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ORIGINAL ARTICLE

High-risk human papillomavirus 16/18 associated with improved survival in sinonasal squamous cell carcinoma

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Abstract

Background: There has been conflicting evidence on the independent prognostic role of human papillomavirus (HPV) status in sinonasal cancer. The objective of this study was to assess whether the survival of patients with sinonasal cancer differs based on various HPV statuses, including HPV-negative, positive for the high-risk HPV-16 and HPV-18 (HPV16/18) subtypes, and positive for other high-risk and low-risk HPV subtypes.

Methods: In this retrospective cohort study, data from the National Cancer Database were extracted from the years 2010–2017 for patients who had primary sinonasal cancer (N = 12,009). The outcome of interest was overall survival based on HPV tumor status.

Results: Study included an analytic cohort of 1070 patients with sinonasal cancer who had confirmed HPV tumor status (732 [68.4%] HPV-negative; 280 [26.2%] HPV16/18-positive; 40 [3.7%] positive for other high-risk HPV; and 18 [1.7%] positive for low-risk HPV). HPV-negative patients had the lowest all-cause survival probability at 5 years postdiagnosis (0.50). After controlling for covariates, HPV16/18-positive patients had a 37% lower mortality hazard than HPV-negative patients (adjusted hazard ratio, 0.63; 95% confidence interval [CI], 0.48–0.82). Patients aged 64–72 years (crude prevalence ratio, 0.66; 95% CI, 0.51–0.86) and 73 years and older (crude prevalence ratio, 0.43; 95% CI, 0.31–0.59) presented with lower rates of HPV16/18-positive sinonasal cancer than those aged 40–54 years. In addition, Hispanic patients had a 2.36 times higher prevalence of non-HPV16/18 sinonasal cancer than non-Hispanic White patients.

Conclusions: These data suggest that, for patients with sinonasal cancer, HPV16/18-positive disease may confer a significant survival advantage compared with HPV-negative disease. Other high-risk and low-risk HPV subtypes have survival rates similar to the rates for HPV-negative disease. HPV status might be an important independent prognostic factor in sinonasal cancer that could be used in patient selection and clinical decisions.

The last two authors contributed equally to this article as co-senior author.

KEYWORDS
cancer survival, high-risk human papillomavirus, human papillomavirus (HPV), human papillomavirus 16/18, National Cancer Database (NCDB), sinonasal cancer

INTRODUCTION

Sinonasal cancer is rare, accounting for <3% of all head and neck malignancies, with an incidence rate of less than one case per 100,000.[1–4] Despite the rarity, sinonasal cancer warrants study because of the tumor's location in close proximity to skull base, orbits, and central nervous system, which accounts for difficult management and poor survival outcomes.[3,5,6] Whereas the traditional risk factors include tobacco use, alcohol use, and occupational exposure to carcinogens,[7] a proportion of cases have also been linked to human papillomavirus (HPV).[8–10]

Up to 32% of patients with sinonasal cancer test positive for HPV,[11,12] underscoring the importance of establishing HPV's prognostic significance. Of the >200 HPV subtypes, there are at least 12 oncogenic types found in the oral mucosa that are considered high-risk.[13,14] Of these types, HPV-16 and HPV-18 (HPV16/18) are the most common subtypes found in biopsies of head and neck squamous cell carcinoma[15] and have a clear etiologic role specifically within the oropharynx.[16,17]

The possibility of HPV playing a causal role in sinonasal cancer warrants further investigation. HPV is now accepted as the leading cause of oropharyngeal cancers and confers a better survival rate than HPV-negative oropharyngeal cancers.[18] Generally, HPV has not been proven to be a common driver of oncogenesis in non-oropharyngeal head and neck cancers and is not independently associated with prognosis when accounting for demographic differences.[19] Recent evidence, including meta-analyses, suggests differential survival of nonoropharyngeal head and neck cancer sites based on HPV status, although evidence is mixed.[20–24]

For example, in sinonasal cancers, several studies have found no significant survival advantage in HPV-positive patients compared with HPV-negative patients, whereas several other studies did conclude a significant mortality benefit.[20–24] These differences might be attributable to the patient demographics in each study or the heterogeneity in HPV testing methods and classifications.[25] If HPV can directly affect survival, then the presence of high-risk subtypes, known to cause cancer in other sites, should differ from that of low-risk HPV[26] despite similar demographic profiles. Prior studies specifically addressing high-risk HPV did not assess its effect on survival or were underpowered to detect a difference.[24,27] To date, no studies have analyzed the survival of patients with low-risk HPV in sinonasal cancer.

The objective of the current study was to expand upon the current literature and assess whether HPV positivity, and particularly HPV16/18 positivity, is associated with overall survival, which would provide further support for the hypothesis that high-risk HPV is causative in some sinonasal cancers. Extrapolating from HPV-associated oropharyngeal disease[18,27,28] and the available literature on HPV-associated sinonasal cancer,[20–25,27–29] we hypothesized that survival prognosis based on HPV status is driven by the high-risk HPV16/18-positive group. Furthermore, we hypothesized that patients who have sinonasal tumors with low-risk HPV subtypes will have survival similar to that of patients who have HPV-negative tumors, despite having demographics similar to those with HPV-positive cancer.

MATERIALS AND METHODS

Study population

This study included patients in the National Cancer Database (NCDB) from the American Cancer Society and the Commission on Cancer of the American College of Surgeons.[30] The NCDB, established in 1989, is a nationwide, hospital-based database that captures 72% of annual incident cancers in the United States. The NCDB is made available to Commission on Cancer-accredited hospitals included in the database through a data use agreement. The American Cancer Society and the Commission on Cancer have not confirmed the analysis or conclusions of this study. Because NCDB data are deidentified, this study did not require additional review from the St Louis University and Duke University Institutional Review Boards.

Patients diagnosed with sinonasal cancer as their only cancer (sequence number 00) from the years 2010–2017 were included; 2010 was the first year patients with sinonasal cancer had HPV status recorded. Sinonasal cancers included cases with an *International Classification of Diseases for Oncology*, third edition (ICD-O-3) primary site of nasal cavity (C30.0) or sinuses (C31.0-C31.9). Records were excluded if they had unknown or unspecific HPV status, noninvasive behavior (in situ behavior/stage 0/tumor size 0 millimeters), nonsquamous histology (ICD-O-3 histology values outside 8050–8076, 8078, 8083, 8084, and 8094), non-microscopically confirmed histology, a diagnosis that was done at the reporting facility with all treatment decisions made elsewhere, were aged birth to 39 years (facility type was not captured for those ages), or were missing survival information (Figure 1).

Category definitions

The main variable of interest was HPV status of sinonasal cancer, which was based on testing for HPV performed on pathologic

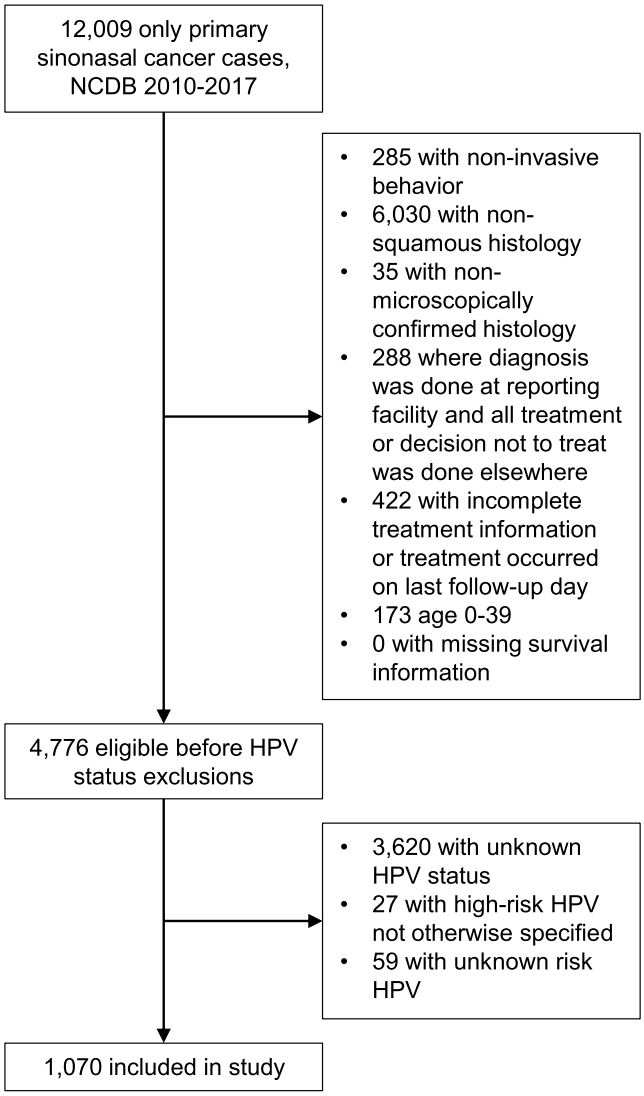

FIGURE 1 Selection criteria and flowchart. HPV indicates human papillomavirus; NCDB, National Cancer Database.

specimens, including lymph nodes, from a primary or metastatic site.[31] *HPV16/18* indicated that the tumor tested positive for subtypes 16 and/or 18. *Other high-risk HPV* indicated that the tumor did not test positive for subtypes 16 or 18 but tested positive for at least one other high-risk subtype (26, 31, 33, 35–36, 45, 51–53, 56, 58–59, 66–70, 73, 82, 85). *Low-risk* indicated that the tumor only tested positive for at least one subtype associated with a low risk of developing sinonasal cancer (6, 11, 32, 34, 40, 42, 44, 54, 61–62, 64, 71, 72, 74, 81, 83, 84, 87, 89). *Negative* indicated that the tumor tested negative for any subtype, tested negative for high-risk subtypes with no mention of low-risk subtypes, or tested negative with no further explanation.

Other clinical and sociodemographic characteristics were also included. Patient-level sociodemographic variables included age at diagnosis in year quartiles (ages 40–54, 55–63, 64–72 years, 73 years and older), sex (woman/man), race/ethnicity (Hispanic, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, non-Hispanic White, and non-Hispanic other/unknown; patients with unknown ethnicity were assumed to be non-Hispanic), year of diagnosis, and insurance status at diagnosis (not insured, private insurance/managed care, Medicaid, Medicare, other government insurance, unknown). County-level variables based on patients' county of residence included population density (metropolitan, nonmetropolitan, unknown) and median household income quartiles (<$40,227, $40,227–$50,353, $50,354–$63,332, ≥$63,333, unknown). Clinical variables included facility type (community cancer program, comprehensive community cancer program, academic/research program, integrated network cancer program), sinonasal cancer site (nasal cavity, paranasal sinus), subtype of squamous cell carcinoma based on ICD-O-3 code (basaloid [8083, 8094], keratinizing [8071], nonkeratinizing [8072–8073], papillary [8050, 8052], not otherwise specified [8051, 8053, 8054, 8070, 8074–8076, 8078, 8084]), the American Joint Committee on Cancer, 7th edition stage at presentation (I, II, II, IV, not applicable, unknown), ICD-O-3 tumor grade/differentiation (grade 1: well differentiated; differentiated NOS; grade 2: moderately differentiated; grade 3: poorly differentiated; and grade 4: undifferntiated; anaplastic) surgery (yes, no/unknown), radiation (yes, no/unknown), chemotherapy (yes, no/unknown), Charlson–Deyo comorbidity score (0, 1, 2, ≥3),[32] and all-cause mortality after sinonasal cancer diagnosis at 5 years.

Analysis

Patient characteristics were summarized using counts and percentages. All-cause survival stratified by HPV status was plotted using Kaplan–Meier curves. By using univariable Cox proportional hazards regression models, crude hazard ratios (cHRs) with 95% confidence intervals (CIs) estimated the association of all sociodemographic and clinical characteristics with all-cause mortality. A multivariable Cox proportional hazards model provided adjusted hazard ratios (HRs) with 95% CIs to control for the effects of all sociodemographic and clinical variables in the association of HPV status with all-cause mortality. For all survival analyses, patients were censored if they were alive 5 years postdiagnosis or at their last follow-up if they did not have 5 years of follow-up time. Univariable Poisson regression models with robust standard errors were used to estimate the association of all sociodemographic variables (except year) and nontreatment-related clinical variables with the prevalence of HPV16/18 or low-risk and other high-risk HPV subtypes (referred to as *non-HPV16/18*) compared with HPV-negative status. In addition, χ^2 test p values are provided for these associations (see Table S1). Poisson models also compared the prevalence of receiving surgery, radiation, and chemotherapy among HPV16/18-positive and non-HPV16/18–positive patients with HPV-negative patients. The Poisson models provided crude prevalence ratios (cPRs) and 95% CIs. Analyses were conducted using SAS version 9.4 (SAS Institute Inc.). All analyses were two-tailed with significance set at $\alpha = .05$.

RESULTS

Patient characteristics

The study cohort consisted of 1070 patients with sinonasal cancer. Most patients were HPV-negative (68.4%), followed by HPV16/18-positive (26.2%), positive for other high-risk HPV subtypes (3.7%), and positive for low-risk HPV subtypes (1.7%). Most patients were men (64.7%), non-Hispanic White (76.8%), and lived in metropolitan areas (83.9%). The most common type of insurance was Medicare (44.1%) followed by private insurance/managed care (40.3%). The average age at sinonasal cancer diagnosis was 64.2 years (Table 1).

Survival

Within 5 years postdiagnosis, 40.2% of patients died, 31.0% were censored before 5 years, and 28.8% were confirmed to have remained alive. Patients with HPV-negative sinonasal cancer had the lowest all-cause survival probability at 5 years postdiagnosis (0.50; 95% CI, 0.46–0.54) followed by those with other high-risk HPV subtypes (all-cause survival probability, 0.60; 95% CI, 0.42–0.74), low-risk HPV subtypes (all-cause survival probability, 0.63; 95% CI, 0.35–0.81), and HPV16/18 (all-cause survival probability, 0.70; 95% CI, 0.63–0.76). No HPV status reached median survival (Figure 2 and Figure S1). In crude analysis, patients who were positive for HPV16/18 had a 52% lower mortality hazard than HPV-negative patients (cHR, 0.48; 95% CI, 0.37–0.62). After controlling for covariates, HPV16/18-positive patients had a 37% lower mortality hazard than HPV-negative patients (adjusted HR, 0.63; 95% CI, 0.48–0.82). Patients who were positive for low-risk and other high-risk HPV subtypes did not have a significantly different mortality hazard than HPV-negative patients (Table 1).

HPV prevalence

Patients with sinonasal cancer aged 64–72 years (cPR, 0.66; 95% CI, 0.51–0.86) and 73 years or older (cPR, 0.43; 95% CI, 0.31–0.59) had a lower HPV16/18-positive versus HPV-negative prevalence than those aged 40–54 years. Men had a 36% higher HPV16/18-positive versus HPV-negative prevalence than women (cPR, 1.36; 95% CI, 1.09–1.71). The prevalence of non-HPV16/18–positive versus HPV-negative cancer among Hispanic patients was 2.36 times higher than that for non-Hispanic White patients (cPR, 2.36; 95% CI, 1.21–4.59). The prevalence of HPV16/18-positive versus HPV-negative cancer was 39% lower among non-Hispanic Black patients than among non-Hispanic White patients (cPR, 0.61; 95% CI, 0.40–0.93). The HPV16/18-positive versus HPV-negative prevalence among patients with Medicare was 28% lower than that for patients with private insurance/managed care (cPR, 0.72; 95% CI, 0.58–0.90). The HPV16/18-positive versus HPV-negative prevalence among patients in the third quartile (cPR, 1.69; 95% CI, 1.18–2.42) and the fourth quartile (cPR, 1.55; 95% CI, 1.09–2.19) of median county-level household income was higher than that for patients in the first quartile. Patients who had sinus cancer had both a lower HPV16/18-positive versus HPV-negative prevalence (cPR, 0.51; 95% CI, 0.41–0.62) and lower non-HPV16/18–positive versus HPV-negative prevalence (cPR, 0.57; 95% CI, 0.34–0.93) than patients who had nasal cavity cancer. Patients who had basaloid (cPR, 2.26; 95% CI, 1.70–3.01), nonkeratinizing (cPR, 1.54; 95% CI, 1.18–2.00), and papillary sinonasal cancer (cPR, 1.85; 95% CI, 1.20–2.83) had a higher HPV16/18-positive versus HPV-negative prevalence than patients who had squamous cell cancer not otherwise specified, and patients who had papillary cancer had a higher non-HPV16/18–positive versus HPV-negative prevalence than those who had squamous cell cancer not otherwise specified (cPR, 3.17; 95% CI, 1.24–8.14). Patients with stage II cancer had a 50% higher HPV16/18-positive versus HPV-negative prevalence than those with stage I cancer (cPR, 1.50; 95% CI. 1.11–2.03). Patients with grade 2 (cPR, 3.90; 95% CI, 1.87–8.13), grade 3 (cPR, 4.68; 95% CI, 2.25–9.72), or unknown grade cancer (cPR, 4.80; 95% CI, 2.28–10.11) had a higher HPV16/18-positive versus HPV-negative prevalence than patients with grade 1 cancer, and patients with unknown grade had a higher non-HPV16/18–positive versus HPV-negative prevalence than those with grade 1 cancer (cPR, 5.62; 95% CI, 1.32–23.90; Table 2).

Treatment

Patients with HPV16/18-positive or non-HPV16/18–positive sinonasal cancer did not receive surgery at a different rate than HPV-negative patients. However, HPV16/18-positive patients were 12% more likely to receive radiation (cPR, 1.12; 95% CI, 1.03–1.23) and 24% more likely to receive chemotherapy (cPR, 1.24; 95% CI, 1.06–1.45) than HPV-negative patients (Table 3).

DISCUSSION

The primary objective of this study was to determine associations between specific HPV subtypes and overall survival in a cohort of patients with sinonasal cancer. Although several studies have previously analyzed the survival differences of patients with sinonasal cancer based on HPV-positive or HPV-negative status,[20–24] the role of high-risk versus low-risk HPV subtypes was unclear.[27] Our results showed that patients with high-risk HPV16/18 positivity had superior overall survival compared with HPV-negative patients even after controlling for covariates. In addition, other HPV-positive cohorts who are demographically similar to HPV16/18-positive patients had survival similar to the poor outcomes of HPV-negative patients. These findings support the idea of high-risk HPV16/18 as an important, independent prognostic factor in sinonasal squamous cell carcinoma and may have a causative role similar to other cancer sites.

To date, no studies have assessed the sociodemographic features of patients who present specifically with HPV16/18 subtypes of

TABLE 1 Characteristics of patients with sinonasal cancer and regression models estimating all-cause mortality.

	Total (*N* = 1070), No. (%)	Crude HR (95% CI)	Adjusted HR (95% CI)
HPV status			
Negative	732 (68.4)	Reference	Reference
HPV16/18	280 (26.2)	0.48 [0.37–0.62]	0.63 [0.48–0.82]
Other high-risk HPV	40 (3.7)	0.82 [0.49–1.37]	1.12 [0.65–1.91]
Low-risk HPV	18 (1.7)	0.73 [0.33–1.63]	0.92 [0.39–2.14]
Age quartile			
First, 40–54 years	255 (23.8)	Reference	Reference
Second, 55–63 years	282 (26.4)	1.21 [0.90–1.62]	1.34 [0.99–1.82]
Third, 64–72 years	261 (24.4)	1.19 [0.88–1.60]	1.28 [0.89–1.85]
Fourth, ≥73 years	272 (25.4)	2.32 [1.77–3.03]	2.23 [1.56–3.21]
Sex			
Women	378 (35.3)	Reference	Reference
Men	692 (64.7)	1.18 [0.97–1.45]	1.37 [1.11–1.69]
Race/ethnicity			
NH/U White	822 (76.8)	Reference	Reference
Hispanic	73 (6.8)	0.88 [0.58–1.33]	0.74 [0.48–1.14]
NH/U Asian/Pacific Islander	39 (3.6)	2.06 [1.35–3.14]	1.76 [1.10–2.81]
NH/U Black	111 (10.4)	1.22 [0.90–1.64]	0.90 [0.65–1.24]
NH/U other/unknown	25 (2.3)	1.25 [0.68–2.27]	1.25 [0.65–2.38]
Year of diagnosis			
2017	181 (16.9)	Reference	Reference
2010	41 (3.8)	1.25 [0.72–2.17]	1.28 [0.72–2.27]
2011	102 (9.5)	1.75 [1.19–2.57][a]	1.74 [1.15–2.63][a]
2012	129 (12.1)	1.37 [0.94–2.01]	1.19 [0.80–1.77]
2013	146 (13.6)	1.58 [1.10–2.27][a]	1.64 [1.12–2.39][a]
2014	148 (13.8)	1.53 [1.07–2.20][a]	1.46 [1.004–2.13][a]
2015	164 (15.3)	1.16 [0.80–1.69]	1.42 [0.97–2.09]
2016	159 (14.9)	1.08 [0.73–1.59]	1.16 [0.77–1.74]
Insurance status			
Private insurance/managed care	431 (40.3)	Reference	Reference
Not insured	35 (3.3)	1.61 [0.95–2.75]	0.98 [0.55–1.74]
Medicaid	96 (9.0)	1.71 [1.20–2.42]	1.29 [0.89–1.87]
Medicare	472 (44.1)	1.80 [1.45–2.23]	1.20 [0.90–1.60]
Other government	18 (1.7)	0.92 [0.38–2.25]	0.77 [0.31–1.94]
Insurance status unknown	18 (1.7)	1.15 [0.51–2.60]	0.97 [0.41–2.27]
County population density			
Metropolitan	898 (83.9)	Reference	Reference
Nonmetropolitan	135 (12.6)	1.16 [0.89–1.53]	0.96 [0.71–1.29]
Unknown	37 (3.5)	0.86 [0.50–1.50]	0.81 [0.45–1.45]
County-level median household income			
<$40,227	173 (16.2)	Reference	Reference
$40,227–$50,353	218 (20.4)	0.98 [0.74–1.30]	0.95 [0.70–1.29]

(Continues)

TABLE 1 (Continued)

	Total (*N* = 1070), No. (%)	Crude HR (95% CI)	Adjusted HR (95% CI)
$50,354–$63,332	221 (20.7)	0.64 [0.47–0.87]	0.69 [0.49–0.97]
≥$63,333	329 (30.7)	0.64 [0.49–0.85]	0.75 [0.55–1.01]
Unknown	129 (12.1)	0.49 [0.33–0.71]	0.53 [0.35–0.79]
Facility type			
Academic/research program	588 (55.0)	Reference	Reference
Community cancer program	43 (4.0)	1.26 [0.79–2.02]	1.22 [0.75–1.98]
Comprehensive community cancer program	256 (23.9)	0.96 [0.76–1.22]	0.88 [0.68–1.13]
Integrated network cancer program	183 (17.1)	1.22 [0.95–1.57]	1.17 [0.90–1.53]
Sinonasal site			
Nasal cavity	519 (48.5)	Reference	Reference
Sinus	551 (51.5)	2.07 [1.70–2.52]	1.40 [1.10–1.76]
Charlson–Deyo comorbidity score			
0	819 (76.5)	Reference	Reference
1	171 (16.0)	1.32 [1.03–1.69]	1.20 [0.92–1.55]
2	48 (4.5)	1.74 [1.18–2.58]	1.38 [0.91–2.09]
≥3	32 (3.0)	1.87 [1.16–3.01]	1.80 [1.10–2.93]
Squamous cell histology			
Not otherwise specified	619 (57.9)	Reference	Reference
Basaloid	53 (5.0)	0.67 [0.41–1.10]	1.01 [0.61–1.70]
Keratinizing	222 (20.7)	1.09 [0.86–1.38]	1.15 [0.89–1.48]
Nonkeratinizing	143 (13.4)	0.76 [0.56–1.03]	0.89 [0.64–1.23]
Papillary	33 (3.1)	0.54 [0.28–1.06]	0.78 [0.39–1.54]
AJCC stage at presentation			
I	213 (19.9)	Reference	Reference
II	126 (11.8)	1.09 [0.69–1.74]	1.21 [0.74–1.98]
III	158 (14.8)	2.05 [1.39–3.02]	1.90 [1.22–2.94]
IV	456 (42.6)	3.56 [2.58–4.90]	3.03 [2.04–4.51]
Not applicable	82 (7.7)	2.44 [1.57–3.80]	2.02 [1.21–3.38]
Unknown	35 (3.3)	1.32 [0.64–2.70]	1.51 [0.72–3.17]
Tumor grade/differentiation			
1	104 (9.7)	Reference	Reference
2	377 (35.2)	1.03 [0.73–1.46]	0.99 [0.69–1.42]
3	377 (35.2)	1.07 [0.75–1.51]	1.03 [0.71–1.50]
4	14 (1.3)	1.87 [0.84–4.17]	1.80 [0.73–4.41]
Unknown	198 (18.5)	1.04 [0.71–1.52]	1.14 [0.75–1.72]
Received chemotherapy			
No	652 (60.9)	Reference	Reference
Yes	418 (39.1)	1.50 [1.24–1.82]	1.03 [0.81–1.33]
Received radiation			
No	348 (32.5)	Reference	Reference
Yes	722 (67.5)	1.14 [0.92–1.41]	0.74 [0.57–0.96]

TABLE 1 (Continued)

	Total (*N* = 1070), No. (%)	Crude HR (95% CI)	Adjusted HR (95% CI)
Received surgery			
No	270 (25.2)	Reference	Reference
Yes	800 (74.8)	0.44 [0.36–0.53]	0.58 [0.46–0.74]

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; HPV, human papillomavirus; HR, hazard ratio; NH/U, non-Hispanic or unknown ethnicity.

[a]These values indicate a significant difference.

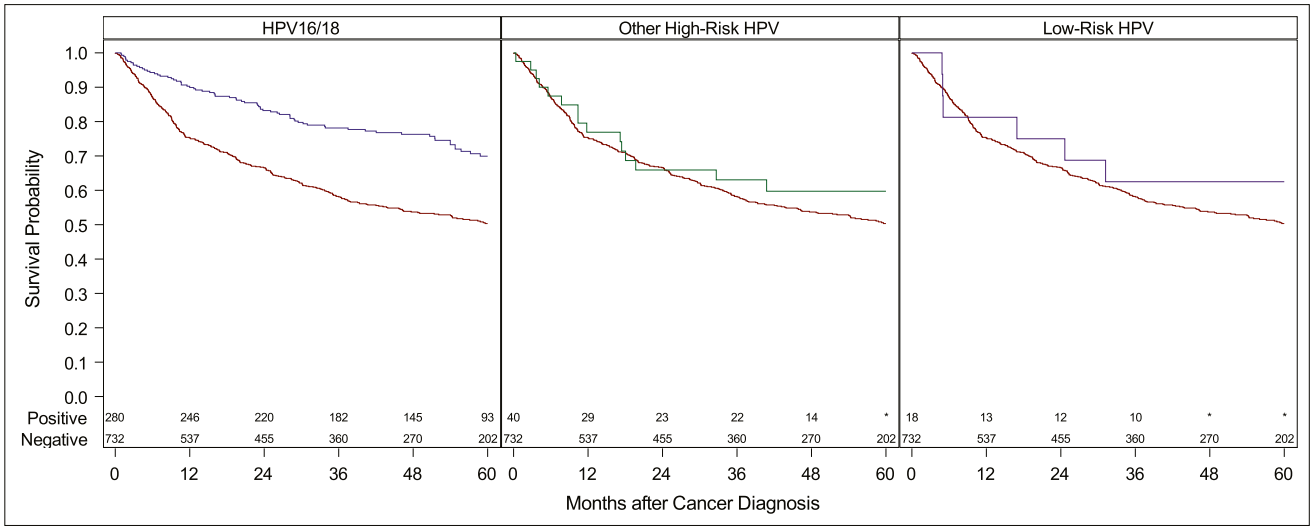

FIGURE 2 Kaplan–Meier curves of all-cause survival among patients with sinonasal cancer stratified by HPV status. The numbers of patients at risk for HPV-positive and HPV-negative disease are included in each chart. Note that the asterisk (*) indicates fewer than 10 patients at risk. HPV indicates human papillomavirus.

sinonasal cancers. Our study indicated that older patients with sinonasal cancer are less likely to have HPV16/18, similar to previous studies assessing all HPV subtypes combined.[33] Previous studies in both cervical and oropharyngeal cancer have demonstrated that patients who are positive for high-risk non–HPV-16 present at a statistically significantly older mean age than patients who have HPV-16.[34–36] In addition to age, Hispanic patients with sinonasal cancer were more than twice as likely to present with non-HPV16/18 compared with non-Hispanic White patients.

The demographic associations with HPV status, rather than the HPV infection itself, could account for the prognostic differences; however, our study determined that high-risk HPV16/18-positive patients had a 37% lower mortality HR than HPV-negative patients even after adjusting for available demographic confounders. Our study also indicated that the survival of low-risk HPV-positive patients was similar to and not significantly different from that of HPV-negative patients. One possible explanation for these findings could be the alternative splicing of E6/E7, which may be significantly different between HPV-16 and HPV-18 subtypes than what is reported in other subtypes of high-risk HPV.[37] Another possible explanation could be attributed to the pathogenesis of HPV infection. Many recent studies have found that high-risk subtypes of HPV are mutually exclusive of the EGFR mutation, and those who had EGFR mutations had a significantly worse prognosis compared with HPV-positive patients with sinonasal squamous cell carcinoma.[10,38] This finding has previously been established in oropharyngeal squamous cell carcinoma with emerging research regarding sinonasal squamous cell carcinoma.[39] Based on these findings, routine testing for HPV16/18 might be useful to guide targeted treatment for patients. Future studies regarding differential treatment modalities based on HPV subtype, such as the promising results currently seen in radiotherapy combined with EGFR-targeted therapy and the new understanding of EGFR's role on E6, should continue to be investigated.[40]

In terms of oncology, both HPV16/18 and non-HPV16/18 infections were less likely to present in the sinuses than in the nasal cavity. Because of the close anatomic association of the sinuses with important facial structures, previous studies have found that sinus cancers have lower median survival than nasal cavity cancers.[41] Combined with our findings on HPV differences, it could be argued that these anatomic differences might contribute to the differential survival. However, this study also demonstrated that survival was only significantly different for the HPV16/18-positive cohort, and not for all HPV-positive cohorts, compared with the HPV-negative cohort. In addition, increasing cancer tumor grade/differentiation also had higher prevalence of both HPV16/18 and non-HPV16/18 subtypes compared with HPV-negative cancers. Based on these

TABLE 2 Characteristics of patients with sinonasal cancer stratified by human papillomavirus subtype.

	No. (%)			Crude prevalence ratio [95% CI] vs. HPV-negative	
	Negative, *n* = 732	HPV16/18, *n* = 280	Non-HPV16/18, *n* = 58	HPV16/18	Non-HPV16/18
Age quartile					
First, 40–54 years	148 (20.2)	92 (32.9)	15 (25.9)	Reference	Reference
Second, 55–63 years	183 (25.0)	82 (29.3)	17 (29.3)	0.81 [0.63–1.03]	0.92 [0.48–1.79]
Third, 64–72 years	188 (25.7)	—[a]	—[a]	0.66 [0.51–0.86][b]	0.50 [0.22–1.10]
Fourth, ≥73 years	213 (29.1)	—[a]	—[a]	0.43 [0.31–0.59][b]	0.80 [0.41–1.56]
Sex					
Women	277 (37.8)	80 (28.6)	21 (36.2)	Reference	Reference
Men	455 (62.2)	200 (71.4)	37 (63.8)	1.36 [1.09–1.71][b]	1.07 [0.64–1.79]
Race/ethnicity					
NH/U White	550 (75.1)	231 (82.5)	41 (70.7)	Reference	Reference
Hispanic	—[a]	—[a]	—[a]	0.95 [0.63–1.43]	2.36 [1.21–4.59]
NH/U Asian/Pacific Islander	—[a]	—[a]	—[a]	0.61 [0.31–1.20]	—[a]
NH/U Black	—[a]	—[a]	—[a]	0.61 [0.40–0.93][b]	0.94 [0.41–2.15]
NH/U other/unknown	—[a]	—[a]	—[a]	0.73 [0.34–1.61]	1.44 [0.37–5.55]
Insurance status					
Private insurance/managed care	274 (37.4)	134 (47.9)	23 (39.7)	Reference	Reference
Not insured	—[a]	—[a]	—[a]	0.65 [0.33–1.26]	0.92 [0.23–3.71]
Medicaid	—[a]	—[a]	—[a]	0.81 [0.56–1.18]	1.08 [0.45–2.54]
Medicare	341 (46.6)	106 (37.9)	25 (43.1)	0.72 [0.58–0.90][b]	0.88 [0.51–1.52]
Other government	—[a]	—[a]	—[a]	0.90 [0.42–1.89]	0.99 [0.15–6.80]
Insurance status unknown	—[a]	—[a]	—[a]	0.72 [0.30–1.71]	0.92 [0.13–6.35]
County population density					
Metropolitan	610 (83.3)	240 (85.7)	48 (82.8)	Reference	Reference
Nonmetropolitan	103 (14.1)	—[a]	—[a]	0.74 [0.52–1.05]	0.63 [0.26–1.56]
Unknown	19 (2.6)	—[a]	—[a]	1.44 [0.93–2.22]	2.86 [1.25–6.52][b]
County-level median household income					
<$40,227	132 (18.0)	—[a]	—[a]	Reference	Reference
$40,227–$50,353	159 (21.7)	45 (16.1)	14 (24.1)	1.10 [0.74–1.64]	1.42 [0.61–3.28]
$50,354–$63,332	141 (19.3)	—[a]	—[a]	1.69 [1.18–2.42][b]	0.94 [0.36–2.44]
≥$63,333	214 (29.2)	96 (34.3)	19 (32.8)	1.55 [1.09–2.19][b]	1.43 [0.64–3.17]
Unknown	86 (11.7)	—[a]	—[a]	1.42 [0.93–2.15]	1.66 [0.66–4.14]
Facility type					
Academic/research program	392 (53.6)	163 (58.2)	33 (56.9)	Reference	Reference
Community cancer program	33 (4.5)	—[a]	—[a]	0.73 [0.40–1.32]	0.38 [0.05–2.69]
Comprehensive community cancer program	172 (23.5)	69 (24.6)	15 (25.9)	0.97 [0.77–1.24]	1.03 [0.58–1.86]
Integrated network cancer program	135 (18.4)	—[a]	—[a]	0.76 [0.56–1.04]	0.80 [0.39–1.64]
Sinonasal site					
Nasal cavity	305 (41.7)	181 (64.6)	33 (56.9)	Reference	Reference
Sinus	427 (58.3)	99 (35.4)	25 (43.1)	0.51 [0.41–0.62][b]	0.57 [0.34–0.93][b]

TABLE 2 (Continued)

	No. (%)			Crude prevalence ratio [95% CI] vs. HPV-negative	
	Negative, $n = 732$	HPV16/18, $n = 280$	Non-HPV16/18, $n = 58$	HPV16/18	Non-HPV16/18
Charlson–Deyo comorbidity score					
0	561 (76.6)	217 (77.5)	41 (70.7)	Reference	Reference
1	120 (16.4)	—[a]	—[a]	0.90 [0.67–1.20]	1.23 [0.65–2.33]
2	31 (4.2)	—[a]	—[a]	1.06 [0.66–1.69]	1.68 [0.64–4.42]
≥3	20 (2.7)	—[a]	—[a]	1.20 [0.71–2.01]	1.33 [0.34–5.17]
Squamous cell histology					
Not otherwise specified	446 (60.9)	143 (51.1)	30 (51.7)	Reference	Reference
Basaloid	23 (3.1)	—[a]	—[a]	2.26 [1.70–3.01][b]	1.27 [0.32–5.01]
Keratinizing	163 (22.3)	46 (16.4)	13 (22.4)	0.91 [0.68–1.21]	1.17 [0.63–2.19]
Nonkeratinizing	84 (11.5)	—[a]	—[a]	1.54 [1.18–2.00][b]	1.54 [0.75–3.13]
Papillary	16 (2.2)	—[a]	—[a]	1.85 [1.20–2.83][b]	3.17 [1.24–8.14][b]
AJCC stage at presentation					
I	143 (19.5)	57 (20.4)	13 (22.4)	Reference	Reference
II	68 (9.3)	—[a]	—[a]	1.50 [1.11–2.03][b]	1.12 [0.47–2.69]
III	112 (15.3)	35 (12.5)	11 (19.0)	0.84 [0.58–1.20]	1.07 [0.50–2.31]
IV	329 (44.9)	109 (38.9)	18 (31.0)	0.87 [0.66–1.15]	0.62 [0.31–1.24]
Not applicable	59 (8.1)	—[a]	—[a]	0.85 [0.55–1.34]	0.76 [0.26–2.25]
Unknown	21 (2.9)	—[a]	—[a]	1.05 [0.58–1.90]	2.31 [0.90–5.93]
Tumor grade/differentiation					
1	—[a]	—[a]	—[a]	Reference	Reference
2	263 (35.9)	96 (34.3)	18 (31.0)	3.90 [1.87–8.13][b]	3.11 [0.73–13.15]
3	241 (32.9)	114 (40.7)	22 (37.9)	4.68 [2.25–9.72][b]	4.06 [0.97–16.93]
4	—[a]	—[a]	—[a]	3.12 (0.91–10.70)	—[a]
Unknown	—[a]	—[a]	—[a]	4.80 [2.28–10.11][b]	5.62 [1.32–23.90][b]

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; HPV, human papillomavirus; NH/U, non-Hispanic or unknown ethnicity.

[a]Either there were <10 patients for this table cell or the cell's value could be subtracted from the row/column total to obtain a value <10 patients.

[b]These values indicate a significant difference.

TABLE 3 Treatment received based on human papillomavirus subtype.

	Received surgery, No. (%)	cPR [95% CI]	Received radiation, No. (%)	cPR [95% CI]	Received chemotherapy, No. (%)	cPR [95% CI]
Negative, $n = 732$	544 (74.3)	Reference	479 (65.4)	Reference	270 (36.9)	Reference
HPV16/18, $n = 280$	210 (75.0)	1.01 [0.93–1.09]	206 (73.6)	1.12 [1.03–1.23][a]	128 (45.7)	1.24 [1.06–1.45][a]
Non-HPV16/18, $n = 58$	46 (79.3)	1.07 [0.93–1.23]	37 (63.8)	0.97 [0.80–1.19]	20 (34.5)	0.93 [0.65–1.35]

Abbreviations: CI, confidence interval; cPR, crude prevalence ratio; HPV16/18, human papillomavirus subtypes 16 and 18.

[a]These values indicate a significant difference.

findings, HPV-positive cancers present differently than HPV-negative cancers, contributing to the idea that HPV status, particularly HPV16/18, is an important factor in sinonasal cancer.

Because HPV16/18 presents promising personalized treatment options in other cancer sites, we analyzed treatment trends in sinonasal cancers by HPV status. HPV16/18-positive patients were slightly more likely to receive radiation therapy and chemotherapy than HPV-negative patients. However, radiation therapy had a significantly lower mortality hazard after adjusting for covariates. At this point, it is unclear why HPV-related sinonasal cancers seem to be treated differently based on HPV status. Previous studies in oropharyngeal squamous cell carcinoma have found that HPV-induced tumors demonstrated high chemoradiosensitivity.[42] It is possible that these findings may play a role in why these trends are seen in sinonasal squamous cell carcinoma. Based on our data, it is difficult to draw conclusions on whether the improved survival of patients who have HPV-positive tumors is associated either with the potential chemoradiosensitivity of the tumors or with the subsequent molecular changes caused by HPV infection itself. De-escalated treatment approaches are promising for HPV-related disease in the oropharynx but remain unproven at this time, and much additional research is needed before de-escalation for sinonasal sites could be considered.

This study has important limitations to consider. The findings may not be generalizable to all sinonasal cancers because a large portion of the initial cohort lacked HPV data (Figure 1). Patients diagnosed in 2010 were less likely to have known HPV status than those diagnosed in later years, and having private insurance/managed care was more common among patients with known HPV status (see Table S2). Although there were other significant differences between patients with known HPV status and unknown/vague HPV status, we do not believe that patients who have sinonasal cancer with known HPV status are representative of the entire population of patients who have sinonasal cancer. The cohort was also identified through the NCDB, which is hospital-based rather than population-based. In addition, the documented HPV testing methods were unknown and could differ regarding their sensitivity and specificity for HPV detection. The survival outcome measure was limited to all-cause mortality, with no information on disease-specific mortality. Although this study adds support to the conclusion that HPV16/18 may be involved in the oncogenesis of some sinonasal tumors, causal inferences could be drawn, and there may be residual confounding because of the retrospective nature of the study.

Despite these limitations, the NCDB is the largest source of information to analyze survival outcomes of rare cancers such as sinonasal cancer. Using the NCDB allowed for the differentiation of HPV by subtype, so specific analysis of HPV16/18 was possible while also controlling for several demographic and socioeconomic characteristics. Unfortunately, HPV data are not routinely collected for patients with sinonasal cancer or by many institutions and is no longer required to be collected by the NCDB as of 2018, resulting in an incomplete data set to further assess its role in oncogenesis and survival. Based on our findings, patients with sinonasal cancer should be considered for routine testing of HPV subtypes because these markers might have prognostic significance and warrant further study.

In conclusion, this study demonstrated that the HPV16/18 subtypes are associated with improved survival compared with other HPV-positive and HPV-negative subtypes, after controlling for sociodemographic covariates. In addition, patients who were positive for low-risk and other high-risk HPV subtypes had survival similar to that of HPV-negative patients despite presenting with characteristics similar to those of HPV16/18-positive patients. Because of the promising findings of our study, we believe that the association of sinonasal cancer and HPV subtype warrants further investigation with a complete data set through the collection of HPV16/18 status and the status of other high-risk and low-risk HPV subtypes.

AUTHOR CONTRIBUTIONS

Shreya P. Ramkumar: Conceptualization, investigation, writing–original draft, and writing–review and editing. **Matthew C. Simpson:** Conceptualization, investigation, data curation, formal analysis, methodology, writing–original draft, and writing–review and editing. **Eric Adjei Boakye:** Formal analysis, investigation, methodology, and writing–review and editing. **Aleksandr R. Bukatko:** Conceptualization, investigation, data curation, formal analysis, methodology, validation, visualization, writing–original draft, and writing–review and editing. **Jastin L. Antisdel:** Investigation, project administration, resources, and writing–review and editing. **Sean T. Massa:** Conceptualization, investigation, methodology, project administration, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Nosayaba Osazuwa-Peters:** Conceptualization, data curation, investigation, methodology, project administration, supervision, validation, visualization, writing–original draft, and writing–review and editing.

CONFLICTS OF INTEREST STATEMENT

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SUPPORTING INFORMATION

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

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