses for oral and/or oropharyngeal anatomical sites separately,^{5,18,20-24} whereas two studies analyzed all HNC sites together.^{17,19} Overall, the included studies were good quality (score > 6 out of 9), but the studies by Schwartz et al.¹⁷ and Auguste et al.²⁴ had the highest quality scores (score = 8.5) (Table 2).

Interaction was inferred from stratified analysis, joint analysis, or both. Studies in which stratified analysis was used compared the cancer risk related to smoking by HPV status, which compared the OR of cancer with smoking once with HPV and once without HPV. A similar comparison was made for alcohol exposure and for both factors (smoking and alcohol drinking) combined. For studies that used joint analysis, the risk of cancer in different exposure categories was compared to a reference group such as that used in regression analysis. The type of interaction was determined on additive and multiplicative scales, as described previously in the methods section.

All nine studies assessed the interaction between smoking status and HPV status in the etiology of HNC, but only six studies assessed the interaction in the development of OPSCC.^{5,18,20,22-24} Overall, on both stratified and joint analysis, smoking was associated with a high risk of developing primary OPSCC, this risk being less when combined with HPV. A similar result was shown with alcohol exposure and even with all exposures combined.

3.3 | Quantitative assessment

3.3.1 | Stratified analysis

HPV and smoking

Five of the included studies presented stratified analysis.^{5,20-23} Data for smoking were extracted as the lowest versus the highest exposure to account for the different smoking categorizations used in the included articles. In all studies, investigators tested for HPV 16 and/or HPV 18 by using ELISA testing, except for D'souza et al. and Farsi et al.^{20,23} where PCR testing was used. The summary OR for primary OPSCC risk in heavy smokers with a positive HPV test result was 1.31 (95% CI, 0.67-2.59), lower than that for heavy smokers with a negative HPV result (4.51, 95% CI, 2.08-9.81) (Figure 2).

HPV and alcohol

Five studies reported data about alcohol use,^{5,20-23} the majority of which categorized alcohol intake by number of drinks per week.^{5,20,21} However, Farsi et al.²³ computed alcohol consumption as liters of ethanol consumed, which was categorized into quartiles. The lowest versus highest exposure was included in this analysis. The summary OR of primary OPSCC among the HPV-positive group in relation to the

TABLE 1 The main characteristics of the included studies

Author, year	Country	Recruitment period	Source of cases/N	Source of controls/N	HPV assay method/type of HPV tested	Smoking categories	Results-smoking and HPV	Alcohol categories	Results-alcohol and HPV	Smoking/alcohol categories	Results-smoking/alcohol and HPV
Schwartz, 1998 ¹⁷	USA	1990–1995	Cancer Surveillance System (CSS)/259	Population/466	Capsid antibodies, ELISA/HPV 16	Current vs. Not current <20 vs. ≥20 pack/year	Supra-additive interaction Sub-multiplicative interaction	<15 vs. ≥15 drinks/week	No additive or multiplicative interaction	Current vs. Not current/ <15 vs. ≥15 drinks/week	Supra-additive interaction Supra-multiplicative interaction
Herrero, 2003 ¹⁸	Multicentre International	April 1996–December 1999	Hospital/255	Community, Hospital/1732	E6, E7 and L1 VLP, ELISA/HPV16	SMK+ vs. SMK–	Supra-additive interaction				
Smith, 2004 ¹⁹	USA	1994–1997	Hospital/201	Hospital/333	PCR/HPV 16, 18, 31, 33, and 58 (high-risk types)	Never vs. ≤30 vs. >30 pack/year	Supra-additive interaction Supra-multiplicative interaction	Never vs. ≤21 vs. >21 drinks/week	Supra-additive interaction	Never vs. ≤30 pack/year / Never vs. >21 drinks/week	Supra-additive interaction Supra-multiplicative interaction
Applebaum, 2007 ⁵	USA	1999–2003	Hospital/485	Town book, community/549	L1 antibodies, ELISA/HPV 16	None vs. >0–<20 vs. 20–<45 vs. ≥45 pack/year	Less risk based on stratified analysis Sub-additive interaction Sub-multiplicative interaction	<3 vs. 3 to <8 vs. 8 to <25 vs. ≥25 drinks/week	Less risk based on stratified analysis Sub-additive interaction Sub-multiplicative interaction		Less risk based on stratified analysis Sub-additive interaction Sub-multiplicative interaction
D'Souza, 2007 ²⁰	USA	2000–2005	Hospital/100	Hospital/200	PCR and L1 antibodies, ELISA/HPV 16	<20 vs. ≥20 pack/year	Less risk based on stratified analysis Sub-additive interaction	<15 vs. ≥15 drinks/week	Less risk based on stratified analysis Sub-additive interaction	<20 vs. ≥20 Pack/Year/ <15 vs. ≥15 drinks/week	Less risk based on stratified analysis Sub-additive interaction
Smith, 2012 ²¹	USA	2001–2004	Hospital/74	Hospital/428	PCR/HPV 16, 18 and 33	Never vs. ≤30 vs. >30 pack/year	Less risk based on stratified analysis Sub-multiplicative interaction	Never vs. 1–21 vs. >21 drinks/week	Less risk based on stratified analysis Sub-multiplicative interaction	Never vs. ≤30 pack/year / Never vs. 1 to 21 vs. >21 drinks/week	Less risk based on stratified analysis Sub-multiplicative interaction

(Continues)

TABLE 1 (Continued)

Author, year	Country	Recruitment period	Source of cases/N	Source of controls/N	HPV assay method/ type of HPV tested	Smoking categories	Results-smoking and HPV	Alcohol categories	Results-alcohol and HPV	Smoking/alcohol categories	Results-smoking/alcohol and HPV
Anantharaman, 2016 ²⁷	Europe	1992–2000 and 2002–2005	434	2739	L1 and E6 antibodies, ELISA/HPV 16	SMK+ vs. SMK– Never vs. ≤15 vs. >15 cig/day	Less risk based on stratified analysis Sub-additive interaction	≤7 vs. 7–28 vs. >28 gm/day	Less risk based on stratified analysis Sub-additive interaction		
			*Data were collected from ARCAGE nested case control study and EPIC cohort study								
Farsi, 2017 ²³	Canada	September 2005–November 2013	Hospital/74	Hospital/428	PCR/HPV 16	Non to moderate (<37) pack/year vs. heavy ≥37) pack/year	Less risk based on stratified analysis Sub-additive interaction	Non to moderate (<369 L ethanol) vs. Heavy (>369 L ethanol) in lifetime	Not protective based on stratified analysis Sub-additive interaction		Supra-multiplicative interaction
Auguste, 2020 ²⁴	French West Indies	1 April 2013–30 June 2016	Hospital/145	Population/405	PCR/HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 (high-risk types)	SMK+ vs. SMK–	Sub-additive interaction Sub-multiplicative interaction	ALC+ vs. ALC–	Sub-additive interaction Sub-multiplicative interaction	SMK+ vs. SMK–/ ALC+ vs. ALC–	Less risk based on stratified analysis

TABLE 2 The quality of the included studies

Author, Year	1-Selection			2-Comparability		3A-SMK & Alchl		3B-HPV			Quality score
	Definition	Cases	Controls	Definition of controls	Controls for age and sex	Other factors	Ascertainment of exposure		Ascertainment of exposure		
							Secure record	Same method for CC	Secure record	Same method for CC	
Schwartz, 1998 ¹⁷	1	1	1	1	1	1	0	0.5	0.5	1	8.5
Herrero, 2003 ¹⁸	1	1	0	1	1	1	0	0.5	0.5	0	6.5
Smith, 2004 ¹⁹	1	1	0	1	1	1	0	0.5	0.5	1	7.5
Applebaum, 2007 ⁵	1	1	1	0	1	1	0	0.5	0.5	0	6.5
D'souza, 2007 ²⁰	1	0	0	1	1	1	0	0.5	0.5	1	6.5
Smith, 2012 ²¹	1	1	0	1	1	1	0	0.5	0.5	1	7.5
Anantharaman, 2016 ²²	1	0	1	1	1	1	0	0.5	0.5	0	6.5
Farsi, 2017 ²³	1	1	0	1	1	1	0	0.5	0.5	1	7.5
Auguste, 2020 ²⁴	1	1	1	1	1	1	0	0.5	0.5	1	8.5

highest alcohol exposure was 1.11 (95% CI, 0.54–2.29), lower than that for the HPV-negative group (3.69; 95% CI, 2.42–5.63) (Figure 3).

HPV, alcohol, and smoking

Only three studies reported data on all three exposures combined.^{20,21,24} The summary OR of OPSCC among HPV-negative patients with the highest alcohol and smoking exposure, compared with the control group, was 18.36 (95% CI, 7.87–42.82). This risk was less for HPV-positive cases with the highest alcohol and smoking exposure, for whom the summary OR was 2.26 (95% CI, 0.37–13.66) (Figure 4).

3.3.2 | Joint effect analysis

As described previously, this paper is assessing the interaction on two scales: additive and multiplicative.

HPV and smoking

Six studies assessed the interaction between smoking and HPV in the etiology of OPSCC by joint effect analyses.^{5,18,20,22–24} The summary OR for the risk for OPSCC with exposure to smoking only (not HPV) was 5.34 (95% CI, 2.88–9.91). A higher OR for the risk for OPSCC was seen with exposure to HPV only (not smoking): 17.02 (95% CI, 6.80–42.60). Finally, the summary OR for the risk of OPSCC among those who were smokers and had HPV was 20.50 (95% CI, 12.56–33.45). The meta-analyses of the results of these studies are shown in Figure S1 in Supplemental Online Material. There was evidence of antagonistic interaction on the additive scale based on overall risk. Furthermore, a strong sub-multiplicative interaction effect was evident between HPV and smoking, as the multiplicative index was lower than one (Table 3A).

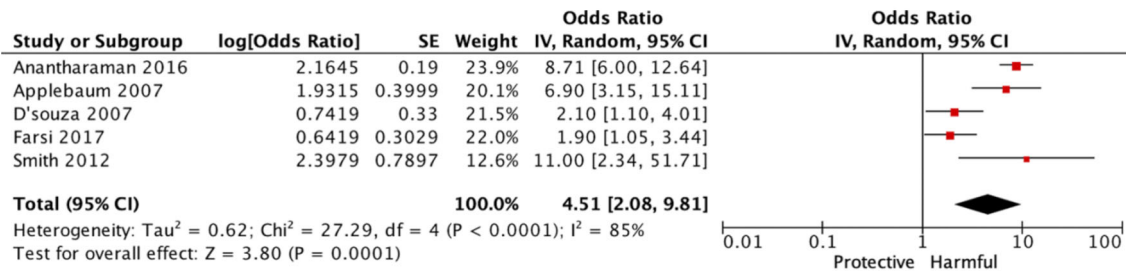
HPV and alcohol

Five studies assessed the interaction between HPV and alcohol by joint effect analyses.^{5,20,22–24} The summary OR for the risk for OPSCC for heavy alcohol drinking and HPV negativity was 3.76 (95% CI, 2.95–4.81), whereas it was 39.32 (95% CI, 14.11–109.59) for HPV positivity and no alcohol drinking. However, the risk of OPSCC among those who were heavy alcohol drinkers and HPV positive was 27.10 (95% CI, 6.72–109.27) (Figure S2 in Supplemental Online Material). Evidence of a sub-additive interaction (antagonism) was seen between HPV and alcohol based on the synergy index, which was less than one. Sub-multiplicative interaction was inferred from these data as well (Table 3B).

3.3.3 | Joint effect analysis, subgroup analysis

Subgroup analyses were performed with the HPV detection method (PCR or serology) for both exposures. Although the heterogeneity was not significantly decreased for the smoking and HPV category, it was markedly reduced for the alcohol and HPV category. Similar observations of interaction (on both additive and multiplicative scales) remained evident in the meta-analysis for HPV; smoking and OPSCC; and HPV, alcohol, and OPSCC.

➤ **SMK+ HPV-**



➤ **SMK+ HPV+**

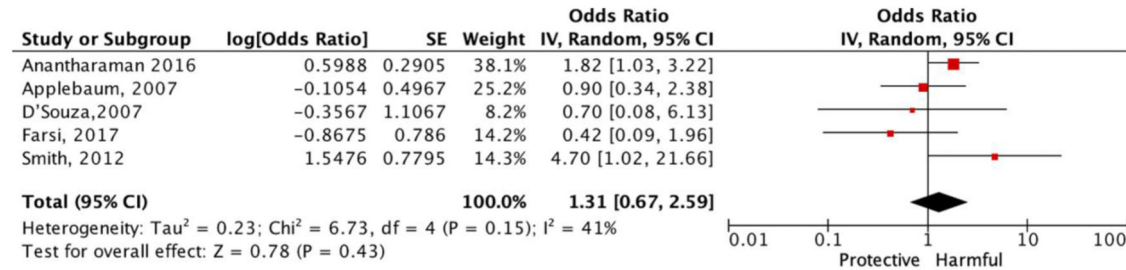
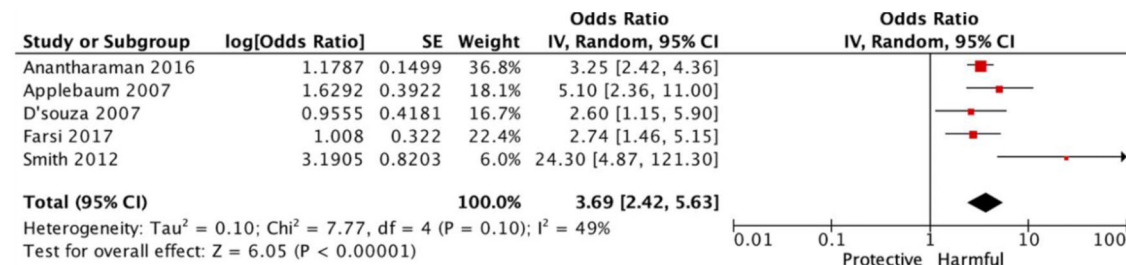


FIGURE 2 HPV-stratified meta-analysis assessing the risk of OPSCC related to smoking. HPV, human papillomavirus; IV, inverse variance; OPSCC, oropharyngeal squamous cell carcinoma; SE, standard error

➤ **ALCHL + HPV-**



➤ **ALCHL + HPV+**

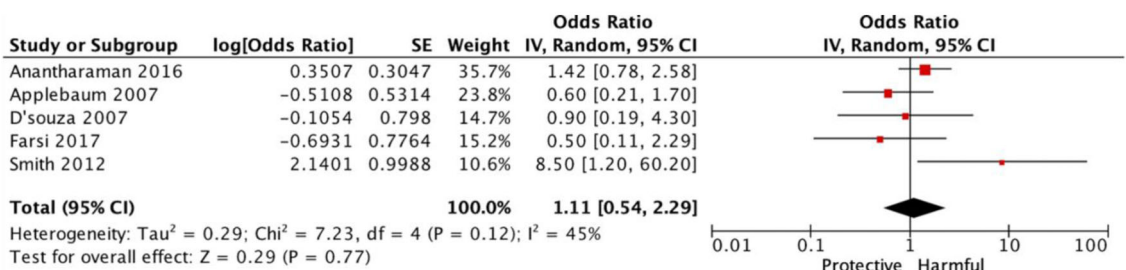


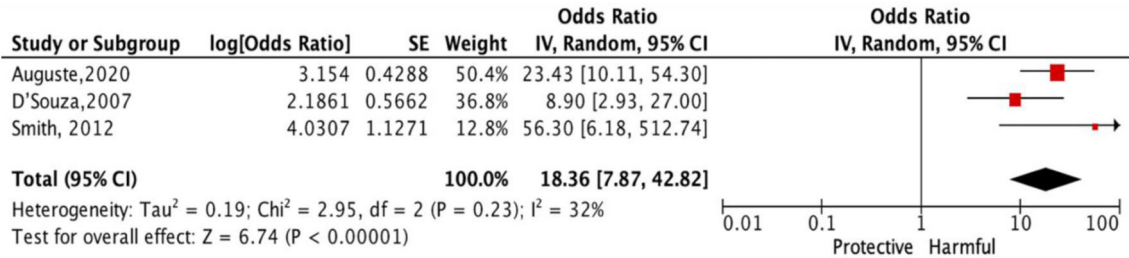
FIGURE 3 HPV-stratified meta-analysis assessing the risk of OPSCC related to alcohol drinking. HPV, human papillomavirus; IV, inverse variance; OPSCC, oropharyngeal squamous cell carcinoma; SE, standard error

3.3.4 | The overall certainty of the evidence

The level of evidence when a single risk factor is investigated (smoking or alcohol drinking or HPV) shown to be high. However, when the

risk factors were combined in pairs (smoking and HPV or alcohol and HPV), the certainty levels were reduced to moderate. When the three risk factors were combined, the evidence became low (Table S1 in the Online Supplemental Material).

➤ **SMK+ ALCHL + HPV-**



➤ **SMK+ ALCHL + HPV+**

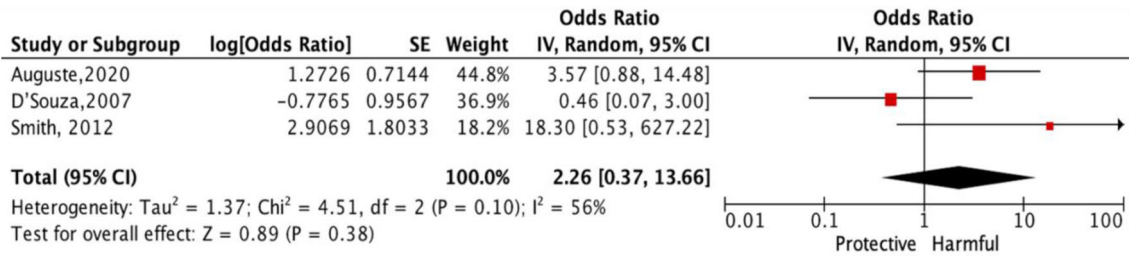


FIGURE 4 HPV-stratified meta-analysis assessing the risk of OPSCC related to smoking and alcohol drinking. HPV, human papillomavirus; IV, inverse variance; OPSCC, oropharyngeal squamous cell carcinoma; SE, standard error.

TABLE 3 Joint effect estimates assessing the risk of OPSCC related to smoking and alcohol drinking

Pooled odds ratio				Multiplicative scale interaction		Additive scale interaction	
A-Smoking status (SMK)				Multiplicative index	Interpretation	Synergy index	Interpretation
SMK- HPV-	SMK- HPV+	SMK+ HPV-	SMK+ HPV+				
1	17.02 (6.8-42.6)	5.34 (2.88-9.91)	20.5 (12.56-33.45)	0.23	Sub-multiplicative	0.96	Sub-additive
B-Alcohol status (ALCHL)				Multiplicative index	Interpretation	Synergy index	Interpretation
ALCHL- HPV-	ALCHL- HPV+	ALCHL+ HPV-	ALCHL+ HPV+				
1	39.32 (14.11-109.59)	3.76 (2.95-4.81)	27.1 (6.72-109.27)	0.18	Sub-multiplicative	0.64	Sub-additive

4 | DISCUSSION

The primary OPSCC risk associated with smoking, alcohol drinking, and HPV infection is highlighted in the literature, but data are scarce and conflicting about the combined effect of these factors, that is, the interaction between these factors in the development of cancer.^{9,20,22-24} Our analysis of nine case-control studies suggests a negatively directed interaction of HPV and smoking, and of HPV and alcohol, in the development of primary OPSCC. The risk of developing primary OPSCC with HPV alone (without smoking or alcohol drinking) was higher than that with HPV and smoking or HPV and alcohol drinking. This result was reflected in both stratified and joint effect analysis.

In general, multiplicative interaction estimates are used to assess the overall effect of the exposures on the outcome and therefore helps in causality assessment which was the main focus of this study. On the other hand, additive interaction estimates are frequently used

to prioritize prevention and/or intervention modalities. Therefore, it is more useful for public health measures.²⁵

Our findings provide another perspective in OPSCC epidemiology that may affect patient counseling and suggest a future research opportunity to investigate carcinogenesis at the molecular level in order to better understand OPSCC pathophysiology. Some studies have suggested that smoking might prevent HPV infections secondary to increased expression of secretory leukocyte protease inhibitors and have recommended future studies to better elucidate their role in the pathogenesis of OPSCC.^{24,26,27}

Moderate to high levels of heterogeneity were detected across studies. Technical differences between modalities used for data collection or data expression may introduce bias to the summary effect estimates. Such differences included quantification of smoking exposure, alcohol drinking exposure categories, and method of HPV assessment (immunohistochemistry, HPV deoxyribonucleic acid [DNA] in situ hybridization, DNA by PCR). However, subgroup analysis HPV testing

methods (PCR vs serology) reduced the heterogeneity, at least for the alcohol exposure category. The same pattern of interaction remained evident on the overall meta-analysis for HPV, smoking and OPSCC; and HPV, alcohol, and OPSCC. The differences in definitions and categorizations of exposure (smoking and alcohol) nonetheless made it difficult to investigate smoking exposure in terms of an ordinal variable (number of packs/year) when the majority of studies used a different exposure stratification (current/previous vs non-smoker). In that case, we used the highest against the lowest exposure reported by each study and compared the extremes of exposure. This approach was also used for alcohol intake. In addition, the included case-control studies had different geographical backgrounds and populations, which may have involved variations in genetic makeup and HPV prevalence. The pool of controls that were matched to cases might also have been different, some studies using hospital-based matching and others community matching. Heterogeneity was decreased when we excluded studies that did not stratify the analysis on the basis of cancer anatomical sites, since the role of HPV in the development of OPSCC is well established compared with its role in other HNC subsites.²⁴ We did not generate separate summary estimates for other anatomical subsites, as doing so was out of the scope of this meta-analysis. This approach also reflects a different pathogenesis for OPSCC and that of other HNC anatomical sites.^{21,24,28,29}

Interaction was assessed on two scales: multiplicative and additive. Different methods to assess interaction in the included case-control studies have been described in the literature, including relative excess risk due to interaction and synergy index.^{17,20,24} Meta-analysis using these methods will require parameters extracted from the original data that were not available or easily attainable. Hence, we assessed for interaction in this meta-analysis by using a stratified analysis and joint effect analyses. Analysis of the interaction was then performed on additive and multiplicative scales as described earlier.

Sinha et al.,⁹ in 2012, suggested an additive or synergistic interaction between smoking and HPV in the risk of head and neck squamous cell carcinoma (HNSCC) in general. However, it was a narrative review that included 12 studies with different study designs,⁹ and no meta-analysis was conducted to further explore the overall interaction. Moreover, the data were not stratified by anatomical site. In our meta-analysis, we based our findings on the results of case-control studies, which allowed us to better estimate the risk of disease by comparing a group with a positive outcome (cancer) directly to a group without cancer. In addition, we used ORs as measures of effect to assess for interaction. We also restricted our analyses to primary OPSCC, for which there is the strongest evidence for HPV in its etiology among other HNSCC sites.²⁴

In a systematic review and meta-analysis conducted by Skoulakis et al., 2161 patients with HNSCC were included in order to investigate the role of smoking and HPV in the development of HNSCC. They highlighted that smoking might not play a major role in HPV-positive HNSCC. This suggestion was based on an assessment of the number of smokers in the HPV-positive group of HNSCC patients compared with the number in the HPV-negative group. They did not investigate the possible association of smoking and HPV infection in

OPSCC specifically. No direct risk assessment measures such as OR were used for comparisons between cases and controls.⁶

Our study, however, presents some limitations. The high level of heterogeneity observed could have been caused by variabilities in the studies included. The inconsistent definitions of exposure across studies made it difficult to use all exposure categories in the meta-analysis. Therefore, the dose and duration effect could not be addressed in our study. Overall, these types of exposure are usually self-reported, and thus if misclassification occurred, it would be non-differential. Moreover, the CI of synergy index and multiplicative index could not be estimated as the original data of each included study were not available. Finally, different well-known detection methods for HPV were used with different reported specificities and sensitivities. Therefore, we opted to use random effects models in the meta-analyses.

Our meta-analysis has several strengths. It is the first comprehensive meta-analysis on the interaction between the major risk factors in the development of primary OPSCC to include case-control studies (2191 cases and 7575 controls). We also used rigorous methodology: two independent reviewers performed each step of the systematic review, including quality assessment; no language limitations were placed on the search; we thoroughly searched reference lists and reviews to retrieve additional articles and made efforts to contact the original authors for unpublished data; the quality of studies was assessed with a validated tool specifically designed for case-control studies;¹² and subgroup analyses were performed to identify sources of heterogeneity.

5 | CONCLUSION

This is the first systematic review and meta-analysis to investigate the interaction between smoking, alcohol drinking, and HPV in the development of primary OPSCC. Our results demonstrated a negative interaction on stratified and joint effect analysis of HPV in its development among smokers and heavy alcohol drinkers. The exact mechanism underlying these interactions in primary OPSCC risk are yet to be investigated. Further molecular studies are warranted to elucidate these findings.

CONFLICT OF INTEREST

The authors declares there is no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Arif RT, Mogaddam MA, Merdad LA, Farsi NJ. Does human papillomavirus modify the risk of oropharyngeal cancer related to smoking and alcohol drinking? A systematic review and meta-analysis. *Laryngoscope Investigative Otolaryngology*. 2022;7(5):1391-1401. doi:10.1002/lio2.877