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REVIEW

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Etiology of sinonasal inverted papilloma: An update

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Abstract

Objective: Sinonasal inverted papilloma (IP) and its clinical features have been widely studied, but there are few studies delving into its etiology and risk factors. A narrative review was conducted to summarize a contemporary understanding of the potential etiologies of IP, including immunologic/inflammatory, viral, genetic, and environmental causes.

Study Design: Review.

Methods: A MEDLINE search was conducted through August 11, 2021, focusing on studies investigating the etiology and risk factors for sinonasal IP and its malignant transformation.

Results: High- and low-risk human papillomavirus have been connected with the formation of IP, but conflicting evidence exists regarding their role. Occupational and industrial exposures may also contribute to IP formation, while smoking may increase the odds of malignant progression. Exon 20 mutations in EGFR are an active area of research in IP with mixed evidence. Finally, several cell cycle and angiogenic factors such as Ki67, VEGF, and Akt/mTOR have been implicated in the development and progression of IP.

Conclusion: There continues to be conflicting evidence around the development of IP, but significant progress has been made in recent years. Further study is needed for all these potential etiologies to elucidate risk factors and therapeutic strategies.

KEYWORDS
etiology, inverted papilloma, rhinology, surgery

1 | INTRODUCTION

Sinonasal inverted papilloma (IP) is a type of benign tumor arising from the nasal epithelial mucosa or within the paranasal sinuses.[1] These tumors can be locally destructive with frequent recurrence. IPs are fairly rare, accounting for only 0.4%–4.7%[2] of all sinonasal neoplasms, but can malignantly transform to squamous cell carcinoma (SCC) with a lifetime risk of 5%–15%.[3] While the features of IP have been widely studied, there are few recent peer-reviewed articles comprehensively reviewing its etiology and risk factors, with the most recent published over 5 years ago.[4–6] With an informationist, a MEDLINE search was conducted through August 11, 2021 on studies investigating etiologies and risk factors of IP and its malignant transformation. The following MeSH headings were used: papilloma, inverted; nose, nasal

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cavity, paranasal sinuses, etiology, and causality. This initial search was supplemented with an additional search on the association of EGFR exon 20 mutations and IP. In this review, we summarize the contemporary understanding of potential etiologies of IP, including immunologic/inflammatory, viral, genetic, and environmental causes.

2 | VIRAL ETIOLOGY AND CELL CYCLE REGULATION

2.1 | Human papillomavirus

Viruses have long been suspected to be involved in the etiology of sinonasal IP, and human papillomavirus (HPV) has been the most studied. While HPV is often sub-categorized from an oncologic perspective into "low-risk" HPV (LR-HPV, HPV-6, and -11) and "high-risk" HPV (HR-HPV, HPV-16, and -18), this is a complex issue, and several other clinically relevant strains exist. One of the earliest studies on this relationship[7] used immunohistochemistry (IHC) and in situ hybridization (ISH) of 11 IP and 3 SCC cases, finding all SCC patients to be positive for HPV-16 DNA, but not all with HPV antigen positivity. However, a 1990 Southern blot study of IP samples found only HPV-6 in one of 7 cases, and no HPV-11, 16, or 18.[8] In 1992, using polymerase chain reaction (PCR), Kashima et al. found HPV-6 and HPV-11 in 7/26 IP (2 with HPV-6, 5 with HPV-11) and HPV-18 in 1/24 de novo sinonasal SCCs.[9] The latter group concluded that HPV may cause sinonasal IP and conjectured that benign and malignant IPs may be differentiable by HPV status.

Most recently, three new studies were published with regard to HPV and IP. First, Liu et al.[10] used PCR for HPV DNA to show that 47/80 cases of IP were HPV-positive, most commonly HPV-11. Fulla et al.,[11] using PCR and p16 IHC, detected HPV-11 DNA in only 4/77 patients. The authors reported a low prevalence of HPV DNA in IP and discounted HPV as an etiologic factor. On the other hand, Frasson et al.,[12] found 34/55 patients to be HPV-positive using PCR (19 HR-HPV, 15 LR-HPV), with HPV-16 most prevalent. This is a marked difference from prior studies, adding to the confusion in the HPV literature.

In 2006, Hoffman et al.[13] introduced the idea that HR-HPV subtypes may alter cell proliferation. They studied 26 IPs and 20 *de novo* sinonasal SCCs, finding that 3/26 IPs were positive for HPV-6 and -11 while 4/20 SCCs were HPV-16-positive. They believed that infection with HR-HPV may induce malignant transformation. Soon after, Lawson et al.[14] conducted a SR of HPV types between benign IPs, IPs with dysplasia, and malignant IPs (SCC *ex*-IP), finding a 2.8:1 ratio of LR to HR cases. Benign IPs were 4.8 times more likely to have LR- than HR-HPV, and malignant IPs, were 2.4 times more likely to have HR-HPV. They also found that HPV was more often detected in SCC *ex*-IP and in high-grade compared to mild dysplasia. They suggested that LR-HPV may induce IP formation and then is lost to detection as infected cells are shed. This hit-and-run theory stipulates that HPV and other viruses can induce mutations and damage genetic structure, enabling the formation of tumor cells.[15] IP epithelium is usually non-keratinizing, occasionally making it difficult to detect HPV as it is shed.[14] This theory may explain why HPV detection rates were lower in the benign group.

In 2011, Jenko et al.[16] retrospectively analyzed HPV DNA with PCR in 68 IP samples, 5 SCC *ex*-IP samples, and 47 controls. There were significantly higher HPV detection rates in the study group than the control, but HPV DNA was a significant predictor of neither recurrence nor associated carcinoma, leading the authors to conclude that HPV may not be an important etiological factor of IP. Similar results were found in a study[17] using p16 IHC as a proxy for HPV status, finding that of 76 IPs, only 10 were p16-positive, with only 4 showing greater than 75% p16 staining. In addition, there were no p16-positive specimens in the SCC group. This group concluded that HPV is not associated with the development of IP or its progression to SCC.

There has also been speculation as to whether HPV can lead to higher recurrence rates. The 2008 Lawson[14] reported an odds ratio (OR) of 10.2 when estimating the risk of HPV-positivity in recurrence. More recently, Der Holte et al.[18] used PCR and DNA microarrays to detect HPV in 80 IP patients. First and second recurrent IPs were more HPV-positive than non-recurrent IP (60% and 65%, respectively, vs. 38.8%). Younger age and incomplete resection were other risk factors for recurrence. Lastly, HPV may be associated with higher recurrence rates.

2.2 | HPV and cell cycle regulation

HPV affects the cell cycle and the regulation of cell growth. Its E6 and E7 proteins target tumor suppressors p53 and Rb, respectively. This disruption of the cell cycle regulation induces oncogenesis,[19] a relationship well-explored in the IP literature.

Caruana et al.[20] studied p53 alterations in benign and dysplastic IP, SCC *ex*-IP, and *de novo* SCC, finding p53 alterations in no benign IPs but in over half of dysplastic IPs and 75% of SCCs *ex*-IP. In addition, they found more HPV infections in dysplastic or malignant IPs. None of the p53-altered tumors contained oncogenic HPV-16, leading them to suggest that there may be an inverse relationship between HPV-16 and p53 alterations. In 1998, Mirza et al.[21] found that in sinonasal papillomas (not only IP), p53-altered cases had a 19% higher odds of malignancy. HPV-positive IP samples were more likely to be strongly p53-positive (OR 2.2) and associated with a carcinoma (OR 11.5). In contrast, in 30 cases of SCC *ex*-IP, Buchwald et al.[22] found only 4 to be HPV-positive and 0 with p53 overexpression. Twenty-one of 24 HPV-negative cases showed p53 overexpression.

HPV host integration has also been investigated. McKay et al.[23] analyzed 14 IP samples, 3 of which were SCC *ex*-IP. Three samples showed HPV positivity and the 2 SCC cases demonstrated integration. This issue of viral integration has been discussed by Lawson et al.[14] as a potential reason why HPV detection has been widely found to be higher in dysplastic and malignant IP.

2.3 | Epstein–Barr virus

The Epstein–Barr virus (EBV) has also had conflicting data published with relation to IP. Macdonald et al. used PCR to assess for EBV DNA in 20 IP specimens and 10 controls. Thirteen of 20 IP specimens but no controls showed EBV positivity. The investigators suggested EBV as a potential etiological factor in the pathogenesis of IP.[24]

However, other studies do not show this link. Gaffey et al.[25] performed a very small study looking for EBV DNA in one benign IP and one SCC ex IP, finding EBV in rare stromal lymphocytes in the SCC *ex*-IP sample, but not the epithelium. The benign specimen was EBV-negative. Dunn et al.[26] evaluated 25 resected IPs, of which none were EBV-positive by ISH and only one was EBV-positive by PCR. Most recently, Nukpook et al.[27] reviewed 64 sinonasal IPs, 80 controls, and 82 SCC, finding higher EBV infection rates by PCR in sinonasal IP (64%) than nasal polyps (34%) and SCC (38%) and an association between EBV and IP (OR 3.52). On ISH, however, like prior studies, EBV was mostly detected in stromal lymphocytes and not in the epithelium. The authors suggested that EBV-positive lymphocytes could enhance tumorigenesis, but perhaps were not causative. Notably, EBV is endemic in Thailand, where this study was conducted, with >96% population seropositivity.[28]

2.4 | Summary

The latest evidence surrounding the association of HPV, p53, and EBV with IP is mixed (Tables 1 and 2). Studies on P53 overexpression as an etiologic factor revealed conflicting data, with one study[20] finding 75% overexpression in SCC *ex*-IP and another concluding 0% overexpression.[22] Lastly, while previous studies have not revealed a role for EBV in IP, it was recently shown in 64% of a Thai IP cohort[27] (Table 2). The evidence for viral integration is slightly clearer and it may play an important role in HPV's association with malignant transformation in IP. In clinical practice, otolaryngologists should keep in mind that exposure to HPV and EBV may result in IP formation and p53 overexpression and viral integration may be markers of malignant transformation, but these observations are not yet ready for clinical workflows.

3 | CHRONIC SINONASAL INFLAMMATION: ENVIRONMENTAL AND OCCUPATIONAL ETIOLOGIES

Chronic inflammation has been another important etiologic factor investigated in the development of IP. In 2002, Orlandi et al.[29] compared CT scans of 16 patients with unilateral IP with 9 with other sinonasal tumors and 12 controls with nontraumatic orbital conditions. Contralateral Lund-McKay scores in IP tended to be higher than other tumors and controls. In 2004, Roh et al.[30] described a theory of IP formation from chronic inflammation, suggesting that IP tumorigenesis first arises from early inflammation and progresses to secondary

TABLE 1 Latest literature regarding HPV association with IP.

Study	Oxford level of evidence	Study design	Study groups	Endpoints	Conclusion
Liu et al.[10]	IV	Case–control	40 control tissue samples, 80 IP tissue samples	HPV-positivity/sub-types. Akt/mTOR/s6 expression.	Using PCR of HPV DNA, showed that 47/80 cases of IP were HPV-positive. HPV-11 was the most common subtype.
Fulla et al.[11]	IV	Case–series	Group of 46 IPs from Spain and a group of 33 IPs from Poland	HPV DNA detection and genotyping, recurrence, time to recurrence, smoking and alcohol history, malignant transformation	The authors concluded that there is a low prevalence of HPV DNA in patients with sinonasal IP and discounted HPV as an etiologic factor.
Frasson et al.[12]	IV	Case Series	55 IP patients	HPV detection and genotyping	34/55 patients were HPV-positive using PCR and HPV-16 was the most prevalent subtype.
der Holte et al.[18]	IV	Case–control	Compared 91 IP patients, 7 fungiform papilloma, 2 oncocytic papilloma, 6 patients with malignant CIS/SCC *ex* IP	Age, gender, tumor size and localization, tobacco smoking, regular alcohol consumption, essential hypertension, anticoagulant medication, allergies, surgical approach, and HPV infection.	Young age at initial diagnosis and incomplete tumor resection were risk factors for recurrence of sinonasal IPs.

Abbreviation: CIS, carcinoma in situ; HPV, human papillomavirus; IP, inverted papilloma; PCR, polymerase chain reaction; SCC, squamous cell carcinoma.

TABLE 2 Latest literature regarding EBV and IP.

Study	Oxford level of evidence	Study design	Study groups	Endpoints	Conclusion
Nukpook et al.[27]	IV	Case–control	80 nasal polyp samples as the control group. 64 IP and 82 SCC ex IP samples as 2 different study groups	EBV presence using PCR and ISH.	Lymphocytes containing EBV may enhance tumorigenesis of sinonasal IP/SCC.

Abbreviation: EBV, Epstein–Barr virus; IP, inverted papilloma; ISH, in situ hybridization; PCR, polymerase chain reaction; SCC, squamous cell carcinoma.

metaplasia after continued inflammation. They cited the Orlandi study as a possible role of inflammation in the development of IP, but also emphasized there was limited evidence to support the theory. An updated, 2020 retrospective cohort study by Papagiannopoulous et al.[31] replicated these results, comparing CT scans to determine contralateral sinus inflammation in patient with unilateral IP. They found that IP patients had a higher prevalence of contralateral sinusitis than the control group (58.9% vs. 26.7%) with higher Lund-McKay scores in IP patients than controls (1.9 vs. 0.26).

Occupational exposures have also been implicated as a risk factor in IP formation. D'errico et al.[32] explored the association of industrial exposures to IP, demonstrating that the risk of IP was increased for ever-exposure to welding fumes (OR 2.14) and organic solvents (OR 2.11). The formation of IP was associated with increased cumulative exposure to organic solvents. Barbieri et al.[33] administered a questionnaire to 70 IP patients, finding that only 5% of the patients had risk factors (e.g., wood, leather dusts). They did not feel that a causative link was likely between occupation and IP. A few years later, however, Sham et al.[34] used a questionnaire to assess risk factors of 50 patients with IP and 150 matched controls, finding that outdoor and industrial occupations were associated with IP. Tobacco, alcohol, history of allergic rhinitis/sinusitis, and nasal polyps were not significant factors, however.

Finally, smoking is another suspected risk factor for the formation of IP. In 1996, Deitmer et al.[35] showed no significant difference between smokers and nonsmokers in the IP incidence, supported later by the Sham et al. More recently, however, smoking has been thought to be more related to recurrence and dysplasia rather than initial IP development, as Dictor et al. revealed a disparity in recurrence rates between smokers (28.2%) and non-smokers (10.7%).[36] Further, Hong et al.[37] reported that 26.4% of smokers developed malignancy from IP versus 2.8% of nonsmokers.

3.1 | Summary

The data show an association between IPs and contralateral sinusitis (58.9% vs. 26.7%),[31] while case–control studies reveal that organic solvents may be risk factors in IP development (OR 2.11).[32] The evidence around industrial exposures is contradictory.[33,34] Finally, while previous studies stated no significant association between smoking and IP, recent studies (Table 3) show increased in smokers. For clinical practice, while the work on exposures is still ongoing, otolaryngologists should bear in mind higher rates of IP malignant transformation and recurrence in smokers.

4 | PROLIFERATIVE AND ANGIOGENIC FACTORS

4.1 | Proliferative factors

At a molecular level, angiogenic and proliferative factors have long been suspected of being involved in the formation of IP. In 1998, Guichard[38] analyzed 13 IP samples and 10 nasal polyp samples, evaluating cell proliferative factors PCNA and BCL-2 by IHC analysis and apoptosis. A more recent study on proliferative factors and apoptotic markers[39] used IHC and flow cytometry. PCNA and Ki67 markers were increased in IP samples compared to nasal epithelium and apoptosis markers caspase-8 and BAX were less frequently observed in IP. Furthermore, increased Ki67 correlated with IP recurrence. The authors concluded that higher levels of PCNA and Ki67 with lower levels of BAX and caspase-8 suggested that cell proliferation is increased while apoptosis is inhibited in IP.

A relatively new proposal regarding the growth of IP is how HPV promotes proliferation through the Akt/mTOR signaling pathway. The aforementioned 2017 Liu study[10] found that HPV-positive samples (74.5%) showed higher phosphorylated Akt staining compared to HPV-negative (51.6%) or control samples (26.3%). Another very recent proposal by Wang et al.[40] regards the speckled 100 protein (Sp100) protein, which stimulates p53 protein and inhibits the invasion of cancerous cells. Using samples from 40 IP and 10 control patients, they showed Sp100 protein downregulation in IP patients, suggesting a potential role for Sp100 in the development and proliferation of IP.

4.2 | Epidermal growth factor receptor and insertion mutations

The epidermal growth factor receptor (EGFR) is another avenue that has been suspected to be involved in the formation of IPs. A 2018 study by Udager et al.[41] analyzed 58 IPs and 22 SCCs *ex*-IP. Of all 80 samples, only one IP was both HPV- and EGFR-positive. Yet, a more recent study by Wang et al.[42] revealed that 35/44 IP patients had EGFR mutations, and all IP samples had exon 20 insertion mutations. Lastly, a 2021 study by Zonnur et al.[43] support this result, with most of their IP 40 samples having an EGFR exon 20 mutation.

Some studies have sought to investigate the association between HPV and EGFR mutations in IPs. An early study by Scheel et al.[2]

TABLE 3 Latest literature regarding occupational exposures and IP

Study	Oxford level of evidence	Study Design	Study groups	Endpoints	Conclusion
Papagiannopoulous et al.[31]	IV	Case–control study	15 patients with unilateral, sino-nasal, non-IP, non-SCC tumors as controls. 56 patients with unilateral IP as the study group.	Lund–Mackay scores to assess radiologic sinonasal inflammation ipsilateral and contralateral to the unilateral IP.	Unilateral IPs are associated with more severe contralateral sinusitis than controls.

Abbreviation: IP, inverted papilloma; SCC, squamous cell carcinoma.

reviewed 90 patients with IP, 11 of whom were positive for LR-HPV. EGFR staining proportion was higher in HPV-positive IPs (56.2%) versus HPV-negative specimens (23.6%). In three samples analyzed for viral integration, the malignant tumors were positive, but the precursor IP was negative. They concluded that LR-HPV may accentuate EGFR expression and predispose patients to neoplastic progression through viral integration. On further investigation, however, a new 2020 study by Mehrad et al.[44] showed 11/15 LR-HPV-negative IP samples to be positive for EGFR exon 20 insertion mutations, whereas the 5 LR-HPV-positive samples were EGFR-wild type. Contrary to previous thinking, the authors concluded that LR-HPV-positive samples are mutually exclusive with EGFR mutations.

EGFR exon 20 mutations have been heavily investigated in recent years, but conflicting data exist. A 2019 study by Sahnane et al.[45] showed that EGFR mutations occurred in 72% of IPs, 30% of SCC *ex*-IP and 17% of *de novo* SCCs. However, SCC arose from only 30% of EGFR-mutated IP, compared to 76% of IPs with wild-type EGFR, and the authors determined that EGFR mutations are associated with IPs that carry a lower risk of malignancy. In support of the Sahnane study, a more recent study by Cabal et al.[46] found EGFR expression in 92% of IP samples. Delving further, they found EGFR exon 20 mutations in 7/18 IP and 6/12 SCC *ex*-IP patients and that IP patients with EGFR activation by phosphorylation or genetic mutation had longer IP-free survival times.

In 2021, Hongo et al.[47] studied SCC *ex*-IP and SCC *de novo* samples, finding an association between SCC *ex*-IP and EGFR mutation. Mutations were present in 13/14 SCC *ex*-IP samples (with the exon 20 mutation present in most of the samples) versus 8/129 *de novo* SCCs. The authors concluded that the EGFR mutation may play a vital part in the development of SCC *ex*-IP, contradicting the previous two studies. In short, EGFR and exon 20 mutations are the most currently active area of research around the etiology of IPs, and perhaps the most controversial. Further research is necessary to clarify some of the conflict findings reported thus far.

4.3 | Angiogenic factors

Other growth factors such as osteopontin and vascular endothelial growth factor (VEGF) have been implicated in the development of IP. Liu et al. found osteopontin and VEGF immunostaining and mRNA levels to be higher in IP tissue versus controls,[48] and in high-stage versus low-stage IP. The authors concluded that osteopontin and VEGF were overexpressed in IP tissues and were associated with neoplastic advancement by promoting vessel formation. Byun et al.[49] found increased expression of angiomotin (a pro-angiogenic factor) in IP ($N = 10$) samples compared to controls, concluding this too may be a factor in IP's angiogenic growth.

4.4 | Summary

There is strong evidence for a role for angiogenic/proliferative factors in the formation of IP (Tables 4 and 5). Cell signals such as PCNA, Ki67, and, most importantly, EGFR (exon 20 mutations) have been implicated in the development of IP within the last 5 years (Table 5). Osteopontin, VEGF, and angiomotin are pro-angiogenic factors that may also promote IP progression. While these observations are not ready for application in clinical practice, they may portend potential future therapeutic options.

5 | MALIGNANT TRANSFORMATION

Malignant transformation from a benign IP is seen in approximately 5%–15% of cases.[3] These can be either synchronous (within 6 months) or metachronous (after 6 months of IP formation), with a ratio of approximately 2:1.[50] A review by Mirza et al., ($N = 3058$) showed a 10.7% overall rate of malignant transformation.[50] The genetic profile of IP and its malignant transformation was recently published by Tong et al.,[51] and an 11-gene panel was assembled in which increased expression was noted in IP samples with carcinoma or carcinoma in situ compared to those without dysplasia. IP with carcinoma *in situ* has been shown to be highly associated with high recurrence rates, but rarely converts to invasive SCC.[52]

From an etiology standpoint, however, HPV is one of the more heavily studied potential causes of malignant transformation in sinonasal IP. A 2016 study by Jalilvand et al.[53] included 40 total IP patients (37 benign and 3 SCC *ex*-IP). HPV was detected in 18.9% of IP specimens and 100% of all SCC *ex*-IP, and the authors concluded that HPV-16 and 18 can play an important role in malignancy formation, and also that HPV-6 and 11 may be a risk factor in IP progression. This conclusion aligns with the aforementioned hit-and-run

TABLE 4 Latest literature on proliferative factors and IP development.

Study	Oxford level of evidence	Study design	Study groups	Endpoints	Conclusion
Liu et al.[10]	IV	Case–control	40 control tissue samples, 80 IP tissue samples	HPV-positivity/sub-types. Akt/mTOR/s6 expression.	Using PCR of HPV DNA, showed that 47/80 cases of IP were HPV-positive. HPV-11 was the most common subtype.
Wang et al.[40]	IV	Case–control	10 inferior turbinate controls, 40 nasal mucosa samples.		There may be a potential role for Sp100 in the development of IP.

Abbreviation: HPV, human papillomavirus; IP, inverted papilloma; PCR, polymerase chain reaction.

TABLE 5 Latest literature on EGFR/insertion mutation and IP.

Study	Oxford Level of Evidence	Study Design	Study groups	Endpoints	Conclusion
Sahnane et al.[45]	IV	Case series	Groups: 5 oncocytic papilloma patients, 18 IP, 19 SCC ex IP, 12 SCC de novo	Smoking and occupational exposures. HPV, Gene mutation and LINE-1 hypomethylation analysis.	EGFR mutations are associated with IPs that carry a lower risk of malignancy.
Wang et al.[42]	IV	Case series	Groups: 44 IP, 33 oncocytic papilloma	EGFR, KRAS mutation expression	35/44 IP patients were found to have EGFR mutations, and all IP samples had exon 20 insertion mutations.
Mehrad et al.[44]	IV	Case–control	15 HPV RNA-negative IPs (control), 44 HPV RNA-positive IPs (study group)	EGFR mutation analysis, high-risk/low-risk mRNA positivity	Low-risk HPV positive samples are mutually exclusive with EGFR mutations.
Cabal et al.[46]	IV	Case–control	Groups: 55 IP, 14 SCC ex IP, 60 de novo SCC	EGFR gene mutation and protein expression, phosphorylated EGFR, HPV infection, KRAS mutations	IP patients with EGFR activation by phosphorylation or mutation had longer IP-free survival times.
Hongo et al.[47]	IV	Case series	Groups: 14 SCC ex IP and 129 SCC de novo	EGFR gene mutations and copy number gain, KRAS mutation, hr-HPV infection	EGFR mutation may play a vital role in the development of SCC ex IP.
Zonnur et al.[43]	IV	Case series	60 IP samples from 40 patients	EGFR exon 19/20 mutations, BRAF exon 15 mutation	A majority of the 40 patients had an EGFR exon 20 mutation present in IP samples.

Abbreviation: EGFR, epidermal growth factor receptor; HPV, human papillomavirus; IP, inverted papilloma; PCR, polymerase chain reaction; SCC, squamous cell carcinoma.

theory. As evidenced by a 2016 meta-analysis (MA),[54] stratification by HPV type can reveal which viral strains have stronger associations in malignant progression. It was found that HR-HPV (specifically HPV-18), is associated with SCC *ex*-IP, supporting conclusions from the 2008 Lawson study.

In 2017, Rooper et al.[55] studied transcriptionally-active HR (TAHR) HPV using RNA ISH, allowing for the direct visualization of active HPV. Fifty-two IPs (30 benign, 7 dysplastic, and 16 SCC *ex*-IP) did not have TAHR HPV. However, 2/7 non-keratinizing, *de novo* SCCs detected TAHR-HPV. The study concluded that TAHR-HPV does not play a role in the development of IP or transformation into carcinoma, but a limitation of this study was that only 4 HPV-positive tumors were included in the study.

Most recently, a 2021 MA by Ding et al.[56] found that patients infected with HPV types 16, 11/16, 18, and 16/18 were associated with an increased risk of SCC *ex*-IP (8.51, 7.59, 23.26, and 24.34-fold increases, respectively). However, patients infected with HPV types 6, 11, and 6/11 did not have a significant risk. This association of HR-HPV subtypes with malignant transformation of IP was supported by two 2021 meta-analyses. McCormick et al.,[57] after stratification by HR-HPV subtype, found HPV-18 patients to be associated with a 2.68-higher-odds of malignancy. Stepp et al. found a similar 2.80 weighted OR of progression to malignancy when there was identified HPV infection in the IP specimen.[58] Another 2017 study by Yan et al.[59] compared *de novo* SCC with SCC *ex*-IP, revealing no differences when comparing age, smoking, tumor origin, or tumor stage between type of SCC.

TABLE 6 Latest literature on IP malignant transformation.

Study	Oxford level of evidence	Study design	Study groups	Endpoints	Conclusion
Zhao et al.[54]	II	Meta-analysis	31 case–control studies investigating association between IP and malignant transformation	HPV DNA detection and genotyping	Stratification by HPV type can reveal which viral strains have stronger associations in malignant progression.
Ding et al.[56]	II	Meta-analysis	26 case–control studies investigating HPV type and malignant transformation	HPV type, risk of malignant IP reported by studies	Patients with HPV- 16, 11/16, 18, and 16/18 have increased risk of SCC ex IP. Patients with HPV - 6, 11, and 6/11 did not have risk.
Stepp et al.[58]	II	Meta-analysis	19 case–control and cohort studies with tissue-diagnosed IP or SCC *ex* IP.	HPV detection and diagnosis	There is a significant association between HPV infection and malignant progression of IP, with weighted OR of 2.80.
McCormick et al.[57]	II	Meta-Analysis	21 case–control studies including 56 malignant IP and 551 benign IP	HPV detection, sub-type analysis,	HPV-18 showed a 2.68-fold increase in risk of malignancy.
Maina et al.[52]	III	Retrospective Cohort	37 IP w/ CIS, 178 IPs.	Primary site, median follow-up, age, gender, recurrence rate, treatment types	IP w/ CIS demonstrates higher recurrence rate and involvement, but lower rate of transformation to invasive carcinoma.
Tong et al.[51]	III	Cohort study	6 IP, 5 IP w/ CIS and 13 SCC *ex* IP	Next-generation sequencing to look for up-regulation of genes.	An 11-gene panel was assembled in which increased expression was noted in IP samples with carcinoma or carcinoma in situ compared to those without dysplasia.
Jalilvand et al.[53]	IV	Case–control	Comparing 37 IP patients, 3 SCC ex IP patients	HPV DNA detection via PCR and genotyping	HPV-16 and 18 can play an important role in malignancy formation, and also that HPV-6 and 11 may be a risk factor in IP progression.
Rooper et al.[55]	IV	Case–control	30 benign IPs, 7 IPs with dysplasia, 16 SCC *ex* IP, 7 non-keratinizing SCC	HPV RNA detection, TAHR HPV	TAHR HPV does not play a role in the development of IP or transformation into carcinoma.
Yan et al.[59]	IV	Case–control	38 SCC ex IP and 28 de novo SCC	Patient age, smoking history, tumor origin, stage	Compared de novo SCC with SCC ex IP: no differences in groups when comparing age, smoking history, tumor origin or stage.

Abbreviation: CIS, carcinoma in situ; HPV, human papillomavirus; IP, inverted papilloma; PCR, polymerase chain reaction; SCC, squamous cell carcinoma.

5.1 | Summary

The latest studies on the malignant transformation of IP have focused on the genetic profile of malignant transformation and HPV-based risk stratification (Table 6). The data show upregulation of specific genes in IP samples with carcinoma or carcinoma-*in-situ* in comparison to IP without dysplasia.[51] In addition, most studies showed HPV-16 and -18 to be associated with malignant transformation of IP. In clinical practice, otolaryngologists should recognize the strong evidence for HPV-16/-18 in IP and consider HPV testing of IP specimens.

6 | CONCLUSION

Sinonasal IP is a benign, hyperplastic tumor with propensity for recurrence and malignant transformation. The rarity and complexity of this

tumor have made for significant challenges in unraveling etiologic factors. Perturbations of cell cycle biology including E6/E7 proteins and p53 expression have long been suspected as a key cause, but evidence continues to be mixed. While chronic sinonasal inflammation and perhaps even industrial exposures do appear to be associated with IP, causative evidence is still missing. Currently, the most highly active and promising areas of research include exon 20 insertion mutations in the *EGFR* gene and viral integration, but further study is needed to elucidate their potential causative role in the development of IP and to help risk stratify for malignant transformation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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