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ORIGINAL ARTICLE

Human papillomavirus (HPV) and somatic *EGFR* mutations are essential, mutually exclusive oncogenic mechanisms for inverted sinonasal papillomas and associated sinonasal squamous cell carcinomas

A. M. Udager[1], J. B. McHugh[1], C. M. Goudsmit[2], H. C. Weigelin[1], M. S. Lim[3], K. S. J. Elenitoba-Johnson[3], B. L. Betz[1], T. E. Carey[2] & N. A. Brown[1*]

Departments of [1]Pathology; [2]Otolaryngology/Head and Neck Surgery, University of Michigan Medical School, Ann Arbor; [3]Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA

*Correspondence to: Dr Noah A. Brown, Department of Pathology, University of Michigan Medical School, 1107 Traverwood II, 2910 Huron Parkway, Ann Arbor, MI 48105, USA. Tel: +1-734-764-0500; Fax: +1-734-764-4102; E-mail: noahbr@umich.edu

Background: Inverted sinonasal (Schneiderian) papilloma (ISP) is a locally aggressive neoplasm often associated with sinonasal squamous cell carcinoma (SNSCC). While the etiology of ISP is not well understood, human papillomavirus (HPV) has been detected in a subset of cases. Our group recently identified activating somatic *EGFR* mutations in the majority of ISP and ISP-associated SNSCC. However, the relationship between *EGFR* mutations and HPV infection has not been explored.

Patients and methods: We evaluated 58 ISP and 22 ISP-associated SNSCC (including 13 patients with matched ISP/SNSCC samples), as well as 14 SNSCC without clinical or pathologic evidence of an associated ISP. Formalin-fixed, paraffin-embedded samples were evaluated for *EGFR* mutations using Sanger sequencing and for HPV infection using GP5+/GP6+ PCR. HPV subtyping based on the L1 sequence was done for HPV positive cases including temporally distinct tumors for four patients. Clinicopathologic data including progression free survival was also analyzed.

Results: All ISP and ISP-associated SNSCC demonstrated either an *EGFR* mutation or HPV infection. HPV and *EGFR* mutation were mutually exclusive in all cases of ISP-associated SNSCC and all but one ISP; this case was only weakly HPV positive, and analysis of a prior temporally distinct ISP specimen from this patient failed to show HPV infection, suggesting transient infection/incidental colonization. HPV subtypes in ISP and ISP-associated SNSCC were predominantly low-risk, in contrast with SNSCC without ISP association, which showed frequent high-risk HPV. All paired ISP and associated SNSCC samples demonstrated concordant HPV status and *EGFR* genotypes. ISP progression to SNSCC was significantly associated with the presence of HPV infection and the absence of an *EGFR* mutation (log-rank = 9.620, $P = 0.002$).

Conclusions: Collectively our data show that *EGFR* mutations and HPV infection represent essential, alternative oncogenic mechanisms in ISP and ISP-associated SNSCC.

Key words: sinonasal (Schneiderian) papilloma, sinonasal squamous cell carcinoma (SNSCC), Sanger sequencing, human papillomavirus (HPV) subtypes, *EGFR* mutations

Introduction

Inverted sinonasal (Schneiderian) papilloma (ISP) is a benign neoplasm that arises from the respiratory-type (Schneiderian) epithelium of the lateral nasal wall or paranasal sinuses [1–3]. From a clinical standpoint, ISP is important due to its propensity for local recurrence and association with synchronous or metachronous sinonasal squamous cell carcinoma (SNSCC) in 10%–25% of patients [1, 4, 5]. The pathogenesis and etiology of

ISP has been the subject of intense debate since before the first large-scale clinicopathologic analysis by Dr Vincent Hyams in 1971 [6], and over the past several decades, a possible role for human papillomavirus (HPV) infection has been explored by a number of independent groups [1, 7]. Recent meta-analyses have found evidence of HPV infection in up to 38% of ISP [7] and ~33% of SNSCC (although not necessarily ISP-associated SNSCC) [8]. HPV infection in ISP was also found to be associated with an increased risk of progression to SNSCC [9].

Recently, utilizing targeted next-generation and conventional Sanger sequencing, our group identified activating, somatic *EGFR* exon 19 and 20 mutations in 88% of ISP and 77% of ISP-associated SNSCC [10]. We also demonstrated that matched pairs of ISP and associated SNSCC had concordant *EGFR* genotypes, providing the first genetic evidence of biological link between ISP and SNSCC. *EGFR* mutations were not found in exophytic papillomas, oncocytic papillomas or SNSCC without known ISP association, suggesting that ISP and associated SNSCC are biologically distinct from these other sinonasal tumors. We also showed that *EGFR* mutation status in ISP was an independent prognostic factor for progression to SNSCC. Finally, ISP-associated SNSCC cells showed increased EGFR signaling, which could be blocked using irreversible EGFR inhibitors causing potent growth inhibition.

Importantly, the pathogenesis of *EGFR* wild-type ISP and ISP-associated SNSCC remains uncertain and the relationship between *EGFR* mutations and HPV infection status in these tumors has never been explored. In this study, we sought to evaluate the association and clinical significance of *EGFR* mutations and HPV infection in a large retrospective cohort of ISP and ISP-associated SNSCC at our institution.

Patients and methods

Case selection

This study was approved by the Institutional Review Board at the University of Michigan Medical School. An unselected cohort of ISP and SNSCC cases was retrospectively identified from pathology records at Michigan Medicine: 58 ISP, 22 ISP-associated SNSCC (including 13 matched ISP/SNSCC pairs), and 14 SNSCC without clinical or pathologic evidence of associated ISP (SNSCC without known ISP association). Four exophytic sinonasal papillomas (ESP) and 27 oncocytic sinonasal papillomas (OSP) were also selected. The majority of the cases in this cohort were reported in two previous studies [10–12]. All diagnoses were confirmed by experienced head and neck pathologists (AMU and JBM).

Tissue extraction and DNA isolation

Representative non-decalcified formalin-fixed paraffin-embedded (FFPE) tissue was obtained for each case, and areas for extraction were designated by experienced head and neck pathologists (AMU and JBM). FFPE tissue was macrodissected from 10-μm sections on glass slides, and DNA was extracted using the Pinpoint Slide DNA Isolation System (Zymo Research, Irvine, CA) according to the manufacturer's instructions. For ISP and SNSCC cases, areas of extraction were required to contain at least 30% tumor nuclei.

EGFR mutation status

Samples were examined for the presence of *EGFR* mutations using bi-directional Sanger sequencing and nested primers spanning exons 18, 19, 20, and 21, as described previously [10].

HPV infection status

Samples were examined for the presence of HPV DNA using GP5+/GP6+ consensus primers for L1 (~150 bp product) [13]. Specimen adequacy was determined using PCO3/KM38 primers for β-globin (167 bp product) [14]. PCR products were evaluated by capillary electrophoresis using an Applied Biosystems 3130 Genetic Analyzer. Samples with a GP5+/6+ PCR product were deemed positive and subsequently evaluated by Sanger sequencing using the same primers. Samples were deemed negative if there was no GP5+/6+ PCR product and there was adequate amplification of β-globin [≥7000 relative fluorescence units (RFU)]. HPV subtypes were determined based on the L1 sequence using the NCBI Basic Local Alignment Search Tool (http://blast.ncbi.nlm.nih.gov/Blast.cgi (15 November 2017, date last acessed)).

Statistical analysis

All statistical analyses were carried out in Excel (Microsoft, Redmond, WA) using the XLSTAT package (Addinsoft SARL, Paris, France). Fisher's exact and χ^2 tests (as indicated) were utilized to examine associations between *EGFR* mutation and HPV infection status and categorical clinicopathologic parameters (i.e. gender, smoking history, and progression to SNSCC), while the relationship between *EGFR* mutation and HPV infection status was explored using the Student's *t*-test. Progression-free survival analysis was carried out for patients diagnosed with ISP as described previously [10]. One patient without clinical follow-up was excluded from analysis. Given the 100% concordance between *EGFR* mutation and HPV status in paired ISP and associated SNSCC samples ([10] and see below), metachronous ISP-associated SNSCC without available ISP material included in the survival analysis were assumed to have the same *EGFR* and HPV status as the corresponding sequenced SNSCC. The Kaplan–Meier (log-rank) method was utilized to examine the association between *EGFR* mutation and HPV infection status and time to development of SNSCC, and univariate Cox regression analysis was used to estimate hazard ratios (HR) for progression. A P-value <0.05 was considered statistically significant.

Results

We previously identified *EGFR* mutations in 44 (88.0%) of the 50 ISP and 17 (77.3%) of the 22 ISP-associated SNSCC; no *EGFR* mutations were identified in any of the 20 SNSCC without known ISP association [10]. Forty-seven (94.0%) ISP, 21 (95.5%) ISP-associated SNSCC, and 13 (65.0%) SNSCC without known ISP association from this previous cohort were available for assessment of HPV status and included in this study. Eleven additional ISP cases were also included in this study, and nine (81.8%) were found to harbor an *EGFR* mutation; one additional ISP-associated SNSCC and one additional SNSCC without known ISP association were also included, and neither had an *EGFR* mutation. Therefore, in the current cohort, *EGFR* mutations were identified in 53 (91.4%) of 58 ISP and 17 (77.3%) of 22 ISP-associated SNSCC, while no *EGFR* mutations were identified in any of the 14 SNSCC without known ISP association (Tables 1 and 2; supplementary Table S1, available at *Annals of Oncology* online). HPV DNA was detected in 6 (10.3%) of 58 ISP, 5 (22.7%) of 22 ISP-associated SNSCC, and 5 (35.7%) of 14 SNSCC without known ISP association (Figure 1); all 4 (100.0%)

Table 1. Clinicopathologic characteristics of inverted sinonasal (Schneiderian) papillomas, stratified by EGFR mutation and HPV infection status

Clinicopathologic parameter		*EGFR*^{mut}/HPV^{neg} ($n = 53$)	*EGFR*^{wt}/HPV^{pos} ($n = 5$)	*P*-value
Age at initial diagnosis (years)	Mean	50.8	46.2	0.515
	Median	50	47	
	Min	26	24	
	Max	84	62	
Gender	Female	9 (17.0%)	2 (40.0%)	0.209
	Male	44 (83.0%)	3 (60.0%)	
Smoking history	Current/Former	33 (62.3%)	4 (80.0%)	0.678
	Never	19 (35.8%)	1 (20.0%)	
	Unknown	1 (1.9%)	0 (0.0%)	
Associated sinonasal squamous cell carcinoma	Yes	11 (20.8%)	3 (60.0%)	0.050
	No	42 (79.2%)	2 (40.0%)	
Human papillomavirus (HPV) status	Positive	0 (0.0%)	5 (100.0%)	**<0.0001**
	Negative	53 (100.0%)	0 (0.0%)	

Mut, mutant; wt, wild-type; pos, positive; neg, negative.
Statistically significant P-value in bold.

Table 2. Clinicopathologic characteristics of sinonasal squamous cell carcinoma (SNSCC), stratified by inverted sinonasal (Schneiderian) papilloma (ISP) association

Clinicopathologic parameter		ISP-associated SNSCC ($n = 22$)	SNSCC without known ISP association ($n = 14$)	*P*-value
Age at initial diagnosis (years)	Mean	53.8	61.9	**0.006**
	Median	54	65	
	Min	34	28	
	Max	72	76	
Gender	Female	8 (36.4%)	5 (35.7%)	0.968
	Male	14 (63.6%)	9 (64.3%)	
Smoking history	Current/Former	18 (81.8%)	12 (85.7%)	1.000
	Never	3 (13.6%)	2 (14.3%)	
	Unknown	1 (4.6%)	0 (0.0%)	
EGFR mutation status	Mutant	17 (77.3%)	0 (0.0%)	**<0.0001**
	Wild type	5 (22.7%)	14 (100.0%)	
Human papillomavirus (HPV) status	Positive	5 (22.7%)	5 (35.7%)	0.396
	Negative	17 (77.3%)	9 (64.3%)	
Low-risk HPV subtype status	Positive	4 (18.2%)	0 (0.0%)	0.118
	Negative	18 (81.8%)	13 (92.9%)	
	Unknown	0 (0.0%)	1 (7.1%)	
High-risk HPV subtype status	Positive	1 (4.5%)	4 (28.6%)	**0.024**
	Negative	21 (95.5%)	9 (64.3%)	
	Unknown	0 (0.0%)	1 (7.1%)	

Statistically significant P-value in bold.

ESP but none (0.0%) of the 27 OSP harbored HPV DNA. Importantly, all ISP and ISP-associated SNSCC harbored either an *EGFR* mutation or HPV DNA. In addition, *EGFR* mutations and HPV infection were mutually exclusive in ISP-associated SNSCC and showed a strong negative correlation in both ISP ($P < 0.0001$) and ISP-associated SNSCC ($P < 0.0001$).

Only a single case of ISP was found to have both an *EGFR* mutation (P772_H773insTNR) and evidence of HPV DNA. However, the HPV product in this sample was low-level (870 RFU) in spite of a strong β-globin product (8070 RFU), nearly 100% neoplastic cells in the extracted sample, and an *EGFR* variant allele frequency of ~50%. The observed HPV positivity was also significantly lower than other positive samples (all ≥6000 RFU). Sample contamination was excluded by re-extracting this sample and confirming low-level HPV positivity (1120 RFU). To determine whether the low-level HPV positivity in this sample reflected transient infection/incidental colonization, a separate ISP sample from this patient collected 5 years prior was evaluated. This sample was negative for HPV in spite of a high percentage of neoplastic cells in the extracted sample and a high β-globin

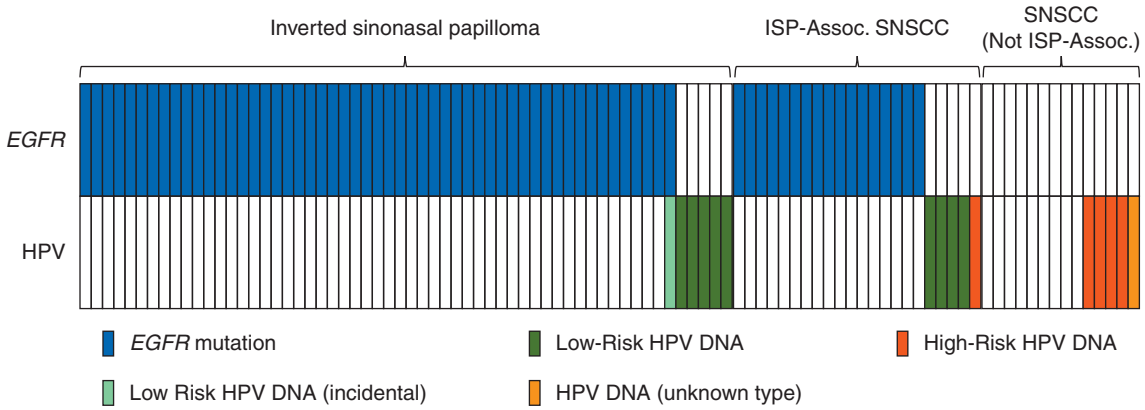

Figure 1. *EGFR* mutations and HPV infection are essential, mutually exclusive oncogenic events in inverted sinonasal papillomas and associated sinonasal squamous cell carcinomas. Frequency of *EGFR* mutations (blue), low-risk HPV DNA (green), and high-risk HPV DNA (red) in inverted sinonasal papilloma (ISP), ISP-associated sinonasal squamous cell carcinoma (ISP-Assoc. SNSCC) and sinonasal squamous cell carcinoma without a known ISP associated [SNSCC (Not ISP-Assoc.)]. A single case of ISP demonstrated both an *EGFR* mutation and transient, low-level HPV DNA that likely reflects incidental HPV colonization (light green). HPV subtype was unknown for one SNSCC (Not ISP-Assoc.; yellow).

product (7854 RFU). In contrast, high-level HPV positivity was detected in temporally distinct samples from three $EGFR^{wt}$/HPV^{pos} cases (two ISP-associated SNSCC and one ISP) separated by 1, 8, and 9 years, respectively.

HPV-associated ISP were more frequently associated with synchronous or metachronous SNSCC ($P = 0.05$), although there were no significant differences in gender, age at initial diagnosis, or smoking history in patients with *EGFR*-mutant or HPV-associated ISP (Table 1). Progression to SNSCC was significantly associated with the presence of HPV infection and the absence of an *EGFR* mutation [log-rank = 9.620, $P = 0.002$; univariate HR = 14.358 (95% confidence interval = 1.631–126.429); $P = 0.016$]. Patients with ISP-associated SNSCC presented at an earlier age than those with SNSCC without known ISP association (median age at diagnosis 54 versus 65 years, respectively; $P = 0.003$). There were no significant differences in gender or smoking history (Table 2).

All ISP with detectable HPV DNA harbored low-risk subtypes (two subtype 6 and four subtype 11). Four (80.0%) of the 5 ISP-associated SNSCC with detectable HPV DNA harbored low-risk subtypes (two subtype 6 and two subtype 11), while high-risk HPV subtype 16 was detected in only one ISP-associated SNSCC. By comparison, four HPV+ SNSCC without any known ISP association harbored high-risk subtypes (two subtype 16, one subtype 18, and one subtype 33); L1 Sanger sequencing failed in one tumor. Altogether, high-risk HPV DNA was significantly more likely to be detected in SNSCC without known ISP association than in ISP-associated SNSCC ($P = 0.024$), while low-risk HPV DNA was more common in ISP-associated SNSCC ($P = 0.118$). Finally, paired ISP and associated SNSCC samples were available from 13 patients (2 metachronous, 9 synchronous, and 2 synchronous and metachronous), and importantly, all patients showed concordant *EGFR* genotypes, HPV status, and (if positive) HPV subtype (Table 3).

Discussion

This is the first study to examine the relationship between *EGFR* mutations and HPV infection status in ISP and SNSCC. The importance of *EGFR* and HPV is highlighted by the fact that all ISP and ISP-associated SNSCC harbored either an activating *EGFR* mutation or high-level HPV DNA positivity. In addition, we found that *EGFR* mutations and HPV infection are strongly and negatively correlated in both ISP and ISP-associated SNSCC ($P < 0.0001$). We identified only a single ISP patient (<2% of the cohort) that harbored both an *EGFR* mutation (P772_H773insTNR) and HPV infection (low-risk subtype 11). However, previous studies have detected HPV colonization in 4% and 7% of inflammatory nasal polyps and normal sinonasal mucosa, respectively [7]. Given the reported incidence of HPV colonization, a single case of incidental HPV colonization in a cohort of 68 patients with ISP/ISP-associated SNSCC is not an unexpected finding. While HPV PCR positivity was confirmed in multiple extractions from this sample, HPV DNA was detected at an extremely low level—significantly lower than that of every other HPV positive samples in spite of a high neoplastic content and a high-level *EGFR* variant allele frequency. In addition, an ISP specimen collected 5 years prior from the same patient was negative for HPV DNA while other HPV positive cases showed durable, high-level positivity over as long as nine years. These collective findings suggest that this case does indeed reflect transient incidental HPV colonization in an ISP driven by an oncogenic *EGFR* mutation and that *EGFR* mutations and true oncogenic HPV infection *are* mutually exclusive. Regardless, our results strongly suggest that activating *EGFR* mutations and HPV infection are alternative oncogenic mechanisms for the development of ISP [15].

In this study, HPV DNA was detected in 10.3% of ISP and 22.7% of ISP-associated SNSCC. While the frequency of HPV in SNSCC without an ISP association (35.7%) is similar to frequencies reported in SNSCC as a whole [8], the frequency of HPV-associated ISP in this study appears to be significantly lower than the frequency reported in a recent meta-analysis (38%) [7]. The reason for this discrepancy is uncertain. However, there appears to be tremendous variability in the reported HPV positivity rate in various studies. This may reflect HPV detection methodology differences such as limit of detection or comprehensiveness for various HPV subtypes. Indeed, the incidence of apparent

Table 3. EGFR genotype and HPV status for matched pairs of inverted sinonasal papilloma with synchronous or metachronous sinonasal squamous cell carcinoma

Patient	Synchronous/metachronous	Inverted sinonasal papilloma		Sinonasal squamous cell carcinoma	
		EGFR genotype	HPV subtype	*EGFR* genotype	HPV subtype
1	Both	WT	HPV 11	WT	HPV 11
2	Synchronous	D770_N771insGL	Negative	D770_N771insGL	Negative
3	Synchronous	D770_N771insSVE	Negative	D770_N771insSVE	Negative
4	Metachronous	N771_H773dup	Negative	N771_H773dup	Negative
5	Synchronous	S768_D770dup	Negative	S768_D770dup	Negative
6	Synchronous	D770_N771insGD	Negative	D770_N771insGD	Negative
7	Both	WT	HPV 6	WT	HPV 6
8	Synchronous	N771_P772insV	Negative	N771_P772insV	Negative
9	Synchronous	S768_D770dup	Negative	S768_D770dup	Negative
10	Synchronous	N771_H773dup	Negative	N771_H773dup	Negative
11	Metachronous	S768_D770dup	Negative	S768_D770dup	Negative
12	Synchronous	N771delinsGF	Negative	N771delinsGF	Negative
13	Synchronous	S768_D770dup	Negative	S768_D770dup	Negative

incidental colonization in this study is lower than that reported in some other studies. However, geographic differences in the incidence of HPV as a whole may also explain the observed variability in ISP HPV positivity. These environmental factors may also affect the relative proportions of ISP patients with *EGFR* mutations versus HPV infection, as well as the local incidence of ISP and SNSCC.

Our evaluation of patients with paired ISP and associated SNSCC samples not only demonstrated concordant *EGFR* genotypes as previously described [10], but also concordant HPV status and (when positive) HPV subtyping (see Table 3). These findings add further support to the notion that ISP and SNSCC are clonally related and that ISP can be a precursor for SNSCC.

Similar to previous studies, our results show that HPV-associated ISP and ISP-associated SNSCC predominantly carry low-risk subtypes [7, 12], in contrast to SNSCC without known ISP association, which frequently harbor high-risk subtypes [16]. Along with the absence of *EGFR* mutations in SNSCC without an associated ISP, these findings provide further evidence that ISP/ISP-associated SNSCC are biologically distinct from other sinonasal squamous neoplasms. In addition, our findings suggest that papillary sinonasal tumors that harbor high-risk HPV subtypes are only rarely ISP or ISP-associated SNSCC, and thus, cases of high-risk HPV-associated 'ISP with dysplasia' should be examined carefully by pathologists to find convincing morphologic evidence of conventional ISP.

While high-risk HPV subtypes typically promote oncogenic transformation through the actions of E6 and E7 oncoproteins on the p53 and RB pathways, respectively, low-risk HPV subtypes generally lack strong E6 and E7 oncoprotein function [17]. In tumors harboring low-risk HPV subtypes, the E5 oncoprotein is thought play an important role in oncogenic transformation, and one of the major effects of the E5 oncoprotein is enhanced endogenous EGFR pathway signaling via inhibition of EGFR degradation, alteration of endosomal EGFR trafficking, and activation of downstream proteins (including MAPK and ERK1/2) [18]. Interestingly, our group has previously shown that EGFR protein expression is significantly higher in HPV-associated ISP compared with ISP without HPV infection [12]. Given the universal presence of either an *EGFR* mutation or HPV DNA in our cohort, EGFR pathway activation appears to play an essential role in the pathogenesis of ISP and associated SNSCC. We previously showed that treatment of EGFR-mutated ISP-associated SNSCC cells with irreversible tyrosine kinase inhibitors results in inactivation of EGFR signaling and growth inhibition [10]. Further studies are needed to determine whether EGFR pathway activation can be targeted in HPV-driven ISP/SNSCC and if EGFR targeted therapies can be successfully applied clinically. Our data provide a rational basis for exploring such therapies in ISP patients with locally aggressive, unresectable disease and in ISP-associated SNSCC.

Clinicopathologic risk factors and the molecular pathogenesis of ISP progression to SNSCC is not currently well understood [19]. In our previous study, we reported that *EGFR* mutation status was a prognostic risk factor for ISP malignant transformation, with *EGFR* mutated tumors being significantly less likely to progress to SNSCC [10]. This negative association of EGFR mutation with progression to SNSCC was also observed in the current study, while correspondingly, HPV positivity was associated with progression (Figure 2). HPV infection and genomic integration has previously been implicated as a risk factor for ISP malignant transformation in a number of studies [1, 12, 20]. A recent meta-analysis demonstrated that HPV infection is a significant risk factor for ISP progression to SNSCC, with a pooled odds ratio of 2.16 [9]. Therefore, the apparent negative association of *EGFR* mutations and progression may reflect the mutual exclusivity of *EGFR* mutations and oncogenic HPV infection. Additional molecular analysis of paired ISP and associated SNSCC are needed to determine the mechanisms of malignant transformation in both HPV-associated tumors and those without HPV infection.

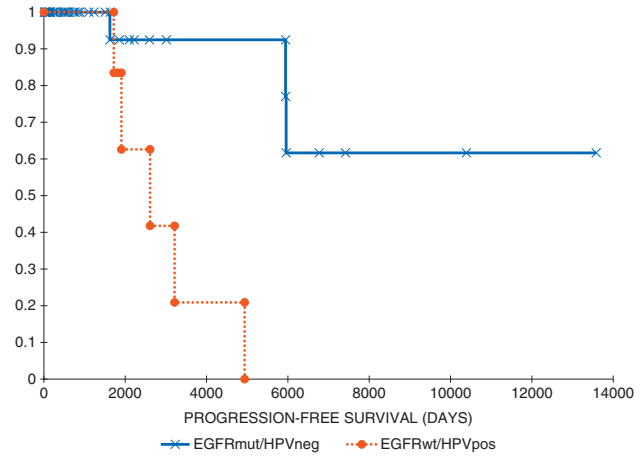

Figure 2. *EGFR* wild-type, HPV positive inverted sinonasal papillomas are associated with increased progression to sinonasal squamous cell carcinoma. Progression-free survival (in days) for *EGFR* mutated, HPV negative ($EGFR^{mut}$/HPV^{neg}) and *EGFR* wild type, HPV positive ($EGFR^{wt}$/HPV^{pos}) ISP using the Kaplan–Meier method [log-rank = 9.620, $P = 0.002$; univariate HR = 14.358 (95% confidence interval = 1.631–126.429); $P = 0.016$]. The single case of *EGFR* mutated, weakly HPV positive ISP was assumed to represent incidental HPV colonization and was allocated to the $EGFR^{mut}$/HPV^{neg} category.

We have shown that *EGFR* mutations and HPV infection represent alternate oncogenic mechanisms in all evaluated cases of ISP and ISP-associated SNSCC. These early etiologic events may have important prognostic and potential targeted therapeutic implications for the clinical management of the ISP/ISP-associated SNSCC disease spectrum, which could be explicitly explored in future studies.

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Disclosure

The authors have declared no conflicts of interest.

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