ACTA ONCOLOGICA
2021, VOL. 60, NO. 9, 1175–1191
https://doi.org/10.1080/0284186X.2021.1950922

Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

Impact of human papillomavirus in sinonasal cancer—a systematic review

Sannia Sjöstedt[a], Christian von Buchwald[a], Tina Klitmøller Agander[b] and Kasper Aanaes[a]

[a]Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Copenhagen University Hospital, Copenhagen, Denmark; [b]Department of Pathology, Copenhagen University Hospital, Copenhagen, Denmark

ABSTRACT

Background: Human papillomavirus (HPV) is an established prognostic marker in oropharyngeal squamous cell carcinoma. Currently, the role of HPV in sinonasal carcinoma is being explored.

Objectives: This systematic review addresses the role of HPV in sinonasal cancer, establishing the occurrence of HPV-positive cancers and the influence of HPV-positivity on prognosis in sinonasal cancer as well as the utility of the putative surrogate marker of HPV (p16) in sinonasal cancer.

Material and methods: Studies were identified with searches of Medline *via* PubMed and Embase *via* OVID (4 May 2020). Articles on original research concerning sinonasal cancer and HPV in humans written in English were included. Case reports with less than five cases were excluded.

Results: Initially, 545 articles were identified; 190 duplicate articles were removed leaving 355 articles for title/abstract screening. Title/abstract screening excluded 243 articles, leaving 112 studies assessed for eligibility. After full-text screening, 57 studies were included. All articles investigated the significance of HPV in sinonasal carcinomas. HPV was reported in approximately 30% of sinonasal squamous cell carcinoma (SNSCC), where it was associated with a better prognosis. In sinonasal cancer, p16 is associated with diagnostic pitfalls and a putative utility of p16 in SNSCC has yet to be established. HPV was not frequently reported in other types of sinonasal carcinomas, besides the recently described subtype, HPV-dependent Multiphenotypic Sinonasal Carcinoma. In other types of sinonasal carcinoma, HPV is not frequently found.

Conclusion: Approximately 30% of SNSCC are HPV-positive. HPV-positivity in SNSCC is associated with improved survival. HPV occurs only rarely in other sinonasal cancers. There is currently not sufficient evidence for p16 as a surrogate marker of HPV in SNSCC.

ARTICLE HISTORY
Received 23 February 2021
Accepted 28 June 2021

KEYWORDS
Sinonasal; cancer; HPV; carcinoma

Background

With recent studies suggesting that Human Papillomavirus (HPV) can play a significant role in the development and prognosis of certain types of sinonasal carcinoma, we systematically reviewed current evidence of the presence of HPV in sinonasal cancers and the prognostic significance of HPV-positivity [1–3].

General background

The majority of sinonasal cancers are carcinomas, of which the most frequent, sinonasal squamous cell carcinoma (SNSCC), may be associated with HPV [1–4]. HPV-positive SNSCCs may have a better prognosis than HPV-negative SNSCCs drawing parallels to oropharyngeal squamous cell carcinomas (OPSCC) [5–8]. The occurrence and prognostic significance of HPV in sinonasal cancer are however still uncertain. Several different methods have been used to determine the HPV status of tumor samples in the studies included in this review: detection of indirect markers such as p16 protein with immunohistochemistry (IHC); *in situ* hybridization (ISH); or detection of viral mRNA or viral DNA (with or without polymerase chain reaction (PCR)) [9]. These different detection methods constitute a challenge in assessing the true occurrence of active HPV infection. Currently, the gold standard for assessing HPV status in head and neck squamous cell carcinomas is the detection of active HPV infection with the use of HPV mRNA ISH and a possible utility of p16 has yet to be established [10].

Human papillomavirus (HPV) and p16

More than 200 HPV genotypes have been identified, including the so-called high-risk HPV types with oncogenic potential, e.g., HPV16 and HPV18 [11–13]. In persistent high-risk HPV infection, HPV DNA is incorporated into the host genome, eventually leading to the genome destabilization seen in cancer [13].

Sinonasal squamous cell carcinomas (SNSCC)

SNSCCs are subdivided into keratinizing (KSCC), non-keratinizing (NKSCC), and other less frequent subtypes (Figure 1). SNSCC can arise *de novo* or originate from a group of benign

CONTACT Sannia Sjöstedt Sannia.mia.svenningsen.sjoestedt@regionh.dk Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Copenhagen University Hospital, Copenhagen, Denmark

© 2021 Acta Oncologica Foundation

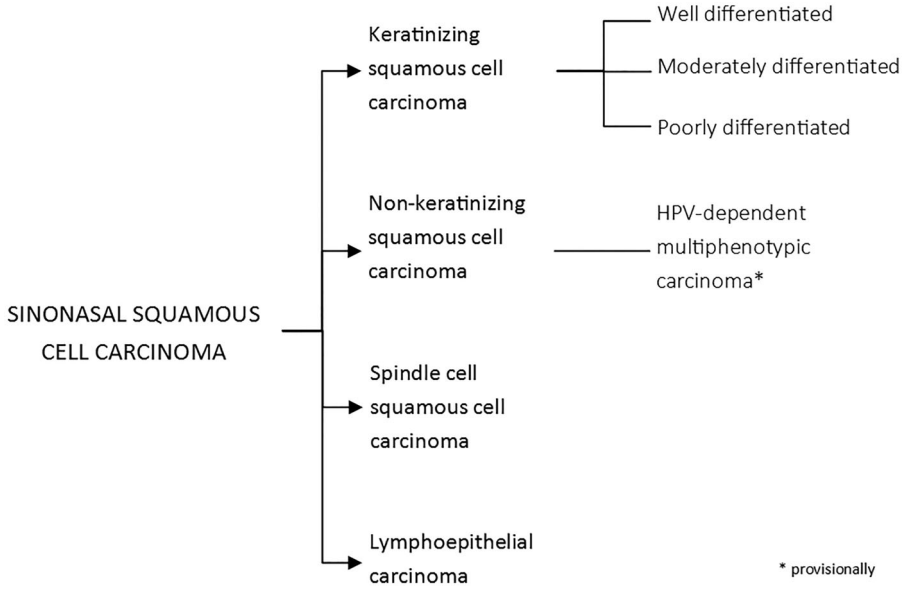

Figure 1. Sinonasal squamous cell carcinoma and subtypes according to WHO Classification of Head and Neck Tumors, 4th edition, International Agency for Research of Cancer, Lyon 2017.

sinonasal tumors; the sinonasal papillomas [14–16]. SNSCC arising in a sinonasal papilloma can occur within the papilloma (synchronous) or develop at the site of a previously resected papilloma (metachronous) [17]—the incidence rate of carcinoma associated with sinonasal papillomas is approximately 0.38 cases per million per year [18].

Since the 1980s, HPV has been considered a potential culprit in both the initiation as well as the malignant transformation of sinonasal papillomas to SNSCC. Of the three types of sinonasal papillomas, inverting papilloma (IP) is the most common, exophytic papilloma (EP) second most common and oncocytic papilloma (OP) the rarest. HPV seems to play a role in both IP and EP whereas OP has no apparent HPV association [17,19]. IP is associated with malignancy in 5–15% of cases (syn- and metachronous), whereas malignant transformation in EP and OP is a very rare event [17]. Several studies have investigated the occurrence of HPV in sinonasal papillomas, but due to an immense discrepancy in HPV-detection rate, the true significance of HPV in these remains unknown [16,20–23].

HPV-related multiphenotypic sinonasal carcinoma (HMSC)

In recent years, a new type of sinonasal carcinoma, HPV-related multiphenotypic sinonasal carcinoma (HMSC), provisionally classified as a subtype of SNSCC by WHO, has been identified [24–26]. Previously, some of these carcinomas have been misdiagnosed as adenoid cystic carcinomas (ACC), which the first described cases bore resemblance to [27]. HMSC usually contains HPV33 or HPV35 and is associated with a better prognosis than the advanced stage often seen at presentation would suggest. HMSC tends to show strong nuclear and cytoplasmic p16 staining and does not harbor the gene fusions often found in ACC [27].

Other sinonasal carcinomas with uncertain relation to HPV

The following carcinomas can pose a diagnostic challenge due to histomorphological similarities with HPV-positive carcinomas: adenoid cystic carcinoma (ACC) is the second most common sinonasal tract cancer (following SNSCC), accounting for 10–18% of all sinonasal malignant neoplasms [28]. ACC shares some morphological traits with HMSC, previously known as HPV-related carcinoma with Adenoid Cystic-Like features. In ACC, the role of HPV has yet to be clarified, but the occurrence of HPV in ACC appears to be low [29].

Sinonasal undifferentiated carcinoma (SNUC) is a rare and aggressive neoplasm, with a poor prognosis [30]. Several histological features are shared with other neoplasms of the sinonasal tract (esthesioneuroblastoma, small-cell undifferentiated neuroendocrine carcinoma, NUT midline carcinoma, malignant mucosal melanoma among others) [8].

NUT midline carcinomas are rare epithelial malignancies of the midline (head and neck region and mediastinum) with no association to HPV demonstrated. They are characterized by chromosomal rearrangement involving the gene encoding a nuclear protein of the testis (NUT). The carcinomas range from undifferentiated carcinomas to carcinomas with squamous differentiation [31,32].

SMARCB1-deficient carcinomas are a recently described entity of sinonasal carcinoma characterized by the loss of nuclear expression of the *SMARCB1* gene. Loss of SMARCB1 expression has also been described in other tumors, such as epithelioid sarcomas. SMARCB1-deficient carcinomas do not appear to be associated with HPV [33,34].

Material and methods

Adhering to the PRISMA guidelines [35], studies were identified with searches of Medline *via* PubMed and Embase *via* OVID (4 May 2020).

The following terms (including MeSH terms) were used:
Sinonasal/ethmoid/maxillary/frontal/sphenoid
Malignan*/cancer/carcinoma
HPV/human papillomavirus/human papilloma virus

Articles containing original research results concerning sinonasal cancer and HPV in humans written in English were included. Nonsystematic reviews and reviews not reporting search strategies were excluded. Other articles not containing original data were also excluded. Case reports containing less than five cases were not included. Conference abstracts were not included.

Information on study population, occurrence of HPV

Literature was managed using Covidence (covidence.org). SS and KA performed Title/abstract screening independently. SS performed full-text screening and data extraction.

This study was registered in Prospero before data extraction: id CRD42020173508.

Results

Initially, 545 articles were identified; 190 duplicate articles were removed leaving 355 articles for title/abstract screening. This excluded 243 articles including 23 articles in the non-English language, leaving 111 studies to be assessed for eligibility. After full-text screening, 57 studies were included (Figure 2).

Selection of articles

Articles containing original research on HPV and sinonasal cancer in more than five patients were included, regardless of detection method—studies using p16 as a single marker for HPV identification were not included. Due to the scarcity of studies, we included studies on selected cohorts as well as register-based studies.

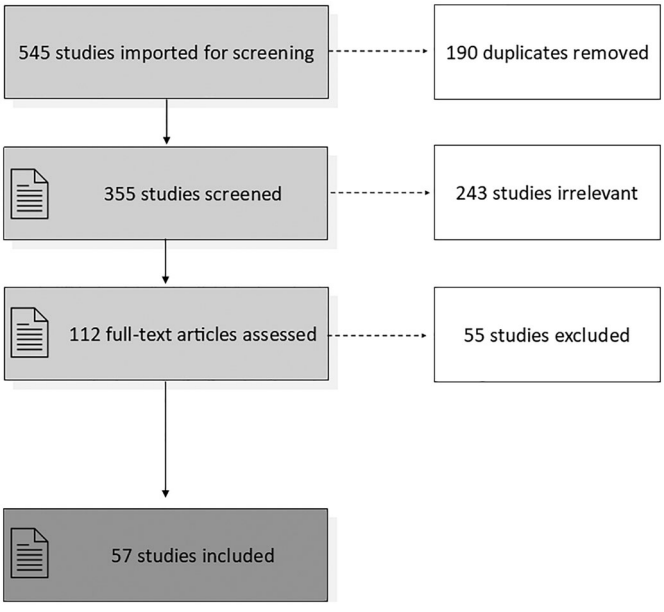

Figure 2. Of 545 studies imported, 57 studies contained data on sinonasal cancer and the occurrence of HPV. Studies containing less than five cancers were excluded, as studied in other languages than English, conference abstracts, studies reporting on the same population as other included studies.

Several articles examined more than one histological type; results for these are reported separately for each histology. SNSCC was investigated in 34 studies (Table 1); SNSCC associated with sinonasal inverted papilloma (SNSCC/IP) in 22 studies (Table 2); ACC in six studies (Table 3); HMSC in seven; and SNUC in six studies (Table 4) (Figure 3).

Sinonasal squamous cell carcinoma (SNSCC)

Several studies examined the occurrence of HPV in SNSCC and whether HPV status was associated with a better prognosis: *Alos et al. (2009)* reported a median disease-free survival of 36 months in the HPV-positive group ($n = 12$) and 14 months in the HPV-negative group ($n = 48$); HPV-status was associated with progression-free survival in a multivariate analysis. Using immunohistochemistry for p16, they reported 100% sensitivity and specificity for the detection of HPV-positive tumors [59]. *Larque et al. (2014).* also reported that a statistically significant difference in mean overall survival was seen with the best prognosis in the HPV-positive group ($n = 14$), all of which showed a strong and diffuse p16 staining (no HPV-negative tumor was p16+) [52]. *Chowdhury et al. (2017)* examined 26 cases of SNSCC using HPV DNA PCR, 16 of these were HPV-positive; an improved median survival was reported for the HPV-positive patients (54 months vs. 12 months median survival in HPV-negative patients, $p < 0.005$). In a large register-based study using data from the National Cancer Database (the USA, 2010–2014), *Kiliç et al. (2017)* compared the survival of 770 cases with known HPV status (31.7% HPV-positive) reporting a better five-year survival in HPV-positive patients. Nasal cavity tumors were more likely to be HPV-positive than sinus tumors, as were NKSCC, papillary, and basaloid tumors compared with KSCC [8]. *Oliver et al. (2019)* also used data from the National Cancer Database (the USA, 2010–2016); of 6458 patients, HPV status was known in 1442 patients. They compared survival in 128 cases of HPV-positive SNSCC matched with the 128 most similar HPV-negative SNSCC cases and found a higher three-year overall survival rate in patients with HPV-positive SNSCC [54]. *Cohen et al. (2020)* reported improved overall survival and progression-free survival in the HPV-positive group of their study ($n = 10$), with one mortality in the HPV-positive group and three in the HPV-negative group [42], as did *Jiromaru et al. (2020)* with none of the patients with HPV-positive SNSCC reported dead. They also reported a better prognosis in patients with p16+ SNSCC [38].

Of the studies investigating the prognostic significance of HPV in SNSCC, only *Doescher et al. (2015)* found no correlation between HPV status and metastasis status or survival in a group of 42 patients with SNSCC, three of which were HPV-positive [37].

In summary, SNSCC and HPV was the subject of 34 studies published from 1989 to 2020 (Table 1, Figure 4). The occurrence of HPV in SNSCC ranged from 0–62%. HPV detection was based on one method in 21 studies (13 studies

Table 1. Sinonasal squamous cell carcinoma (SNSCC).

Article	Study population	Number of cases	Study timespan Country	% HPV	HPV detection method	Significance of HPV
Detection of transcriptionally active high-risk HPV in patients with head and neck squamous cell carcinoma as visualized by a novel E6/E7 mRNA *in situ* hybridization method. Bishop *et al.* [36] (2012)	282 cases of HNSCC	7	1996–2005 USA	29 %	DNA ISH RNA ISH (RNAscope)	-
Epstein–Barr virus infection is strictly associated with the metastatic spread of sinonasal squamous cell carcinomas. *Doescher et al.* [37] (2015)	SNSCC and HNSCC Median age 61 (37–84) 75% males	44	1994–2013 Germany	7%	HPV DNA ISH	No correlation between HPV status and survival or metastasis
HPV-related sinonasal carcinoma: clinicopathologic features, the diagnostic utility of p16 and Rb immunohistochemistry, and EGFR copy number alteration *Jiromaru et al.* [38] (2020)	101 SNSCC Mean age 64.2 (34–103) 70% males	94	2003–2016 Japan	10 %	HPV mRNA ISH RNAscope	HPV associated with nasal location, low clinical-stage, NKSCC, improved prognosis
Human papillomavirus load and physical status in sinonasal inverted papilloma and squamous cell carcinoma. *Hasegawa et al.* [39] (2012)	SNSCC ($n = 11$), IP ($n = 13$), and inflammatory sinonasal disease ($n = 39$)	11	Japan	27 %	HPV DNA PCR and HPV16 viral load by qPCR	Higher viral load in SNSCC (and IP) than inflammatory disease
Importance of tumor suppressor gene methylation in sinonasal carcinomas: (MS-MLPA/DNA methylation/sinonasal carcinoma/epigenetics/ HPV) *Chmelarova et al.* [40] (2016)	Sinonasal carcinoma ($n = 64$) Median age 62.5 years (23–83 years) 67% males	44	1995–2014 Czech Republic	32%	DNA ISH mRNA ISH HPV DNA PCR RT-PCR E6/E7 mRNA	No correlation between DNA methylation and tumor type, stage, histological grade, smoking history or HPV status.
Markers of malignant transformation of sinonasal inverted papilloma *Katori et al.* [41] (2005)	EP ($n = 6$), IP ($0 = 26$), SNSCC ($n = 12$)	12	1999–2004 Japan	42 %	HPV DNA ISH	–
P16 and human papillomavirus in sinonasal squamous cell carcinoma *Cohen et al.* [42] (2020)	SNSCC $N = 47$ patients 60% males, 85% more than 50 years, 60% Caucasians 22 patients with adequate tissue for testing	40	2011–2017 USA	45 %	HPV RNA ISH RNA Scope	HPV + patients were younger, less likely to have a smoking history, increased survival and disease-free survival
Prevalence and clinical features of human papillomavirus in head and neck squamous cell carcinoma in Okinawa, southern Japan. *Deng et al.* [43] (2011)	HNSCC $N = 150$ 87% males Mean age 64.8 (28–90)	10	Japan 2006–2009	30 %	HPV DNA PCR	-
A randomized trial comparing surgery and adjuvant radiotherapy versus concurrent chemoradiotherapy in patients with advanced, nonmetastatic squamous cell carcinoma of the head and neck: 10-year update and subset analysis. *Iyer et al.* [44] (2015)	HNSCC stage III/IV $n = 119$ Median age 59 (27–75) 73% males	10	Singapore 1996–2002	0%	HPV DNA PCR	-
Significance of human papillomavirus positivity in sinonasal squamous cell carcinoma. *Kılıç et al.* [8] (2017)	Register study using SNSCC National Cancer Database (NCDB) mean age: HPV + 58.0 years HPV– 63.7 years 65% males	770	2010–2014 USA	32%	Register study	Improved survival for HPV + patients 5-year OS HPV+: 68.1% HPV–: 51.5%

(*continued*)

Table 1. Continued.

Article	Study population	Number of cases	Study timespan Country	% HPV	HPV detection method	Significance of HPV
Human papillomavirus in sinonasal papillomas and squamous cell carcinoma. *Kashima et al.* [45] (1992)	SNSCC ($n = 24$), IP ($n = 25$), squamous papilloma ($n = 22$)	24	1984–1990 USA	4%	HPV DNA PCR	-
Association of DNA aneuploidy with human papilloma-virus-induced malignant transformation of sinonasal transitional papillomas *Klemi et al.* [46] (1989)	Maxillary sinus SCC ($n = 9$), transitional papilloma ($n = 19$) Mean age 58 years (34–76)	9	1981–1986 Finland	0%	HPV ISH	-
Association of human papillomavirus status at head and neck carcinoma subsites with overall survival *Li et al.* [47] (2018)	Register study using HNSCC *National Cancer database* 74% males Mean age 63.1	41,950	2010–2014 USA	No data	Register study	Better survival in sinonasal SCC HPV+ 5-year OS HPV+: 63.1% HPV–: 45.1%
Comprehensive analysis of HPV infection, EGFR exon 20 mutations and LINE1 hypomethylation as risk factors for malignant transformation of sinonasal-inverted papilloma to squamous cell carcinoma. *Sahnane et al.* [48] (2019)	IP, OP, SNSCC/IP and SNSCC ($n = 54$) Mean age 63.9 (35–79) 67% males	12	2003–2016 Italy	8%	DNA ISH	-
Detection of human papillomavirus DNA in benign and malignant sinonasal neoplasms. *Hoffmann et al.* [49] (2006)	Mucosal lesions of the sinonasal tract ($n = 86$) mean age 61.7 (33–84) 65% males	20	Germany	20%	HPV DNA PCR	-
EGFR mutation and HPV infection in sinonasal inverted papilloma and squamous cell carcinoma. *Cabal et al.* [50] (2020)	IP, SNSCC/IP, SNSCC ($n = 129$) Mean age 66 years (42–92) 74% males	60	1989–2017 Spain	2%	HPV DNA PCR	-
Establishment and genetic characterization of six unique tumor cell lines as preclinical models for sinonasal squamous cell carcinoma. *García-Inclán et al.* [51] (2014)	SNSCC Median age 68.5 (48–79) 83% males	6	Spain	0%	HPV DNA PCR	-
Expression of p16 in sinonasal undifferentiated carcinoma (SNUC) without associated human papillomavirus (HPV). *Wadsworth et al.* [30] (2011)	SNSCC ($n = 5$, poorly differentiated), SNUC ($n = 5$) mean age 62.2 years (53–75) 100 % males	5	2005–2007 USA	0%	HPV DNA ISH HPV DNA PCR	-
High-risk human papillomavirus is transcriptionally active in a subset of sinonasal squamous cell carcinomas *Larque et al.* [52] (2014)	all SNSCC median age 63.6 (40–93) 73% males	56	1985–2010 Spain	23%	HPV ISH HPV RNA RT-PCR HPV DNA PCR	Mean OS HPV+: 156.8 months HPV–: 72 months
Human papillomavirus (HPV) and somatic EGFR mutations are essential, mutually exclusive oncogenic mechanisms for inverted sinonasal papillomas and associated sinonasal squamous cell carcinomas *Udager et al.* [53] (2017)	IP ($n = 58$), SNSCC/IP ($n = 22$), SNSCC ($n = 14$), OP ($n = 27$), EP ($n = 4$) median age 65 (28;76) 64% males	14	USA	36%	HPV DNA PCR	-
Human papillomavirus and survival of patients with sinonasal squamous cell carcinoma. *Oliver et al.* [54] (2019)	Register study using National Cancer Database (NCDB) of 6458 SNSCC only HPV status on 1418 Mean age 64 years 65% males	128 HPV + and HPV HPV-matched patients	2010–2016 USA	32%	(database)	HPV in younger patients (median age 60 vs. 65 years), nasal cavity tumors, 3-year OS HPV+: 74.6% HPV–: 56.1%

(*continued*)

Table 1. Continued.

Article	Study population	Number of cases	Study timespan Country	% HPV	HPV detection method	Significance of HPV
Human papillomavirus DNA in head and neck squamous cell carcinomas in the Free State, South Africa *Bulane et al.* [55] (2019)	HNSCC ($n = 994$) 81% males SNSCC mean age HPV + 46, HPV– 57 (35–82)	25	2004–2014 South Africa	16%	HPV DNA PCR	-
Human papillomavirus DNA in squamous cell carcinoma of the upper aerodigestive tract. *Ishibashi et al.* [56] (1990)	SCC of the upper aerodigestive tract ($n = 19$) Median age 60 (44–82) 68% males	5	Japan	20%	Southern blot	-
Human papillomavirus infection and immunohistochemical expression of cell cycle proteins pRb, p53, and p16(INK4a) in sinonasal diseases. *Yamashita et al.* [57] (2015)	SNSCC, SNSCC/IP, IP, chronic rhinosinusitis 88% males mean age 60 (40;82)	16	Japan	25%	HPV DNA PCR	Higher viral load in SNSCC and SNSCC/IP than benign lesions
Human papillomavirus type 6 detected by the polymerase chain reaction in invasive sinonasal papillary squamous cell carcinoma. *Judd et al.* [58] (1991)	Sinonasal carcinomas 89% males Median age 48 (30–76)	5	USA	20%	HPV DNA PCR and ISH	-
Human papillomaviruses are identified in a subgroup of sinonasal squamous cell carcinomas with favorable outcome *Alos et al.* [59] (2009)	SNSCC HPV + median age 69 (49–87), 67% males HPV– median age 62 (42–93), 77% males	60	1981–2006 Spain	20%	HPV DNA PCR	Estimated 5-year survival: 31% HPV– 80% HPV+
Human papillomavirus-related carcinomas of the sinonasal tract *Bishop et al.* [60] (2013)	Sinonasal carcinomas ($n = 161$) HPV + 56 % males, median age 54 years HPV– 55% males, median age 59 years	91	1995–2011 USA	31%	DNA ISH	5-year survival rate: HPV + 69.7% HPV– 50.6%
Outcomes of HPV-related nasal squamous cell carcinoma *Chowdhury et al.* [61] (2017)	All consecutive SNSCC Average age 66.4 years (45–85) 73% males	26	1990–2015 USA	62%	DNA PCR	Median survival HPV + 54 months HPV– 12 months
p53 Alteration and human papillomavirus infection in paranasal sinus cancer *Caruana et al.* [62] (1997)	SNSCC/IP, SNSCC median age 67 (44–91) 60% males	5	1985–1994 USA	20%	HPV DNA PCR	-
Prevalence of high-risk human papillomavirus DNA in nonkeratinizing (cylindrical cell) carcinoma of the sinonasal tract: a distinct clinicopathologic and molecular disease entity. *El-Mofty et al.* [63] (2005)	Sinonasal carcinomas ($n = 39$) average age 63 (33–86) 51% males	29 8 NKSCC 21 KSCC	USA	31%	HPV DNA PCR	–
The presence of high-risk human papillomavirus (HPV) E6/E7 mRNA transcripts in a subset of sinonasal carcinomas is evidence of involvement of HPV in its etiopathogenesis *Laco et al.* [64] (2016)	All sinonasal carcinomas $N = 73$ 64% males median age 62 (23;83) 55% of SCC NKSCC	49	1995–2014 Czech Republic	27 %	HPV DNA ISH E6/E7 mRNA ISH (RNAscope) HPV E6/E7 mRNA RT-PCR	Median survival HPV + 30 months HPV– 14 months (not significant)
Transcriptionally active HPV and targetable EGFR mutations in sinonasal inverted papilloma: an association between low-risk HPV, condylomatous morphology, and cancer risk? *Mehrad et al.* [65] (2020)	IP and SNSCC (controls) ($n = 51$) Median age 55 (45–72) 100% males	7	2005–2015 USA	0%	RT-PCR RNA ISH RNAscope	-
Transitional papilloma of the nasal cavity and paranasal sinuses. Clinical course, viral etiology and malignant transformation *Siivonen et al.* [66] (1989)	IP and SNSCC ($n = 21$) Median age 56 (30–70) 76 % males	1	1981–1986 Finland	0 %	HPV ISH	-

(*continued*)

Table 1. Continued.

Article	Study population	Number of cases	Study timespan Country	% HPV	HPV detection method	Significance of HPV
Down-regulation of p27Kip1 expression is correlated with increased cell proliferation but not the expression of p21waf1 and p53, and human papillomavirus infection in benign and malignant tumors of sinonasal regions *Saegusa et al.* [67] (1999)	Sinonasal tumors ($n = 76$)	48	1980–1997 Japan	28 %	HPV16 OG 18 DNA PCR	-
	TOTAL	2025 samples		28 % HPV+		

Sinonasal squamous cell carcinoma occurrence and significance of HPV in sinonasal squamous cell carcinoma. Of a total of 2025 cases, 558 were HPV-positive (28%). Eleven of the studies reported outcomes; nine of them improved survival in HPV-positive tumors, one a non-significant improvement in HPV-positive tumors and one study found no difference in survival.

used DNA PCR alone, six studies used HPV DNA ISH alone), the remaining studies used more than one method of detection.

Of 11 studies investigating prognosis, nine studies ($n = 1235$ patients) reported an improved prognosis in HPV-positive cases, one ($n = 49$ patients) reported a non-significant improvement in survival and one study ($n = 44$ patients) did not find any difference in survival.

The value of p16 as a surrogate marker for HPV positivity in SNSCC was examined in 11 studies comprising in total of 497 patients. Three of the larger studies ($n = 231$) reported high sensitivity and specificity, which was not reported in most of the remaining studies *(*Table 5*)* [38,52,59].

In total, 28% of 2025 examined cases of SNSCC were HPV-positive (Table 1, Figure 4(A)). A significantly improved prognosis in HPV + SNSCC was reported by nine studies, one study found no correlation between HPV-status and survival [8,37,38,42,47,52,54,59–61,64].

SNSCC associated with sinonasal papilloma (SNSCC/IP)

In addition to the studies examining the occurrence of HPV in SNSCC, 22 studies investigated HPV in SNSCC associated with IP (SNSNSCC/IP). In total, 216 cases of SNSCC/IP/IP were examined, 27% were HPV-positive. No studies relied on p16 IHC alone (Table 2, Figure 4(B)).

A total of eight SNSCC originated in EP. Of these, five were HPV-positive (63%) [18,69,74].

HPV-dependent multiphenotypic sinonasal carcinoma (HMSC)

HMSCs are per definition HPV-positive (most frequently HPV33). The presence of HPV lead to the discovery of this newly described entity, which appears to be associated with a propensity for recurrences, but high survival [42,76,78–81].

Adenoid cystic carcinoma

Five studies examined adenoid cystic carcinoma of the sinonasal tract. Of 156 examined cases, only one was HPV positive. As this sample was positive for HPV33, it probably represented HMSC.

Thompson et al. (2014) examined 86 patients with ACC, none of which were HPV-positive [28]. *Chmelařová et al. (2016)* investigated tissue samples from 64 patients with sinonasal carcinoma; six were ACC (all HPV-negative). *Hang et al. (2017)* investigated all ACC and carcinoma with adenoid cystic-like features (currently HMSC): of 19 identified tumors, 14 were ACC. None of the ACCs were HPV-positive, one had p16 overexpression [76]. Similarly, *Laco et al. (2016)* identified seven ACC in a larger cohort of sinonasal carcinomas, none of the ACC were HPV-positive [64]. *Miller et al. (2017)* examined 17 tissue samples from patients with ACC, identifying HPV33 in one of these—this sample also showed p16 overexpression [29]. As part of a large cohort of sinonasal carcinomas, *Bishop et al. (2013)* examined 26 ACC, none of which were HPV-positive [60]. Four studies compared p16

Table 2. Squamous cell carcinomas associated with inverted papillomas.

Article	Study population	Number of cases	Study timespan Country	% HPV	HPV detection method	Significance of HPV
Down-regulation of p27Kip1 expression is correlated with increased cell proliferation but not the expression of p21waf1 and p53, and human papillomavirus infection in benign and malignant tumors of sinonasal regions *Saegusa et al.* [67] (1999)	Sinonasal tumors ($n = 76$, including 28 IP)	2	1980–1997 Japan	Not reported for SNSCC/IP, 36% of IP	HPV16 and 18 DNA PCR	-
HPV-related Sinonasal Carcinoma: Clinicopathologic Features, Diagnostic Utility of p16 and Rb Immunohistochemistry, and EGFR Copy Number Alteration *Jiromaru et al.* [38] (2020)	101 SNSCC Mean age 64.2 (34–103) 70% males	7	2003–2016 Japan	0%	HPV mRNA ISH RNAscope	-
Markers of malignant transformation of sinonasal inverted papilloma *Katori et al.* [41] (2005)	EP ($n = 6$), IP ($n = 26$), SNSCC ($n = 12$)	6	1999–2004 Japan	67%	HPV DNA ISH	Increased EGFR in HPV+
Sinonasal inverted papilloma associated with squamous cell carcinoma *But-Hadzic J et al.* [68] (2011)	IP ($n = 89$) Median age 73 (45–77) 80% males	5	1995–2005 Slovenia	60 %	HPV PCR	-
Association of DNA aneuploidy with human papilloma-virus-induced malignant transformation of sinonasal transitional papillomas *Klemi et al.* [46] (1989)	Maxillary sinus SCC ($n = 9$), transitional papilloma ($n = 19$) Mean age 58 years (34–76)	3	1981–1986 Finland	33 %	DNA ISH	-
Carcinoma ex-Schneiderian papilloma (malignant transformation): a clinicopathologic and immunophenotypic study of 20 cases combined with a comprehensive review of the literature *Nudell et al.* [69] (2014)	740 sinonasal papillomas (20 carcinomas from papilloma) 65% males Mean age 60.7 (38–86)	15	USA	20 %	HPV ISH	-
Comprehensive analysis of HPV infection, EGFR exon 20 mutations and LINE1 hypomethylation as risk factors for malignant transformation of sinonasal-inverted papilloma to squamous cell carcinoma *Sahnane et al.* [48] (2019)	54 sinonasal papillomas and carcinomas 68% males Mean age 56.1 years (34–78)	19	2003–2006 Italy	11%	DNA ISH	-
Detection of human papillomavirus (HPV) in sinonasal inverted papillomas using polymerase chain reaction (PCR). *Hwang et al.* [70] (1998)	IP ($n = 42$) Mean age 52 (19–79)	6	1990–1995 Korea	33%	HPV DNA PCR	–
EGFR mutation and HPV infection in sinonasal inverted papilloma and squamous cell carcinoma *Cabal et al.* [50] (2020)	Sinonasal papillomas and carcinomas ($n = 129$) 36% males Mean age 58 (22–82)	14	1989–2017 Spain	36%	HPV DNA PCR	–

(*continued*)

Table 2. Continued.

Article	Study population	Number of cases	Study timespan Country	% HPV	HPV detection method	Significance of HPV
Expression of Sp100 Protein in Human Papillomavirus-Associated Sinonasal Inverted Papilloma. *Wang et al.* [71] (2019)	IP and normal nasal mucosa control tissue $N = 40$ 63% males Mean age 51 (26–72)	7	China	43%	HPV DNA PCR (HPV16 og 18)	Low expression of Sp100 in SNSCC/IP compared with IP
High-risk human papillomavirus is transcriptionally active in a subset of sinonasal squamous cell carcinomas *Larque et al.* [52] (2014)	All SNSCC median age 63.6 (40–93) 73% males	14	1985–2010 Spain	7%	RNA ISH	
Human Papilloma Virus and p53 Expression in Carcinomas Associated With Sinonasal Papillomas: A Danish Epidemiological Study 1980–1998 *Buchwald et al.* [18] (2001)	All sinonasal carcinomas associated with papillomas in Denmark $N = 36$ Median age 60 (25–85) 72% males	30	1980–1998 Denmark	13%	PCR	Inverted relationship between p53 overexpression and HPV
Human papillomavirus (HPV) and somatic EGFR mutations are essential, mutually exclusive oncogenic mechanisms for inverted sinonasal papillomas and associated sinonasal squamous cell carcinomas *Udager et al.* [53] (2017)	IP ($n = 58$), SNSCC/IP ($n = 22$), SNSCC ($n = 14$), OP ($n = 27$), EP ($n = 4$) median age 65 (28;76) 64% males	22	USA	23 %	HPV DNA PCR	EGFR mutation and HPV mutually exclusive in SNSCC/IP
Human papillomavirus infection and immunohistochemical expression of cell cycle proteins pRb, p53, and p16(INK4a) in sinonasal diseases *Yamashita et al.* [57] (2015)	SNSCC, SNSCC/IP, IP, chronic rhinosinusitis 88% males mean age 60 (40;82)	5	Japan	40%	HPV DNA PCR	-
Human papillomavirus (HPV) in sinonasal papillomas: a study of 78 cases using in situ hybridization and polymerase chain reaction 1995 *Buchwald et al.* [72] (1995)	Sinonasal papillomas ($n = 78$)	5	1975–1992 Denmark	60%	HPV DNA PCR DNA ISH	-
In Inverted Papillomas HPV more likely represents incidental colonization than an etiological factor *Jenko et al.* [21] (2011)	IP, SNSCC/IP, normal mucosa control group mean age for males 65 (45–77), one female patient 73 years	5	Slovenia	60%	HPV DNA PCR	-
p53 Alteration and Human Papilloma Virus Infection in Paranasal Sinus Cancer *Caruana et al.* [62] (1997)	SNSCC/IP, SNSCC median age 67 (44–91) 60% males	4	1985–1994 USA	50%	HPV DNA PCR	-
Patterns of p21(waf1/cip1) expression in the non-papillomatous nasal mucosa, endophytic sinonasal papillomas, and associated carcinomas. *Schwerer et al.* [73] (2001)	SCC/ endophytic papillomas ($n = 38$) highly selective median age 49 (17–76) 79% males	5	Germany	40%	NCL-PVp antibody, HPV infection in 2/5	-
Schneiderian papillomas and carcinomas: a retrospective study with special reference to p53 and p16 tumor suppressor gene expression and association with HPV *Cheung et al.* [74] (2010)	All IP or carcinoma Median age 65 (53–85) 50% males	6	1995–2006 Hong Kong	50%	HPV DNA PCR and confirmatory DNA ISH	-

(*continued*)

Table 2. Continued.

Article	Study population	Number of cases	Study timespan Country	% HPV	HPV detection method	Significance of HPV
The prevalence of human papillomavirus infection in sinonasal inverted papilloma specimens classified by histological grade *Kim et al.* [75] (2007)	IP ($n = 38$)	7	1998–2002 Korea	0%	HPV DNA chip	-
Transcriptionally Active HPV and Targetable EGFR Mutations in Sinonasal Inverted Papilloma: An Association Between Low-risk HPV, Condylomatous Morphology, and Cancer Risk? *Mehrad et al.* [65] (2020)	IP and SNSCC ($n = 51$) Median age 55 (45–72) 100% males	5	2005–2015 USA	60%	RT-PCR RNA ISH (RNAscope)	
Transitional papilloma of the nasal cavity and paranasal sinuses. Clinical course, viral etiology and malignant transformation *Siivonen et al.* [66] (1989)	IP and SNSCC ($n = 21$) Median age 56 (30–70) 76% males	9	1981–1986 Finland	100%	HPV ISH	-
Total	216 samples			27% HPV+		

SNSCC/IP showing the occurrence of HPV in SNSCC/IP. Of 216 investigated cases of SNSCC/IP, 59 were HPV-positive, corresponding to 27%. Katori et al. reported increased expression of EGFR in HPV-positive tumors, whereas Udager et al. reported HPV-infection and EGFR mutation mutually exclusive. Abbreviations: IP: inverted papilloma; SNSCC/IP: squamous cell carcinoma associated with IP; SNSCC: sinonasal squamous cell carcinoma; ISH: *in situ* hybridization; PCR: polymerase chain reaction; EP: exophytic papilloma.

overexpression and HPV in ACC; these samples were frequently p16+ regardless of HPV status, and p16 is therefore not suitable as a surrogate marker for HPV-status in ACC (Table 3).

Sinonasal undifferentiated carcinoma (SNUC)

Gray et al. identified all SNUCs diagnosed at their institution from 1995–2013; 11 out of 19 cases were p16+, nine were HPV-positive. A statistically significant improvement in survival was seen in patients with p16+ tumors and a non-significant improved survival for HPV-positive patients [77]. *El-Mofty et al. (2005)* investigated 39 sinonasal carcinomas, identifying ten of them as SNUC, nine of which were found in males. HPV DNA was detected in one case [63]. *Wadsworth et al. (2011)* examined all cases of SNUC from 2000–2007, none of which were HPV-positive [30]. In the cohort of carcinomas originating in sinonasal papillomas examined by *Nudell et al. (2014)*, one SNUC was identified (HPV-negative) [69]. *Bishop et al. (2013)* also identified 16 cases of SNUC in their cohort of sinonasal carcinomas, one patient was HPV-positive [60]. Of 73 sinonasal carcinomas identified by *Laco et al. (2016)*, three were SNUC (all HPV-negative) [64].

SMARCB1-deficient carcinomas of the sinonasal tract

Neither *Bishop et al. (2013)* nor *Agaimy et al. (2014)* identified HPV in any of their samples of SMARCB1-deficient carcinomas in a total of 48 cases [33,82].

HPV in other sinonasal cancers

In a large cohort of sinonasal carcinomas examined by *Bishop et al. (2013)*, seven adenocarcinomas (one intestinal-type adenocarcinoma, four non-intestinal low-grade adenocarcinomas, and two non-intestinal high-grade adenocarcinomas) were included, none of which were HPV-positive. In this cohort, three cases of NUT midline carcinoma were also identified, all HPV-negative [60]. In the cohort investigated by *Nudell et al. (2014)*, two cases of mucoepidermoid carcinoma originating in a sinonasal papilloma (one EP, one IP) were investigated, both HPV-negative [69]. *Alos et al. (2009)* identified all high-grade neuroendocrine carcinomas (HGNEC) of the head and neck region, five of which were located in the sinonasal tract; none were HPV-positive [9]. *Judd et al. (1991)* investigated a small cohort of sinonasal carcinomas, one of these was adenocarcinoma with no evidence of HPV infection [58]. An adenocarcinoma originating in an IP in the cohort of carcinomas associated with sinonasal papillomas investigated by *Buchwald et al. (2001)* was HPV-negative [18].

Discussion

In the early 1980s, the first reports of HPV sequences in human tumors were published. Utilizing southern blot, HPV11 and subsequently HPV16 and HPV18, were identified in cervical cancer biopsies. Following this, some anogenital and oropharyngeal cancers were also found to be associated with HPV and these

Table 3. Adenoid cystic carcinoma.

Article	Study population	Number of cases	Study timespan Country	% HPV	HPV detection method
Importance of tumor suppressor gene methylation in sinonasal carcinomas Chmelarova *et al.* [40] (2016)	ACC	6	1995–2014 Czech Republic	0 %	HPV DNA ISH HPV E6/E7 mRNA ISH HPV DNA PCR HPV E6/E7 mRNA RT-PCR
Sinonasal tract and nasopharyngeal adenoid cystic carcinoma: a clinicopathologic and immunophenotypic study of 86 cases Thompson *et al.* [28] (2014)	ACC (sinonasal and nasopharyngeal) 48% males 52% females Median age 58 years (12;91)	86	1970–1998 2003–2011 USA	0%	HPV HR-AB
Human papillomavirus-related carcinoma with adenoid cystic-like features: a series of five cases expanding the pathological spectrum Hang *et al.* [76] (2017)	ACC and carcinomas with adenoid cystic-like features $N = 19$ 68% males 32% females	14	1995–2016 Taiwan	0%	HPV DNA PCR HPV DNA ISH
Sinonasal adenoid cystic carcinoma: Treatment outcomes and association with human papillomavirus. Miller *et al.* [29] (2017)	ACC $N = 23$ (only 17 with available material) Median age 55 years (20–73) 65% males	17	1998–2013 USA	6%	HPV qPCR types 16, 18, 31, 33, 35
The presence of high-risk human papillomavirus (HPV) E6/E7 mRNA transcripts in a subset of sinonasal carcinomas is evidence of involvement of HPV in its etiopathogenesis Laco *et al.* [64] (2016)	Sinonasal carcinoma $N = 73$ 55% of SCC NKSCC 64% males 36% females Median age 62 years (23;83)	7	1995–2014 Czech Republic	0%	HPV DNA ISH E6/E7 mRNA ISH (RNAscope) HPV E6/E7 mRNA RT-PCR
Human papillomavirus-related carcinomas of the sinonasal tract Bishop *et al.* [60] (2013)	161 cases HPV + 56 % males, median age 54 years HPV– 55% males, median age 59 years	26	1995–2011 USA	0%	DNA ISH

Adenoid cystic carcinoma. Only one sample was HPV positive (HPV33).

Table 4. Sinonasal undifferentiated carcinoma (SNUC).

Article	Study population	Number of cases	Study timespan country	% HPV	HPV detection method	Significance of HPV
Carcinoma ex-Schneiderian papilloma (malignant transformation): a clinicopathologic and immunophenotypic study of 20 cases combined with a comprehensive review of the literature Nudell et al. [69] (2014)	740 sinonasal papillomas (20 carcinomas from papilloma) 65% males Mean age 60.7 (38–86)	1	USA	0 %	HPV ISH	-
Expression of p16 in sinonasal undifferentiated carcinoma (SNUC) without associated human papillomavirus (HPV). Wadsworth et al. [30] (2011)	80% males 20% females Mean age 56.8 years (26–75 years)	5	2000–2007 USA	0%	HPV DNA ISH PCR	-
Human papillomavirus-related carcinomas of the sinonasal tract Bishop et al. [60] (2013)	Sinonasal carcinomas ($n = 161$) HPV+ 56 % males, median age 54 years HPV- 55% males, median age 59 years	16	1995–2011 USA	6%	DNA ISH	-
Prevalence of high-risk human papillomavirus DNA in nonkeratinizing (cylindrical cell) carcinoma of the sinonasal tract: a distinct clinicopathologic and molecular disease entity. El-Mofty et al. [63] (2005)	Sinonasal carcinomas ($n = 39$) average age 63 (33–86) 51% males	10	USA	10%	HPV DNA PCR	-
The presence of high-risk human papillomavirus (HPV) E6/E7 mRNA transcripts in a subset of sinonasal carcinomas is evidence of involvement of HPV in its etiopathogenesis Laco et al. [64] (2016)	All carcinomas of the sinonasal tract $N = 73$ 47 males, median age 62 (23;83)	3	1995–2014 Czech Republic	0%	HPV DNA ISH E6/E7 mRNA ISH (RNAscope) HPV E6/E7 mRNA RT-PCR	-
Treatment outcomes and prognostic factors, including human papillomavirus, for sinonasal undifferentiated carcinoma: a retrospective review Gray et al. [77] (2014)	SNUC mean age 52 years (19–88) 79% males	19	1995–2012 USA	64%	HPV DNA ISH PCR	p16+ associated with improved survival, a tendency to improved survival in HPV+ 5-year OS: HPV + 55.7% HPV– 27.8%

Sinonasal undifferentiated carcinoma. In a total of 54 cases of SNUC, 14 were HPV-positive (26%). In one study, Gray et al. found improved survival in p16+ SNUCs and a non-significant increased five-year survival in HPV-positive SNUCs.

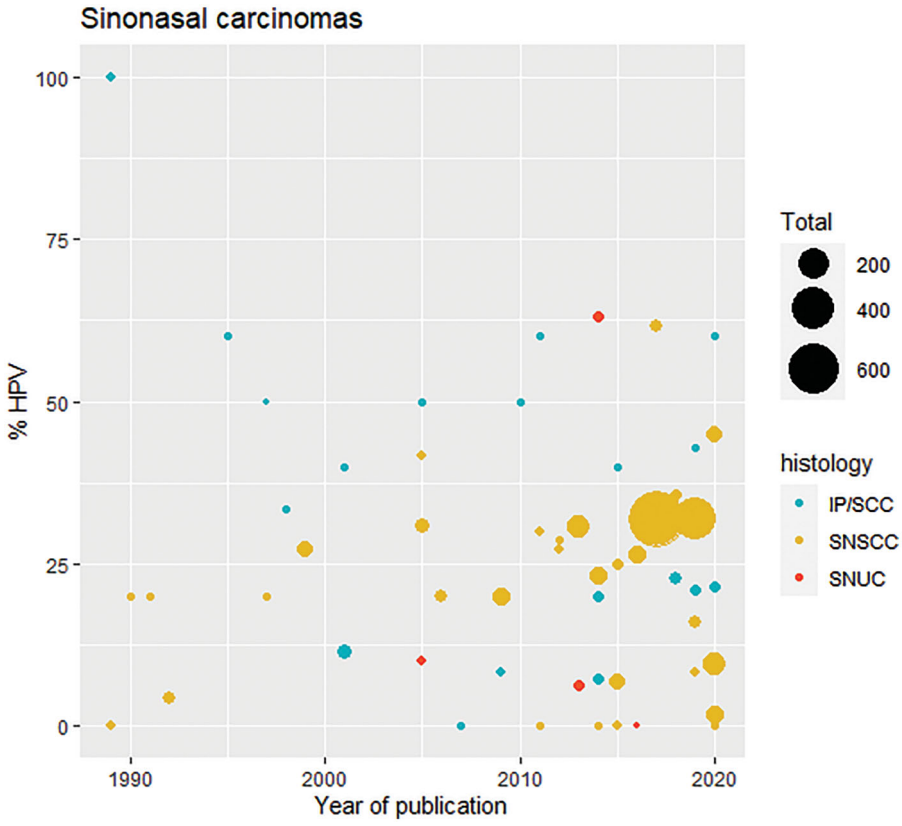

Figure 3. Bubble chart of the occurrence of HPV in the most frequently studies sinonasal cancers: IP/SCC (sinonasal squamous cell carcinoma originating in inverting papilloma); SNSCC (sinonasal squamous cell carcinoma); and SNUC (sinonasal undifferentiated carcinoma). The size of the sample is indicated by the size of the circle, the histology by the color. The occurrence of HPV in the populations is shown as percent HPV-positive tumors (y-axis).

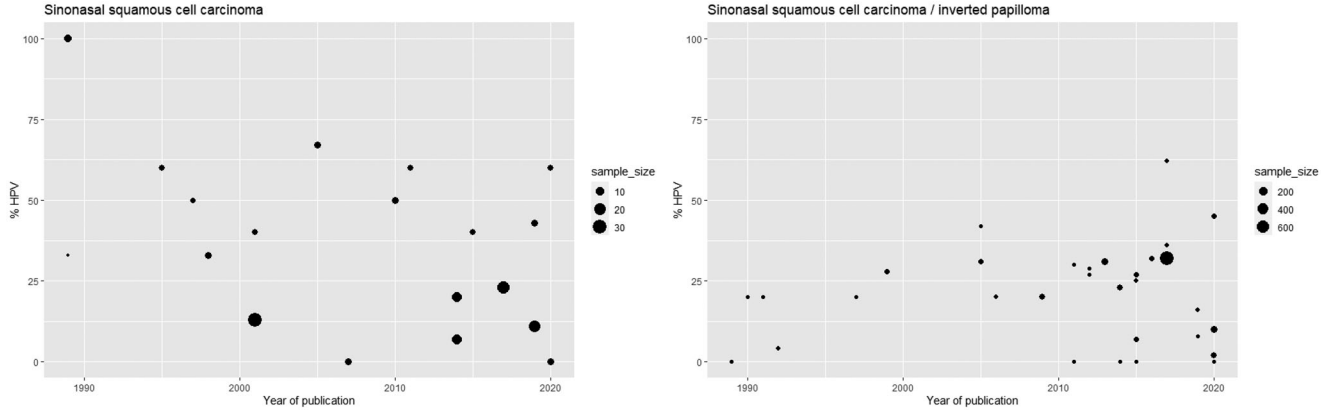

Figure 4. Bubble chart of the occurrence of HPV in SNSCC (sinonasal squamous cell carcinoma) (A) and SNSCC/IP (sinonasal squamous cell carcinoma associated with inverting papilloma) (B). The occurrence of HPV in the carcinomas is shown as a percentage HPV-positive of the total number included in the study (y-axis).

tumors had a better prognosis than their HPV-negative counterparts [7]. In studies originally investigating HPV and sinonasal papillomas, detection of HPV in SNSCC/IP raised the question of whether HPV was involved in sinonasal cancer.

In this review, we find that around 30% of SNSCC (both with and without association to inverted papilloma) are HPV-positive. This is in line with the reported incidence in a systematic review of SNSCC [14]. We have considered SNSCC/IP papilloma separately as some studies report genomic differences between these and *de novo* SNSCC [53]. The occurrence of HPV in these two groups of SNSCC however is similar. The apparent improvement in prognosis associated with HPV positivity warrants further studies of SNSCC as well as other sinonasal carcinomas.

Table 5. p16 Overexpression in sinonasal cancer.

Study	Tumor type (number of cases)	Correlation of p16+ and HPV-status
Thompson et al. [28]	ACC ($n = 86$)	All tumor p16+, no HPV+
Laco et al. [64]	ACC ($n = 7$)	Six of seven tumors p16+, no HPV+
	SNSCC ($n = 49$)	Two of 18 HPV + cases were p16 negative (NKSCC, KSCC)
	ACC, NKSCC, SCNEC, and SNUC	16 of 25 p16+ were HPV+. Of 16 p16 + 15 were HPV+.
		Nine cases were p16+/HPV–
Miller et al. [29]	ACC ($n = 17$)	Two tumors p16+, one of these HPV33+
Bishop et al. [36]	ACC ($n = 26$)	Three of 26 tumors were p16+, no HPV+
	Intestinal type adenocarcinoma ($n = 1$)	P16-, HPV–
	Non-intestinal type adenocarcinoma	None p16+, no HPV+
	High-grade ($n = 4$)	Two tumors p16+, no HPV+
	Low-grade ($n = 2$)	All p16-, HPV–
	Myoepithelial carcinoma ($n = 3$)	One p16+, both HPV–
	Mucoepidermoid carcinoma ($n = 2$)	P16-, HPV–
	Acinic cell carcinoma ($n = 1$)	P16-, HPV–
	Epithelial-myoepithelial carcinoma ($n = 1$)	P16-, HPV–
	Adenocarcinoma, not specified ($n = 1$)	Four p16+
	SNUC ($n = 16$	Three of four HPV + p16+
	SNSCC ($n = 7$)	Four of five HPV– P16–
Gray et al. [77]	SNUC ($n = 19$)	11 p16+, nine of these HPV+
Wadsworth et al. [30]	SNUC ($n = 5$)	Five p16+, no HPV+
Agaimy et al. [33]	SMARCB1-deficient sinonasal carcinoma ($n = 39$)	Four of 29 tested were p16+, no HPV+
Alos et al. [59]	SNSCC ($n = 60$)	Sensitivity 100%, specificity 100%
El-Mofty et al. [63]	KSCC ($n = 21$)	Four HPV + cases, one p16+
	NKSCC ($n = 8$)	Four HPV + cases, five cases were p16+
	SNUC ($n = 10$)	One of ten cases p16+
Larque et al. [52]	SNSCC ($n = 70$)	Sensitivity 100%, specificity 100%
Doescher et al. [37]	SNSCC ($n = 44$)	Three of 42 tumors both HPV and P16+
Chowdhury et al. [61]	SNSCC ($n = 26$)	17 of 19 HPV + samples p16+
Cohen et al. [42]	SNSCC ($n = 47$)	90%, 67% for p16 expression detecting HPV+
Jiromaru et el [38]	SNSCC ($n = 101$)	100%, 93.5%, but a positive predictive value of 60% (40% of cases with p16+ were HPV–)
Mehrad et al. [65]	SNSCC ($n = 7$)	Five of seven were p16 positive, HR-HPV found in all p16+ SNSCCs
	SNSCC/IP ($n = 5$)	All SNSCC/IP were HPV negative
Sahnane et al. [48]	SNSCC ($n = 12$)	HPV identified in 11% of SNSCC/IP and none of SNSCC. In 12/34 samples, p16 overexpression was identified, no data on correlation with HPV
	SNSCC/IP ($n = 19$)	
Yamashita et al. [57]	SNSCC ($n = 16$)	Four cases of SNSCC were HPV+; one of these was p16+. One HPV– case was p16+.
	SNSCC/IP ($n = 5$)	Two cases of SNSCC/IP were HPV+, both were p16+. No HPV– cases were p16+.

Applicability of p16 as a surrogate marker for HPV-infection in sinonasal cancer. The highest sensitivity and specificity were reported in SNSCC. Potential pitfalls are ACC (p16+, HPV-negative), SNUC (p16+, HPV-negative).

The discovery of HMSC clearly illustrates that HPV can play a significant role in the development of sinonasal carcinomas and those new entities can still be discovered within the multitude of sinonasal cancers.

HPV does not seem to be associated with sinonasal cancers such as ACC; SMARCB1-deficient sinonasal carcinoma; salivary gland carcinoma; NUT midline carcinoma; HGNEC; and adenocarcinomas, although the total number of reported cases is low. HPV-detection in SNUC varied greatly, with HPV identified in two of six studies, of which Gray *et al.* discovered HPV in 63% and found improved survival in those tumors positive for p16 and HPV [77]. Besides the cases from this study, only one case of HPV-positive SNUC was discovered [63]. The great difference in HPV-detection in SNUC gives the thought that some tumors were perhaps misclassified, although only a few cases were studied.

Overexpression of p16 as a surrogate marker for high-risk HPV in SNSCC is not recommended due to minimal evidence [83]. The majority of studies were however not designed to evaluate the value of p16 as a surrogate marker for the presence of HPV in sinonasal cancer and several types of other carcinomas show overexpression of p16 without the presence of HPV (Table 5). Thus, methods that detect mRNA of the E6 and E7 proteins are currently considered the gold standard of HPV detection, but this technique requires samples to be stored immediately in RNAlater and is thus not always feasible [10].

As this review demonstrates, current knowledge of the significance of HPV in SNSCC is derived from several small studies. Most studies did not investigate all consecutive patients and thus introduces a risk of selection bias.

Only two large studies were identified; two American register-based studies. Even though these studies contained a large number of cases, there is a risk of selection bias due to the privately financed health care system in the USA. This is clearly illustrated by the study by *Oliver et al. (2020)*, identifying 6458 American patients with SNSCC, of which 78% of patients had an unknown HPV status. Another bias is introduced by the fact that not all studies account for the histological subtype of the SNSCCs. NKSCC seems to be more likely than other subtypes of SNSCC to contain HPV [8,22,59,63,64].

A further limitation is the different methods of HPV detection used in the studies, which may represent a risk of bias; it is however beyond the scope of this review to give detailed accounts of the applicability and validity of the different techniques. Conflicting results in different detection methods and the significance of this also further confuse the matter [22,64].

In conclusion, HPV is identified in approximately 30% of SNSCC (regardless of association to IP) where it appears to be linked with improved prognosis. Most of the studies included in this review are of selected cases, only a few studies have examined all consecutive cancers and only one nationwide study was identified. The disparities in HPV-detection rates in sinonasal carcinomas over time may be due to evolving detection methods. With this in mind, routine HPV-testing in SNSCC could add valuable prognostic information for the benefit of the patients. The value of p16 as a surrogate marker of HPV in SNSCC, if any, is not yet established.

In the absence of large prospective studies examining the significance of HPV in sinonasal cancer, we cannot with a great degree of certainty declare HPV a prognostic factor in SNSCC—current knowledge does however justify such a study, preferably as a multicenter study to obtain the number of patients needed to establish this.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Harboe Foundation and King Christian X Foundation (non-profit foundations).

ORCID

Christian von Buchwald http://orcid.org/0000-0001-6753-8129

References

[1] Sanghvi S, Khan MN, Patel NR, et al. Epidemiology of sinonasal squamous cell carcinoma: a comprehensive analysis of 4994 patients. Laryngoscope. 2014;124(1):76–83.
[2] Ansa B, Goodman M, Ward K, et al. Paranasal sinus squamous cell carcinoma incidence and survival based on surveillance, epidemiology, and end results data, 1973 to 2009. Cancer. 2013;119(14):2602–2610.
[3] Lund V, Stammberger H, Nicolai P, et al. Position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. Rhinol Suppl. 2010;22:1–143.
[4] Dutta R, Dubal PM, Svider PF, et al. Sinonasal malignancies: a population-based analysis of site-specific incidence and survival. Laryngoscope. 2015;125(11):2491–2497.
[5] Grønhøj Larsen C, Jensen DH, Fenger Carlander A-L, et al. Novel nomograms for survival and progression in HPV + and HPV– oropharyngeal cancer: a population-based study of 1,542 consecutive patients. Oncotarget. 2016;7(44):71761–71772.
[6] Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24–35.
[7] Chow LQM. Head and neck cancer. N Engl J Med. 2020;382(1):60–72.
[8] Kılıç S, Kılıç SS, Kim ES, et al. Significance of human papillomavirus positivity in sinonasal squamous cell carcinoma. Int Forum Allergy Rhinol. 2017;7(10):910–980.
[9] Alos L, Hakim S, Larque AB, et al. p16 Overexpression in high-grade neuroendocrine carcinomas of the head and neck: potential diagnostic pitfall with HPV-related carcinomas. Virchows Arch. 2016;469(3):277–284.
[10] Bussu F, Ragin C, Boscolo-Rizzo P, et al. HPV as a marker for molecular characterization in head and neck oncology: looking for a standardization of clinical use and of detection method(s) in clinical practice. Head Neck. 2019;41(4):1104–1111.
[11] Roden RBS, Stern PL. Opportunities and challenges for human papillomavirus vaccination in cancer. Nat Rev Cancer. 2018;18(4):240–254.
[12] Brink AATP, Snijders PJF, Meijer CJLM. HPV detection methods. Dis Markers. 2007;23(4):273–281.
[13] Tsakogiannis D, Gartzonika C, Levidiotou-Stefanou S, et al. Molecular approaches for HPV genotyping and HPV-DNA physical status. Expert Rev Mol Med. 2017;19:1–20.
[14] Syrjänen K, Syrjänen S. Detection of human papillomavirus in sinonasal carcinoma: systematic review and meta-analysis. Hum Pathol. 2013;44(6):983–991.
[15] Yasukawa S, Kano S, Hatakeyama H, et al. Genetic mutation analysis of the malignant transformation of sinonasal inverted papilloma by targeted amplicon sequencing. Int J Clin Oncol. 2018;23(5):835–843.
[16] Von Buchwald C, Bradley PJ. Risks of malignancy in inverted papilloma of the nose and paranasal sinuses. Curr Opin Otolaryngol Head Neck Surg. 2007;15(2):95–98.
[17] Bishop JA. OSPs and ESPs and ISPs, Oh my! An update on sinonasal (Schneiderian) papillomas. Head Neck Pathol. 2017;11(3):269–277.
[18] Buchwald C, Lindeberg H, Pedersen BL, et al. Human papilloma virus and p53 expression in carcinomas associated with sinonasal papillomas: a danish epidemiological study 1980–1998. Laryngoscope. 2001;111(6):1104–1110.
[19] Vorasubin N, Vira D, Suh JD, et al. Schneiderian papillomas: comparative review of exophytic, oncocytic, and inverted types. Am J Rhinol Allergy. 2013;27(4):287–292.
[20] Syrjanen S, Happonen RP, Virolainen E, et al. Detection of human papillomavirus (HPV) structural antigens and DNA types in inverted papillomas and squamous cell carcinomas of the nasal cavities and paranasal sinuses. Acta Otolaryngol. 1987;104(3–4):334–341.
[21] Jenko K, Kocjan B, Zidar N, et al. In inverted papillomas HPV more likely represents incidental colonization than an etiological factor. Virchows Arch. 2011;459(5):529–538.
[22] Rooper LM, Bishop JA, Westra WH. Transcriptionally active high-risk human papillomavirus is not a common etiologic agent in the malignant transformation of inverted Schneiderian papillomas. Head and Neck Pathol. 2017;11(3):346–353.
[23] Thavaraj S. Human papillomavirus-associated neoplasms of the sinonasal tract and nasopharynx. Semin Diagn Pathol. 2016;33(2):104–111.
[24] Bishop JA, Andreasen S, Hang J, et al. HPV-related multiphenotypic sinonasal carcinoma: An expanded series of 49 cases of the tumor formerly known as HPV-related carcinoma with adenoid cystic carcinoma-like features. Am J Surg Pathol. 2017;41(12):1690–1701.
[25] Andreasen S, Bishop JA, Hansen T. v O, et al. Human papillomavirus-related carcinoma with adenoid cystic-like features of the sinonasal tract: clinical and morphological characterization of six new cases. Histopathology. 2017;70(6):880–888.
[26] Shah AA, Lamarre ED, Bishop JA. Human papillomavirus-related multiphenotypic sinonasal carcinoma: a case report documenting the potential for very late tumor recurrence. Head Neck Pathol. 2018;12(4):623–628.

[27] Bishop JA, Westra WH. Human papillomavirus-related multiphenotypic sinonasal carcinoma: an emerging tumor type with a unique microscopic appearance and a paradoxical clinical behaviour. Oral Oncol. 2018;87(October):17–20.
[28] Thompson LDR, Penner C, Ho NJ, et al. Sinonasal tract and nasopharyngeal adenoid cystic carcinoma: a clinicopathologic and immunophenotypic study of 86 cases. Head Neck Pathol. 2014; 8(1):88–109.
[29] Miller ED, Blakaj DM, Swanson BJ, et al. Sinonasal adenoid cystic carcinoma: treatment outcomes and association with human papillomavirus. Head Neck. 2017;39(7):1405–1411.
[30] Wadsworth B, Bumpous JM, Martin AW, et al. Expression of p16 in sinonasal undifferentiated carcinoma (SNUC) without associated human papillomavirus (HPV). Head Neck Pathol. 2011;5(4): 349–354.
[31] Stelow EB. A review of NUT midline carcinoma. Head Neck Pathol. 2011;5(1):31–35.
[32] Bair RJ, Chick JF, Chauhan NR, et al. Demystifying NUT midline carcinoma: radiologic and pathologic correlations of an aggressive malignancy. AJR Am J Roentgenol. 2014;203(4):W391–W399.
[33] Agaimy A, Koch M, Lell M, et al. SMARCB1(INI1)-deficient sinonasal basaloid carcinoma: a novel member of the expanding family of SMARCB1-deficient neoplasms. Am J Surg Pathol. 2014; 38(9):1274–1281.
[34] Agaimy A, Hartmann A, Antonescu CR, et al. SMARCB1 (INI-1)-deficient sinonasal carcinoma: a series of 39 cases expanding the morphologic and clinicopathologic spectrum of a recently described entity. Am J Surg Pathol. 2017;41(4):458–471.
[35] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg. 2021;88:105906–105911.
[36] Bishop JA, Ma X-J, Wang H, et al. Detection of transcriptionally active high-risk HPV in patients with head and neck squamous cell carcinoma as visualized by a novel E6/E7 mRNA in situ hybridization method. Am J Surg Pathol. 2012;36(12):1874–1882.
[37] Doescher J, Piontek G, Wirth M, et al. Epstein–Barr virus infection is strictly associated with the metastatic spread of sinonasal squamous-cell carcinomas. Oral Oncol. 2015;51(10):929–934.
[38] Jiromaru R, Yamamoto H, Yasumatsu R, et al. HPV-related sinonasal carcinoma: clinicopathologic features, diagnostic utility of p16 and Rb immunohistochemistry, and EGFR copy number alteration. Am J Surg Pathol. 2020;44(3):305–315.
[39] Hasegawa M, Deng Z, Maeda H, et al. Human papillomavirus load and physical status in sinonasal inverted papilloma and squamous cell carcinoma. Rhinology. 2012;50(1):87–94.
[40] Chmelařová M, Sirák I, Mžik M, et al. Importance of tumour suppressor gene methylation in sinonasal carcinomas. Folia Biol. 2016;62(3):110–119.
[41] Katori H, Nozawa A, Tsukuda M. Markers of malignant transformation of sinonasal inverted papilloma. Eur J Surg Oncol. 2005; 31(8):905–911.
[42] Cohen E, Coviello C, Menaker S, et al. P16 and human papillomavirus in sinonasal squamous cell carcinoma. Head Neck. 2020; 42(8):2021–2029.
[43] Deng Z, Hasegawa M, Matayoshi S, et al. Prevalence and clinical features of human papillomavirus in head and neck squamous cell carcinoma in Okinawa, southern Japan. Eur Arch Otorhinolaryngol. 2011;268(11):1625–1631.
[44] Iyer NG, Tan DSW, Tan VKM, et al. Randomized trial comparing surgery and adjuvant radiotherapy versus concurrent chemoradiotherapy in patients with advanced, nonmetastatic squamous cell carcinoma of the head and neck: 10-year update and subset analysis. Cancer. 2015;121(10):1599–1607.
[45] Kashima HK, Kessis T, Hruban RH, et al. Human papillomavirus in sinonasal papillomas and squamous cell carcinoma. Laryngoscope. 1992;102(9):973–976.
[46] Klemi PJ, Joensuu H, Siivonen L, et al. Association of DNA aneuploidy with human papillomavirus-induced malignant transformation of sinonasal transitional papillomas. Otolaryngol Head Neck Surg. 1989;100(6):563–567.
[47] Li H, Torabi SJ, Yarbrough WG, et al. Association of human papillomavirus status at head and neck carcinoma subsites with overall survival. JAMA Otolaryngol Head Neck Surg. 2018;144(6): 519–525.
[48] Sahnane N, Ottini G, Turri-Zanoni M, et al. Comprehensive analysis of HPV infection, EGFR exon 20 mutations and LINE1 hypomethylation as risk factors for malignant transformation of sinonasal-inverted papilloma to squamous cell carcinoma. Int J Cancer. 2019;144(6):1313–1320.
[49] Hoffmann M, Klose N, Gottschlich S, et al. Detection of human papillomavirus DNA in benign and malignant sinonasal neoplasms. Cancer Lett. 2006;239(1):64–70.
[50] Cabal VN, Menendez M, Vivanco B, et al. EGFR mutation and HPV infection in sinonasal inverted papilloma and squamous cell carcinoma. Rhin. 2020;58(4):368–376.
[51] García-Inclán C, López-Hernández A, Alonso-Guervós M, et al. Establishment and genetic characterization of six unique tumor cell lines as preclinical models for sinonasal squamous cell carcinoma. Sci Rep. 2014;4(1):4925.
[52] Larque AB, Hakim S, Ordi J, et al. High-risk human papillomavirus is transcriptionally active in a subset of sinonasal squamous cell carcinomas. Mod Pathol. 2014;27(3):343–351.
[53] Udager AM, McHugh JB, Goudsmit CM, et al. Human papillomavirus (HPV) and somatic EGFR mutations are essential, mutually exclusive oncogenic mechanisms for inverted sinonasal papillomas and associated sinonasal squamous cell carcinomas. Ann Oncol. 2017. 2018;29(2):466–471.
[54] Oliver JR, Lieberman SM, Tam MM, et al. Human papillomavirus and survival of patients with sinonasal squamous cell carcinoma. Cancer. 2020;126(7):1413–1423.
[55] Bulane A, Goedhals D, Seedat RY, et al. Human papillomavirus DNA in head and neck squamous cell carcinomas in the Free State, South Africa. J Med Virol. 2020;92(2):227–233.
[56] Ishibashi T, Matsushima S, Tsunokawa Y, et al. Human papillomavirus DNA in squamous cell carcinoma of the upper aerodigestive tract. Arch Otolaryngol Head Neck Surg. 1990;116(3):294–298.
[57] Yamashita Y, Hasegawa M, Deng Z, et al. Human papillomavirus infection and immunohistochemical expression of cell cycle proteins pRb, p53, and p16(INK4a) in sinonasal diseases. Infect Agent Cancer. 2015;10:23.
[58] Judd R, Zaki SR, Coffield LM, et al. Sinonasal papillomas and human papillomavirus: human papillomavirus 11 detected in fungiform Schneiderian papillomas by in situ hybridization and the polymerase chain reaction. Hum Pathol. 1991;22(6):550–556.
[59] Alos L, Moyano S, Nadal A, et al. Human papillomaviruses are identified in a subgroup of sinonasal squamous cell carcinomas with favorable outcome. Cancer. 2009;115(12):2701–2709.
[60] Bishop JA, Guo TW, Smith DF, et al. Human papillomavirus-related carcinomas of the sinonasal tract. Am J Surg Pathol. 2013; 37(2):185–192.
[61] Chowdhury N, Alvi S, Kimura K, et al. Outcomes of HPV-related nasal squamous cell carcinoma. Laryngoscope. 2017;127(7): 1600–1603.
[62] Caruana SM, Zwiebel N, Cocker R, et al. P53 alteration and human papilloma virus infection in paranasal sinus cancer. Cancer. 1997;79(7):1320–1328.
[63] El-Mofty SK, Lu DW. Prevalence of high-risk human papillomavirus DNA in nonkeratinizing (cylindrical cell) carcinoma of the sinonasal tract: a distinct clinicopathologic and molecular disease entity. Am J Surg Pathol. 2005;29(10):1367–1372.
[64] Laco J, Sieglová K, Vošmiková H, et al. The presence of high-risk human papillomavirus (HPV) E6/E7 mRNA transcripts in a subset of sinonasal carcinomas are evidence of involvement of HPV in its etiopathogenesis. Virchows Arch. 2015;467(4):405–415.
[65] Mehrad M, Stelow EB, Bishop JA, et al. Transcriptionally active HPV and targetable EGFR mutations in sinonasal inverted papilloma: an association between low-risk HPV, condylomatous morphology, and cancer risk? Am J Surg Pathol. 2020;44(3): 340–346.

[66] Siivonen L, Virolainen E. Transitional papilloma of the nasal cavity and paranasal sinuses. Clinical course, viral etiology and malignant transformation. ORL J Otorhinolaryngol Relat Spec. 1989; 51(5):262–267.

[67] Saegusa M, Nitta H, Hashimura M, et al. Down-regulation of p27Kip1 expression is correlated with increased cell proliferation but not expression of p21waf1 and p53, and human papillomavirus infection in benign and malignant tumours of sinonasal regions. Histopathology. 1999;35(1):55–64.

[68] But-Hadzic J, Jenko K, Poljak M, et al. Sinonasal inverted papilloma associated with squamous cell carcinoma. Radiol Oncol. 2011;45(4):267–272.

[69] Nudell J, Chiosea S, Thompson LDR. Carcinoma ex-schneiderian papilloma (malignant transformation): a clinicopathologic and immunophenotypic study of 20 cases combined with a comprehensive review of the literature. Head Neck Pathol. 2014;8(3): 269–286.

[70] Hwang CS, Yang HS, Hong MK. Detection of human papillomavirus (HPV) in sinonasal inverted papillomas using polymerase chain reaction (PCR). Am J Rhinol. 1998;12(5):363–366.

[71] Wang F, Zhang J, Wang H, et al. Expression of Sp100 protein in human papillomavirus-associated sinonasal inverted papilloma. Ear Nose Throat J. 2021;100(1):NP21–NP25.

[72] Buchwald C, Franzmann MB, Jacobsen GK, et al. Human papillomavirus (HPV) in sinonasal papillomas: a study of 78 cases using in situ hybridization and polymerase chain reaction. Laryngoscope. 1995;105(1):66–71.

[73] Schwerer MJ, Sailer A, Kraft K, et al. Patterns of p21(waf1/cip1) expression in non-papillomatous nasal mucosa, endophytic sinonasal papillomas, and associated carcinomas. J Clin Pathol. 2001; 54(11):871–876.

[74] Cheung FMF, Lau TWS, Cheung LKN, et al. Schneiderian papillomas and carcinomas: a retrospective study with special reference to p53 and p16 tumor suppressor gene expression and association with HPV. Ear Nose Throat J. 2010;89(10):E5–E12.

[75] Kim J-Y, Yoon J-K, Citardi MJ, et al. The prevalence of human papilloma virus infection in sinonasal inverted papilloma specimens classified by histological grade. Am J Rhinol. 2007;21(6): 664–669.

[76] Hang JF, Hsieh MS, Li WY, et al. Human papillomavirus-related carcinoma with adenoid cystic-like features: a series of five cases expanding the pathological spectrum. Histopathology. 2017;71(6): 887–896.

[77] Gray ST, Herr MW, Sethi RV, et al. Treatment outcomes and prognostic factors, including human papillomavirus, for sinonasal undifferentiated carcinoma: a retrospective review. Head Neck. 2015;37(3):366–374.

[78] Bishop JA, Andreasen S, Hang J-F, et al. HPV-related multiphenotypic sinonasal carcinoma: an expanded series of 49 cases of the tumor formerly known as HPV-related carcinoma with adenoid cystic carcinoma-like features. Am J Surg Pathol. 2017;41(12): 1690–1701.

[79] Andreasen S, Bishop J, Hansen T, et al. Human papillomavirus-related carcinoma with adenoid cystic-like features of the sinonasal tract: clinical and morphological characterization of 6 new cases. Histopathology. 2017;70(6):880–889.

[80] Bishop JA, Ogawa T, Stelow EB, et al. Human papillomavirus-related carcinoma with adenoid cystic-like features: a peculiar variant of head and neck cancer restricted to the sinonasal tract. Am J Surg Pathol. 2013;37(6):836–844.

[81] Hsieh M-S, Lee Y-H, Jin Y-T, et al. Strong SOX10 expression in human papillomavirus-related multiphenotypic sinonasal carcinoma: report of 6 new cases validated by high-risk human papillomavirus mRNA in situ hybridization test. Hum Pathol. 2018;82: 264–272.

[82] Bishop JA, Antonescu CR, Westra WH. SMARCB1 (INI-1)-deficient carcinomas of the sinonasal tract. Am J Surg Pathol. 2014;38(9): 1282–1289.

[83] Chung CH, Guthrie VB, Masica DL, et al. Genomic alterations in head and neck squamous cell carcinoma determined by cancer gene-targeted sequencing. Ann Oncol. 2015;26(6):1216–1223.