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HPV in the malignant transformation of sinonasal inverted papillomas: A meta-analysis

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Abstract

Objectives: To date, there is still a significant debate on the role of human papilloma virus (HPV) infection in transformation of inverted papillomas (IPs) to squamous cell carcinoma (SCC). This study was designed to determine if the presence of HPV in a sinonasal IP increases the risk of malignant transformation to IPSCC.

Methods: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 19 high-quality case-control and cohort studies with tissue-diagnosed IP or IPSCC and HPV diagnosis were analyzed. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the Mantel–Haenszel method with correction for random effects. Subgroup, publication bias and a sensitivity analyses were also performed.

Results: Nineteen studies with minimal bias met the inclusion criteria for quality and identified HPV infection in an IP. The pooled data revealed a strong association with progression to malignancy with an unweighted, pooled OR of 2.38 (CI_{95} 1.47 to 3.83) and a weighted OR of 2.80 (CI_{95} 1.42 to 5.51). Sensitivity analysis revealed that no single study contributed significantly to our pooled OR calculations (ORs 2.52 to 3.57). Subgroup analyses stratified by publication date, nucleic acid target, HPV detection method and type, sample size, and region all demonstrated a positive association of HPV with IPSCC.

Conclusions: There appears to be a significant association between HPV infection and malignant transformation of IPs. While HPV testing is not currently the standard of care for IPs, these data suggest a link between the two and suggest further studies should be performed to identify a link between the virus and malignant transformation.

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CONFLICT OF INTEREST

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Keywords

head and neck cancer; HPV; human papilloma virus; inverted papilloma; sinonasal tumors; skull base cancer

INTRODUCTION

Inverted papillomas (IPs) are rare, benign, sinonasal tumors with the ability to undergo malignant transformation.[1,2] While rare, they are the most common type of papilloma within the sinonasal cavity (up to 70%) and represent up to 5% of primary nasal cavity tumors.[3,4] The association of human papillomavirus (HPV) with IPs was first identified in a squamous cell carcinoma (SCC) derived from an IP,[5] resulting in many subsequent studies attempting to define a causal link between HPV and malignant transformation of IPs, with mixed results.[5] Identification of HPV in IP is likely subject to the sensitivity of the testing method employed (e.g., DNA, RNA, viral protein), and the literature reports HPV association with IPSCC varies wildly (from no positive tissue association to 100%).[6-13] Further, these tumors have a high recurrence rate,[14] and their malignant transformation potential has spurred significant investigation into their etiology, disease course, and treatment. Prior meta-analyses of HPV-mediated transformation of IPs have suggested a near 50% prevalence of HPV in IPSCC[15] and strong bias towards the high-risk virus types HPV16 and HPV18 in IP malignant transformation.[16]

Presently, it is unclear whether or not there is a distinct association between malignant transformation of IPs and the presence of HPV infection. Limited data exist summarizing available studies. In this study, we performed a systematic review of the existing literature on HPV-associated IPSCC and performed a meta-analysis to determine whether there was an association between HPV infection and malignant transformation of IPs.

METHODS

Literature search

A systematic review of the literature following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was performed[17] and identified eligible studies in English published through April 2020 by searching PubMed (1946–present). The medical subject headings (MeSH) search terms included: *((human papillomavirus) OR HPV) AND nasal) OR sinonasal) OR paranasal sinus) AND inverted) OR inverting) OR Schneiderian) AND squamous cell carcinoma))* and all combinations therein. Filters were then applied to narrow the scope of the search to relevant article types and included: English language only, full-text available, and journal article. Additional relevant references in retrieved articles were also reviewed.

Study selection

Criteria for inclusion in this analysis included the following parameters: HPV detection was performed by measurement of nucleic acid (DNA/RNA) either by polymerase chain reaction (PCR) or in situ hybridization (ISH) because these are the primary clinical methods for

detecting nucleic acid; total sample size was disclosed for the cohort; total HPV-positive cases and the subset of both benign and malignant HPV-positive IPs were clearly stated and patient-level data were extractable.

The exclusion criteria included the following: inability to identify the number of total cases of IPs or lack of separation of HPV-positive and -negative IP cases, HPV detection by protein analysis, and studies analyzing sinonasal carcinomas that did not involve IPs. Case reports and review articles were excluded. Two authors independently reviewed the abstracts and all included articles. For any discrepancies, a consensus was achieved between the two reviewers based on these criteria. All studies meeting the aforementioned criteria were included in this analysis. Figure 1 highlights our study selection and exclusion process.

Data extraction

The following data were extracted from each study: lead author information, year of publication, practice setting, study timeframe, sample size, patient demographics including age and sex when available, nucleic acid source for testing tissue for HPV, method of HPV detection, overall number of HPV-positive samples, number of HPV-positive IPs, and number of IPSCCs.

Statistical analysis

The odds ratios (ORs) and 95% confidence intervals (CI_{95}) were calculated using the Cochran–Mantel–Haenszel method with a random effects model unless otherwise noted.[18] All ORs were recalculated by extracting the primary data from each study. Prior to calculating the OR for each study, the Haldane–Anscombe correction was applied to each cell of the contingency table.[19,20] We also performed subgroup analyses of HPV detection method and subtype, choice of nucleic acid, and stratification by sample size. We then performed Egger's regression asymmetry tests to determine whether there was evidence of publication bias among the data and graphed the results using funnel plots.[21] Data were aggregated in Microsoft Excel (Version 2019). Study analyses were all performed using R-Studio (v 4.0.4) with *meta, metafor, demetar*, and *mimR* packages loaded and/or Prism9 (GraphPad, Inc) unless otherwise noted.

Risk of bias in studies

To assess for risk of bias within studies, we used the Newcastle–Ottawa Quality Assessment Scale for nonrandomized studies, which is composed of three different grades: selection, comparability, and exposure.[22]

RESULTS

A total of 19 studies were included in this analysis following exclusion of studies as described (Figure 1; Table 1). Two of the studies that met the inclusion criteria were not included in the pooled effect size calculation, as there were no positive events in the HPV+ IPSCC arm of the study. The studies were performed between 1995 and 2020. The number of enrolled subjects ranged from 6 to 90. A majority of the cases utilized DNA as the nucleic acid of choice (84.2%) for detection of HPV. PCR was the favored detection modality

with 12 of 19 studies (63.1%) utilizing this method. All but one study was performed at a tertiary academic center (94.7%). The studies were conducted over a total of three continents including North America (42%), Europe (22%), and Asia (36%). A total of 134 of 794 of all IPs were HPV-positive (16.9%). In total, 37 of 130 HPV-positive IPs were associated with malignant transformation (28.4%). Mean age (± range) and ratio of male-to-female patients were reported and extractable from most studies. Table 1 highlights the pertinent demographic information from the patient population. We also performed an analysis of bias using the Newcastle–Ottawa scale prior to analyzing our data, which is presented in Table 2.

The presence of HPV was associated with statistically significant higher odds of malignant transformation of IPs into SCC (unweighted, pooled OR = 2.38, CI_{95} 1.47 to 3.83). A weighted analysis controlled for random effects among studies demonstrated a stronger association of HPV presence with malignant transformation of IPs (OR = 2.80, CI_{95} 1.42 to 5.51) (Figure 2).

Subanalysis

Several subgroup analyses were performed including publication year, type of nucleic acid utilized in HPV detection, detection method of HPV status, overall study sample size, as well as geographic distribution of cases. Initially, studies were stratified by publication date by dividing them into pre-2000 and post-2000 publications, which demonstrated ORs of 3.58 (CI_{95} 0.61 to 21.14) and 2.56 (CI_{95} 1.10 to 5.94), respectively. Earlier studies demonstrated relatively low heterogeneity (I^2 = 10.1%), while more contemporary studies had modestly higher heterogeneity (I^2 = 28.5%). A more refined publication date analysis was also conducted that separated studies into 10-year blocks (1990–1999; 2000–2009; 2010–present). This demonstrated ORs of 3.57 (CI_{95} 0.60 to 21.14), 2.77 (CI_{95} .065 to 117.18), and 2.52 (CI_{95} 0.88 to 7.18), respectively. There was no significant difference of the weight-adjusted ORs between any of these groups (p = 0.9050).

Additionally, a subanalysis of both HPV nucleic acid target (RNA vs. DNA) and the method of HPV identification was performed. Studies utilizing HPV DNA as their target had an adjusted OR of 2.65 (CI_{95} 1.29 to 5.44), while RNA-based studies had an adjusted OR of 4.27 (CI_{95} 0.03 to 671.4). HPV detection by PCR had an adjusted OR of 2.40 (CI_{95} 1.07 to 5.36), while detection by ISH had an adjusted OR of 4.08 (CI_{95} 0.75 to 22.15).

Stratification by study sample size also revealed a consistent, positive association of HPV infection with malignant transformation of IPs. Studies with less than 30 patients had an adjusted OR of 3.19 (CI_{95} 0.82 to 12.50), and those with more than 30 had an OR of 2.65 (CI_{95} 1.04 to 6.73).

When the data were stratified by geographic location, we also observed a positive association of malignant transformation of IPs in all three of the geographic regions from which the studies were derived: North America (OR 2.76; CI_{95} 0.89 to 8.57), Europe (OR 2.85; CI_{95} 0.24 to 34.33), and Asia (OR 2.88; CI_{95} 0.62 to 13.55).

Finally, we performed a subtype analysis stratifying studies by HPV oncogenic risk. Using low-risk (LR) versus high-risk (HR) as our study variable, a total of 12 of the original

studies had data available for quantitative extraction. We found that HR-HPV types have higher odds of IPSCC when compared with LR-HPV types (OR 3.42, CI_{95} 1.42 to 8.25; I^2 = 39.1%).

Model diagnostics and publication bias assessment

There was a low overall degree of heterogeneity among the included publications (Iš = 21.0%, tau^2 = 0.98). Our examination of publication bias is demonstrated in the funnel plot shown in Figure 3. Additionally, Figure 3 demonstrates the overall effect size of the included studies, with four studies having a positive association with HPV-mediated transformation significantly impacting the overall pooled OR. Publication bias was not statistically significant using Egger's regression statistic (p = 0.27).

Finally, we also performed multiple tests to determine whether specific studies had a strong contribution to our overall results. No single study had an overwhelming influence (as determined by Cook's distance and covariance ratio variables) on the outcome of our pooled OR, and no studies were excluded as outliers. We then performed a sensitivity analysis by removing one study at a time, which revealed pooled ORs ranging from 2.52 to 3.57 (CI_{95} 1.30 to 6.28) (Figure 4A), similar to the pooled, weighted OR (Figure 2). Finally, using graphic display of heterogeneity plots (GOSH)[23], we found congruence with our study's heterogeneity and weighted OR (Figure 4B).

DISCUSSION

HR-HPVs are the etiological agent of nearly all cervical cancers[24] and are rapidly becoming a major risk factor in the development of head and neck cancer of the oropharynx.[25-27] Given the virus' restriction to replicating in mucosal and cutaneous keratinocytes, it is not surprising that more lesions of the skin and upper aerodigestive tract are being attributed to HPV. In this study, we attempted to objectively summarize the existing literature and highlight the risk of HPV infection in driving an IP toward malignancy. Previous studies have examined the rate of HPV positivity in IPs[28] or demonstrated a mild association of HPV infection with malignant transformation of IPs;[16] however, this study attempted to perform a thorough, quantitative analysis of HPV in its association with malignant IP transformation using 19 high-quality studies.

As demonstrated in Figure 2, the presence of HPV results in significantly higher odds of malignant transformation of IPs (OR 2.80, CI_{95} 1.42 to 5.51). While all of the publications in this study did not identify whether malignant IPs contained HR- or LR-HPVs, it has been shown that LR-HPV infection also carries a risk of malignant transformation in many other conditions.[24,26,29] This prompted a subtype analysis based on HPV oncogenicity which demonstrated that HR-HPV infection is associated with HPV-derived IP transformation when compared with LR-HPV types (OR 3.42, CI_{95} 1.42 to 8.25). Because a small number of studies utilized ISH, we controlled for confounding due to detection method. Even when the analysis was restricted to HPV detection methods or different nucleic acid sources, there was a continued association of HPV infection with malignant transformation. This result held true in both smaller-scale (<30) and larger-scale (>30) studies.

Because all included studies did not use the same detection method, we performed a subgroup analysis stratifying studies based on PCR or ISH. Interestingly, we found that PCR-based studies yielded the lowest risk (2.40; CI_{95} 1.07 to 5.36) when compared with ISH-based studies (4.08; CI_{95} 0.75 to 22.14). However, heterogeneity was much higher in ISH-based studies (Iš = 41.14% vs. 14.1% in PCR-based studies). While ISH is a common method for identifying HPV clinically in head and neck cancers, PCR and other DNA detection methods have become increasingly more popular due to their ease of use and high sensitivity.[30] Thus, the observation of a higher rate of HPV-positive samples in ISH-based studies was unexpected. With the high sensitivity of PCR, we would expect PCR to outperform ISH in a large-scale head-to-head study. Additionally, the OR of ISH-based studies spans 1, suggesting the OR is likely not significant. Taken together, these data suggest PCR would give the most careful estimate of the true OR in this population.

Studies were also stratified by publication date and geographic location. This consistently demonstrated a positive association of HPV with malignant transformation. A previous study suggested significant publication bias in studies published before the year 2000;[16] however, according to these data there was no significant publication bias in studies before or after the year 2000, or when we clustered studies by decade. Furthermore, there was no significant difference in geographical location. Studies from all three continents included in this analysis had a positive association with HPV and malignant transformation. Intrastudy comparison by geographic region also did not reveal a significant difference between these positive associations, suggesting the observed ORs were likely due to chance rather than a true difference between the three study populations and the rate of HPV positivity in IPSCC samples.

While there was no observed, statistically significant publication bias in the overall study, funnel plot analysis does demonstrate that the results of a majority of studies that impact the pooled OR are found to have a positive association of HPV with IP transformation to malignancy (Figure 3). Finally, it is important to note that the predictive interval (PI) (or likelihood of where a future study's OR may fall) includes 1 (CI_{95} 0.23 to 25.83). While such broad PIs are not uncommon in medical research, it does suggest there is a high degree of uncertainty of what a future, similarly conducted single study may find with respect to HPV's association with IPSCC.

Several reviews have attempted to determine factors involved in the progression of IP to cancer. Our findings on method of detection are similar to that of Lawson et al.[15] and show ISH-based detection to have increased odds of HPV progression to IP, though a majority of the studies in this analysis were PCR-based. Interestingly, ISH-based detection (though a higher OR), was not statistically significant in its association of HPV-associated IP progression. While ISH-based staining is considered fast and accurate, it requires visualization and human detection for positive results, which could increase the rate of false positivity and skew the OR (and resultant CIs). The overall weighted OR of our study is also similar to that shown by Zhao et al.,[16] who also found a consistent positive association between HPV and IPSCC (OR 2.16, CI_{95} 1.46 to 3.21). In contrast to their findings, we still find no publication bias in our HPV subtype analysis. Taken together, this study and others suggest HPV does have a potential role in the progression of an IP towards cancer; however,

there is significant room for improvement in the area of understanding HPVs involvement in the transformation of an IP into malignancy. To date, there are no prospective, multicenter studies that have collected IPs and consistently tested for HPV to help further tease out this association. Understanding the true risk of HPV infection in the development and progression of an IP lesion into malignancy could dramatically change patient management, as it has for the treatment of oropharyngeal head neck cancer.[31]

There are several limitations in this study. There were a significant number of studies excluded prior to conducting our data analysis. If studies did not adequately describe the testing method or supply all data necessary to calculate an OR, they were excluded. This could either falsely inflate (or decrease) the pooled OR, though there was a consistent positive association throughout all our subgroup analyses. Additionally, as there were limited clinical data in all of the included studies, it was not possible to perform a subgroup analysis of other environmental risk factors such as smoking or other pre-existing conditions that could contribute to the development of a malignant neoplasm. Finally, as with all studies performed in this manner, there are insufficient data to provide definitive causality or definitively state that HPV is an etiological agent for IP transformation to malignancy, though we do consistently find a positive association with malignancy.

CONCLUSIONS

HPV infection has redefined the treatment paradigm for SCCs in the oropharynx over the past two decades. However, HPV infection is not limited to keratinocytes of the oropharynx and can infect epithelia throughout the upper aerodigestive tract. IPs are a benign lesion of the paranasal sinuses that have demonstrated the potential for malignant transformation into SSC (IPSCC). HPV has been implicated in this progression, but data to date have been contradictory. In this study we shown a consistent association of HPV with IPSCC. If HPV is associated with malignant progression of a benign IP, then HPV testing of IPs after surgical resection could have a critical role in defining the patient population who require oncologic surveillance versus those who do not. The findings presented here support the idea that more carefully conducted molecular-based studies are needed to argue for a potential paradigm shift in the management of patients with IPs that are HPV-positive.

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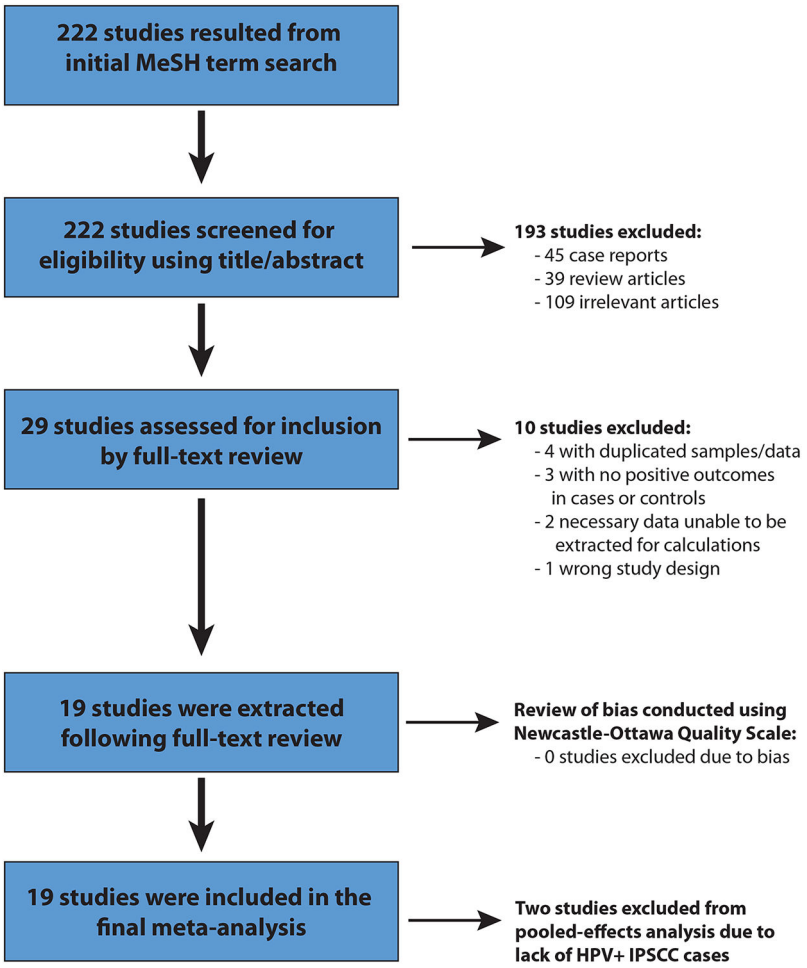

FIGURE 1.

Flowchart: study selection for included studies using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines

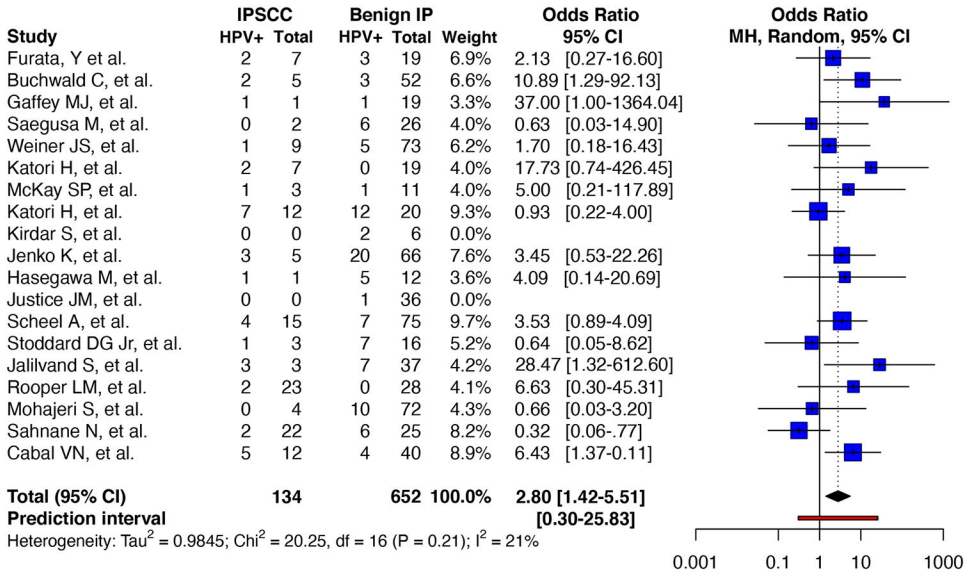

FIGURE 2.

Forest plot of included studies. Pooled odds ratios (ORs) of malignant transformation of inverted papillomas (IPs) associated with infection of human papilloma virus (HPV). Dashed line represents the pooled OR. Error bars represent lower and upper 95% confidence intervals (CIs). Size of blue square indicates the weight of the study. Red line demonstrates the prediction interval or range where the OR of a new study may fall. IPSCC, inverted papilloma squamous cell carcinoma; MH, Mantel–Haenszel

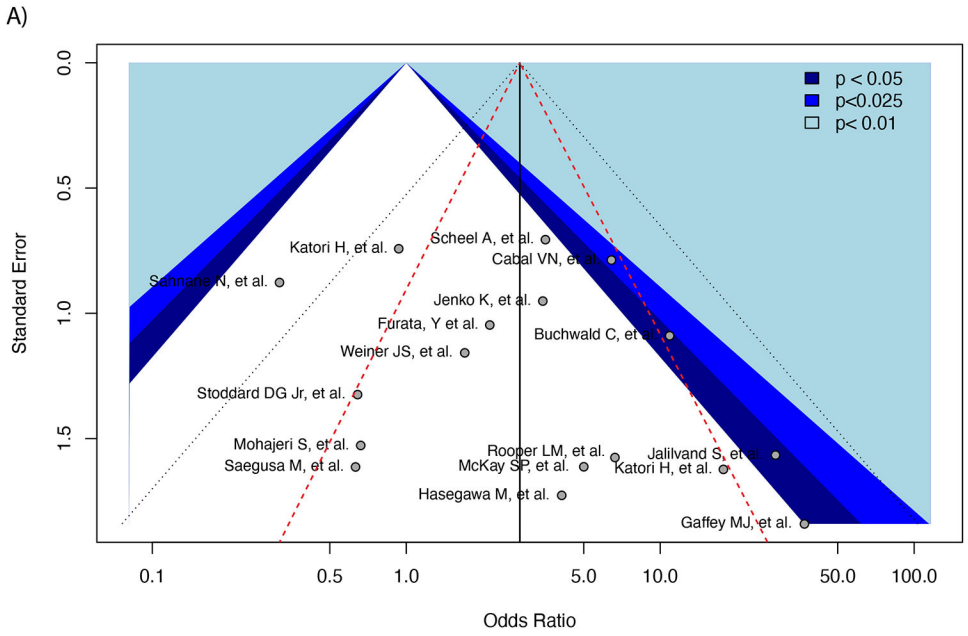

FIGURE 3.

Publication bias analysis. Funnel plot depicting studies which analyzed the association between malignant transformation of inverted papillomas and the presence of human papilloma virus (HPV) infection. Each symbol represents one study. Solid vertical blackline represents the weighted, pooled odds ratio. Dashed diagonal lines represent the pseudo-95% confidence limits. X intercept of the red diagonal lines represents the lower and upper 95% confidence interval for the prediction interval. Significance of the effect size for each study is identified by its background location (cyan, $p < 0.01$; light blue, $p < 0.025$; dark blue, $p < 0.05$)

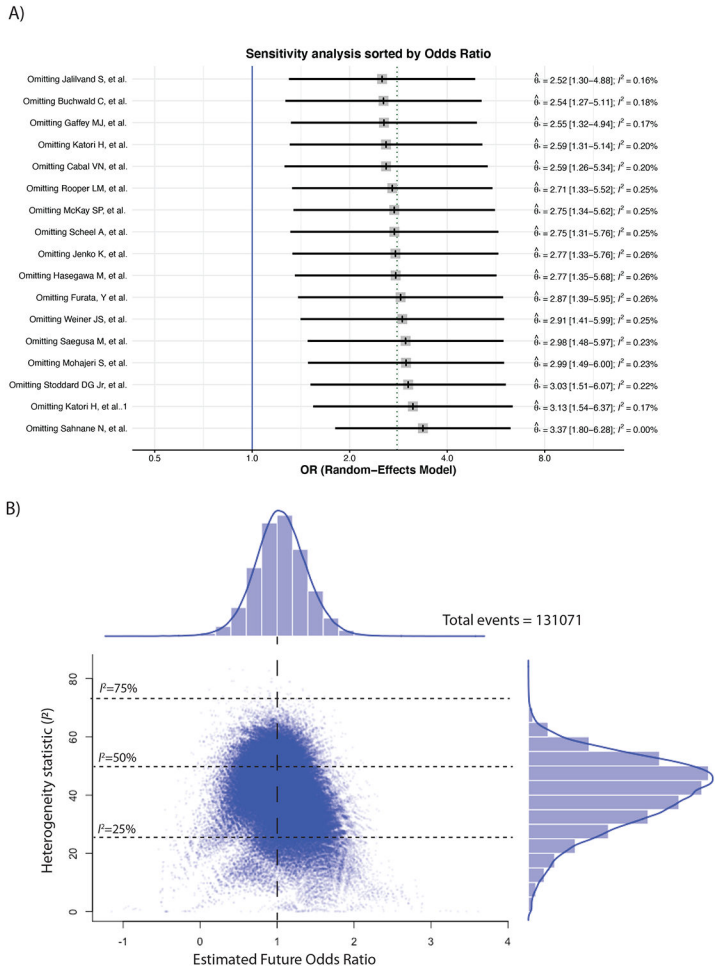

FIGURE 4.

Influence and sensitivity analysis. (A) The study listed on the y-axis was left out of the weighted odds ratio (OR), and the new resultant odds ratio (ô*) is shown in forest plot format. The dashed line represents the weighted OR for all included studies. Each symbol represents the mean OR for all studies minus the excluded study as listed on the left-hand side of the plot. Error bars represent the lower and upper 95% confidence intervals. (B) Graphic display of heterogeneity (GOSH) plot analysis demonstrating all possible included study combinations (2^{k-1}) and their proposed OR (x-axis) versus the aggregate study heterogeneity, I2 (y-axis). Dashed lines along the y-axis represent increasing ranges of study heterogeneity

TABLE 1

Studies reporting on HPV detection in sinonasal IPs

Study	Year	Nucleic acid	Region	Method	Sample size	HPV+ IPSCC	HPV− IPSCC	HPV− IP	HPV− IP
Furata, Y et al.	1991	DNA	Asia	PCR	26	2	5	3	16
Buchwald C, et al.	1995	DNA	Europe	ISH	57	2	3	3	49
Gaffey MJ, et al.	1996	RNA	N America	ISH	20	1	0	1	18
Saegusa M, et al.	1999	DNA	Asia	PCR	28	0	2	6	20
Weiner JS, et al.	1999	DNA	N America	PCR	82	1	8	5	68
Katori H, et al.[a]	2005	DNA	Asia	ISH	26	2	5	0	19
McKay SP, et al.	2005	DNA	N America	PCR	14	1	2	1	10
Katori H, et al.	2006	DNA	Asia	ISH	32	7	5	12	8
Kirdar S, et al.	2009	DNA	Asia	PCR	6	0	0	2	4
Jenko K, et al.	2011	DNA	Europe	PCR	71	3	2	20	46
Hasegawa M, et al.	2012	DNA	Asia	PCR	13	1	0	5	7
Justice JM, et al.	2014	DNA	N America	ISH	36	0	0	1	35
Scheel A, et al. [b]	2015	DNA	N America	PCR	90	4	11	7	68
Stoddard DG Jr, et al.	2015	RNA	N America	ISH	19	1	2	7	9
Jalilvand S, et al.	2016	DNA	Asia	PCR	40	3	0	7	30
Rooper LM, et al.	2017	RNA	N America	ISH	51	2	21	0	28
Mohajeri S, et al.	2018	DNA	N America	PCR	76	0	4	10	62
Sahnane N, et al.[c]	2019	DNA	Europe	PCR	47	2	20	6	19
Cabal VN, et al.	2020	DNA	Europe	PCR	52	5	7	4	36
N = 19 studies					N = 786	37	97	100	552

Abbreviations: HPV, human papillomavirus; IP, inverted papilloma; IPSCC, inverted papilloma squamous cell carcinoma; ISH, in situ hybridization; PCR, polymerase chain reaction.

[a]Odds ratio (OR) is reported for HPV 16/18 samples

[b]A total of 162 paraffin-embedded specimens from 147 patients.

[c]N of patients = 37, N of samples = 48.

TABLE 2

Assessment of bias among included studies using the Newcastle–Ottawa Scale

Study	Year	Country	Selection (max 4*)	Comparability (max 2*)	Exposure (max 2*)
Cabal VN, et al.[32]	2020	Orviedo, Spain	****	**	**
Sahnane N, et al.[33]	2019	Varese, Italy	****	**	**
Mohajeri S, et al.[34]	2018	Ottawa, Canada	****	*	**
Rooper LM, et al.[35]	2017	Baltimore, USA	****	**	**
Jalilvand S, et al.[36]	2016	Tehran, Iran	***	**	**
Scheel A, et al.[37]	2015	Ann Arbor, MI, USA	****	*	**
Stoddard DG Jr, et al.[38]	2015	Rochester, MN, USA	***	**	**
Justice JM, et al.[39]	2014	St. Petersburg, FL, USA	****	**	**
Hasegawa M, et al.[13]	2012	Okinawa, Japan	****	**	**
Jenko K, et al.[40]	2011	Ljubljana, Slovenia	***	*	**
Kirdar S, et al.[41]	2009	Aydin, Turkey	***	**	**
Katori H, et al.[42]	2006	Yokohama, Japan	****	*	**
Katori H, et al.[43]	2005	Yokohama, Japan	****	**	**
McKay SP, et al.[44]	2005	Detroit, MI, USA	****	*	**
Saegusa M, et al.[45]	1999	Sagamihara, Japan	****	*	**
Weiner JS, et al.[46]	1999	Rochester, MN, USA	****	*	**
Gaffey MJ, et al.[47]	1996	Charlottesville, VA, USA	****	*	**
Buchwald C, et al.[48]	1995	Copenhagen, Denmark	****	*	**
Furata, Y et al.[49]	1991	Sapporo, Japan	****	*	**
Average subsection score	3.8/4.0	1.5/2.0	2.0/2.0		