Demographic and Socioeconomic Factors Associated With Metastases at Presentation in HPV–Related Squamous Cell Carcinoma of the Head and Neck: An NCDB Analysis

Marta B. Bean, MD¹; Jeffrey M. Switchenko, PhD²; Conor Ernst Steuer, MD³; Mihir Patel, MD⁴; Kristin Higgins, MD⁵; Mark McDonald, MD⁵; Georgia Z. Chen, PhD³; Jonathan J. Beitler, MD, MBA⁵; Dong M. Shin, MD³; Theresa Gillespie, PhD, MA^{3,6}; and Nabil F. Saba, MD³

QUESTION ASKED: What socioeconomic and demographic factors affect the likelihood of metastasis at presentation in human papillomavirus (HPV)–related oropharyngeal and nonoropharyngeal head and neck cancers?

SUMMARY ANSWER: For HPV-related oropharyngeal carcinomas (HPVOPCAs), there were significantly lower odds of metastasis in privately insured patients and higher odds of metastasis for those living in census tracts with the lowest rates of high school graduates and those with higher tumor and nodal stage. For HPV-related nonoropharyngeal carcinomas (HPVNOPCAs), no demographic features portended a greater likelihood of metastasis at presentation.

WHAT WE DID: The National Cancer Database (NCDB) was queried to assess patients with HPVOPCAs and HPVNOPCAs diagnosed between 2010 and 2014 presenting with metastasis. Multivariable analysis was performed evaluating race, ethnicity, sex, age, facility location, facility type, insurance status, income, education, and tumor and nodal stage using logistic regression.

BIAS, CONFOUNDING FACTORS, DRAWBACKS: There are limitations to our study related to the way data are collected in NCDB. HPV status is not a required

variable to submit to NCDB, both lowering the sample size of patients with HPV-positive metastatic disease and introducing selection bias into the data set. Furthermore, it was not possible to apply characteristics to individual patients for some demographic variables; thus, we relied on zip code averages linked to census tract data. Although the NCDB is an excellent resource and census tract measures are fairly accurate, the database does not fully capture the true demographic features of each patient with cancer.

REAL-LIFE IMPLICATIONS: With HPVOPCA surpassing cervical cancer as the most common HPV-related malignancy in the United States and with the expected aging of the HPV-positive population, it is important to evaluate risks that portend a worse presentation and prognosis for this growing population of patients. Better understanding of the demographic characteristics could help improve patient counseling, encouraging patients to report symptoms for further diagnostic workup earlier, while making a strong case for improving public educational approaches and focusing advocacy in this at-risk population. More investigation should be conducted in HPVNOPCA to further investigate what factors influence metastasis at presentation.

CORRESPONDING AUTHOR

Nabil F. Saba, MD, Emory University Winship Cancer Institute, 1365 Clifton Rd, Building C, Atlanta, GA 30322; e-mail: nfsaba@emory.edu.

Author affiliations and disclosures are available with the complete article at ascopubs.org/journal/op.

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abstract

PURPOSE Human papillomavirus (HPV)–related squamous cell carcinomas of the head and neck (SCCHNs) tend to have a distinct prognosis. Socioeconomic and demographic factors associated with metastatic disease at presentation and diagnosis in patients with HPV-related SCCHN tumors were examined.

METHODS The National Cancer Database (NCDB) was queried to assess patients with HPV-related oropharyngeal carcinomas (HPVOPCAs) and HPV-related nonoropharyngeal carcinomas (HPVNOPCAs) diagnosed between 2010 and 2014. Rate of metastases at presentation was analyzed using clinical M stage. Multivariable analysis was performed evaluating race, ethnicity, sex, age, facility location, facility type, insurance status, income, education, and tumor and nodal stage using logistic regression.

RESULTS A total of 12,857 patients with HPVOPCA and 952 patients with HPVNOPCA were included. Private insurance was carried by 64% and 47% of patients with HPVOPCA and HPVNOPCA, respectively. HPVOPCA was located in the tonsil in 56% of patients. For both HPVOPCA and HPVNOPCA, there was no meaningful difference in distant metastasis at presentation based on facility type or location, sex, race, Hispanic ethnicity, or urban or rural location. For HPVOPCA, there were significantly lower odds of metastasis in privately insured patients compared with uninsured patients (odds ratio [OR], 0.37; 95% CI, 0.21 to 0.64; $P < .001$) and higher odds of metastasis for patients living in census tracts with the lowest rates of high school graduates compared with the highest rates (OR, 1.81; 95% CI, 1.02 to 3.19; $P = .041$) and for patients with higher tumor stage (OR, 3.67, 95% CI, 2.25 to 5.99; $P < .001$) and nodal stage (OR, 3.34; 95% CI, 2.11 to 5.29; $P < .001$). For HPVNOPCA, neither higher T or N stage nor any demographic features were found to be associated with metastasis at presentation.

CONCLUSION This large retrospective analysis identifies likely modifiable risk factors for metastatic presentation in HPVOPCA. Educational interventions may result in modifications of these patterns.

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INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) is a clinically and molecularly heterogeneous disease.^{1,2} Human papillomavirus (HPV)–related SCCHN is a distinct clinical entity that often carries an improved prognosis. Patients with HPV-related oropharyngeal squamous cell carcinoma (HPVOPCA) have an overall improved response to treatment and a lower risk of death or disease progression than patients with non-HPV-related oropharyngeal squamous cell carcinoma.^{3–5}

Importantly, HPV association in SCCHN differentially affects outcomes in different tumor locations within the head and neck.² High-risk HPV positivity is associated

with improved survival in patients with cancers of the oropharynx, hypopharynx, oral cavity, and larynx, whereas a survival difference has yet to be shown in the sinonasal tract and nasopharynx.⁶

Although the overall incidence of non-HPV-related SCCHN has decreased in North America in recent decades, likely as a result of decreasing tobacco use, there has been a relative increase in oropharyngeal carcinoma (OPCA) relative to all head and neck cancers.^{7–9} In addition, there has been a substantial increase in OPCA in white men who have no history of alcohol or tobacco use. This increase has been attributed to HPV-associated tumors.^{7,10} There has been a sharp increase in the prevalence of HPV in OPCAs in

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recent decades, increasing from approximately 40% of OPCAs before 2000 to approximately 72% in 2009.¹¹ Although the initial presentations of the epidemic were in younger white men, there have been significant increases in incidence of OPCA in elderly white men likely related to HPV.⁷ In contrast, the prevalence of HPV in nonoropharyngeal carcinomas has remained unchanged over time, at approximately 20%.⁸

Metastasis at presentation is an ominous sign in SCCHN. HPVOPCA has an approximately equal risk of distant metastasis as HPV-negative disease.^{5,12} Therefore, it is important to take these facts into account when designing deintensification studies in this group.¹³ Little is known about the risk factors that are associated with the advanced presentation of HPV-related SCCHN. Our analysis specifically addresses demographic factors that may be associated with metastatic presentation in patients with HPV-related SCCHN. This is relevant given that HPVOPCA is now the most common HPV-related malignancy in the United States, surpassing cervical cancer in incidence.^{14,15}

Using the National Cancer Database (NCDB), we evaluated factors associated with metastatic disease at presentation in patients with HPVOPCA and HPV-related non-OPCA (HPVNOPCA). The purpose was to examine possible modifiable factors that could influence early detection and abrogate presentation with distant incurable disease. Although demographic factors are not always easily modifiable, understanding these patient characteristics can help tailor health policy and educational interventions aimed at populations that are more likely to present with metastasis, aiming to decrease the frequency of presentation with incurable disease.

METHODS

Data were obtained from the NCDB, a clinical oncology database that tracks and analyzes trends and outcomes of > 70% of patients diagnosed with cancer in the United States.¹⁶ Patients in the NCDB defined as having a histologic category of squamous cell carcinoma were included in this study. For oropharynx sites, the following head and neck 2015 Participant User Files (PUFs) were combined: NCDB oropharynx, NCDB tongue (C019, C024), and NCDB tonsil (C090-C091, C098-C099). For nonoropharynx sites, the following head and neck 2015 PUFs were combined: NCDB tongue (C020-C023), NCDB lip (C003-C009), NCDB gum (C030-C031, C039, C050, C052, C060-C062, C068-C069), NCDB mouth (C040-C041, C048-C049), NCDB hypopharynx, and NCDB pharynx (C140).

HPV status was defined as positive when the tumor was HPV positive for specified high-risk types of HPV other than types 16 or 18; HPV positive for high-risk type 18 without positive results for high-risk type 16 or positivity of high-risk type 16 unknown; HPV positive for high-risk type 16 without positive results for high-risk type 18 or positivity of high-risk

type 18 unknown; HPV positive for high-risk types 16 and 18; or HPV positive for high-risk type(s), not otherwise specified, and high-risk type(s) not stated.

The presence of distant metastasis was defined as clinical M1, whereas patients without distant metastasis were defined as clinical M0. Covariates considered for analysis included race (white, black, or other); ethnicity (Hispanic or non-Hispanic); sex; age; facility location; facility type; insurance status (private insurance, government insurance, or uninsured); income and education (census tract level quartile); urban or rural location; receipt of surgery, radiation, or chemotherapy; clinical T stage (T1, T2, or T3/4); and clinical N stage (N0/1 or N2/3).

Statistical Analysis

Descriptive statistics such as frequencies and percentages were generated for categorical variables, and means and standard deviations were generated for numeric variables. For patients with HPVOPCA and HPVNOPCA separately, categorical patient characteristics were compared across the presence of distant metastasis using χ^2 tests, and numeric patient characteristics were compared using analysis of variance. In addition, a multivariable logistic regression model was fit, modeling the probability of distant metastasis as a function of the covariates listed earlier. Observations missing any variables, such as facility type or location or T or N stage, were removed from the multivariable analysis.

Model assumptions were checked and verified. The analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC). Significance was assessed at the $P = .05$ level.

RESULTS

The database contained 132,033 oropharynx cancers and 109,871 nonoropharynx cancers. After inclusion and exclusion criteria were applied, 12,857 patients had M1 HPVOPCA and 952 patients had M1 HPVNOPCA (Table 1).

For patients with HPVOPCA and HPVNOPCA, the median age at diagnosis was 58 and 59 years, respectively. The majority of patients with HPVOPCA and HPVNOPCA presented to academic centers (50.6% and 57.7%, respectively), followed by comprehensive cancer centers (31.8% and 28.8%, respectively). Patients with HPVOPCA and HPVNOPCA were predominately male (86.5% and 74.4%, respectively) and white (93.7% and 90.2%, respectively). Of patients with HPVOPCA, 63.5% held private insurance and 32.7% held government-provided insurance, whereas of patients with HPVNOPCA, 47.1% held private insurance and 46.6% held government-provided insurance. For HPVOPCA and HPVNOPCA, 48.2% and 41% of patients, respectively, lived in census tracts in the highest median income quartile (earning > \$46,000 per year). For HPVOPCA and HPVNOPCA, 43.3% and 37.7%

TABLE 1. Selection and Exclusion Criteria for Oropharyngeal and Nonoropharyngeal Cases

Selection and Exclusion Criteria	No. of Patients			
	Oropharynx		Nonoropharynx (n = 952)	
	Sample Size	Excluded	Sample Size	Excluded
NCDB PUF cancers	132,033	—	109,871	—
Include positive HPV status	24,282	107,751	1,948	107,923
Include squamous histology codes: 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8078	22,006	2,276	1,835	113
Include invasive behavior	21,954	52	1,785	50
Exclude missing clinical M stage	20,755	1,199	1,686	99
Include nonmissing vital status	15,292	5,463	1,268	418
Exclude patients missing survival time	15,290	2	1,268	0
Include sequence No. = 0 or 1	13,515	1,775	992	276
Exclude class of case = 0	12,857	658	952	40

Abbreviations: HPV, human papillomavirus; NCDB, National Cancer Database; PUF, Participant User File.

of patients, respectively, lived in census tracts with the highest rate of high school education. For HPVOPCA, the most common tumor sites were the base of tongue (36.8%) and tonsil (47.3%), whereas in HPVNOPCA, the most common sites were oral tongue (26%), pyriform sinus (14.1%), hypopharynx or pharynx (18%), and floor of mouth (17.1%). For both HPVOPCA and HPVNOPCA, the most common high-risk HPV type was 16, without high-risk type 18, affecting 73.3% and 78.5% of patients, respectively. Patients with HPVOPCA were more likely to present with advanced nodal disease, defined as N2 or N3 stage (70.7%), than patients with HPVNOPCA (36.4%). These data are listed in [Table 2](#).

Univariable Analysis

On univariable analysis, patients with HPVOPCA who were uninsured, lived in census tracts in the lowest income quartile, had the highest percentage of no high school education, and had higher T (T3/4) and N (N2/3) stage were significantly more likely to present with metastasis ($P < .001$). Patients with HPVNOPCA who were male ($P = .027$) and had higher T stage (T3/4; $P = .022$) and N stage (N2/3; $P < .001$) were significantly more likely to present with metastasis ([Table 3](#)).

Multivariable Analysis

On multivariable analysis in patients with HPVOPCA, the following factors were found to be significant in predicting presentation with advanced metastatic disease: insurance status, education level, and T and N stage. There were decreased odds of presenting with distant metastasis in privately insured patients compared with uninsured patients (odds ratio [OR], 0.37; 95% CI, 0.21 to 0.64; $P < .001$; [Table 4](#)) and significantly increased odds of presenting with distant metastasis in patients coming from census tracts in the highest quartile of no high school education compared with the lowest quartile of no high

school education (OR, 1.81; 95% CI, 1.02 to 3.19; $P = .041$). Patients with T2 (OR, 1.98; 95% CI, 1.21 to 3.24; $P = .007$) or T3/4 (OR, 3.67; 95% CI, 2.25 to 5.99; $P < .001$) tumors had increased odds of presenting with metastasis compared with patients with T1 tumors. For patients with HPVNOPCA, education, insurance status, T stage, and N stage were not found to be relevant with regard to presentation with metastasis.

DISCUSSION

The contemporary diagnosis of OPCA includes the determination of HPV association.¹⁷ Several studies have explored the differences between virally induced and non-virally induced SCCHN. HPV-related SCCHN is known to have a better prognosis and response to treatment, and importantly, metastatic presentation of virally induced SCCHN is relatively infrequent.¹⁰ To our knowledge, this is the first study examining the association between demographic features and presentation with distant advanced metastatic disease in patients with high-risk HPV-positive SCCHN. In the face of a worsening epidemic and the expected continued increase in incidence of this disease and the shift to an older segment of the population, we believe these findings may have significant public health implications.

Kuperman et al¹⁸ examined risk factors for distant metastasis in SCCHN in the SEER database and found that tumor size, nodal status, age, and race were independent risk factors for distant metastasis. This study did not evaluate HPV status in relation to distant metastasis because, at the time the study was conducted, HPV data were not available in the SEER database. Liu et al¹² evaluated patterns of distant metastasis at presentation for all head and neck cancers and found that HPV was associated with a lower risk of distant metastasis presentation in oropharyngeal tumors. However, this study did not specifically evaluate whether there were associated demographic

TABLE 2. Demographic and Patient and Tumor Characteristics for Oropharynx and Nonoropharynx Sites

Characteristic	Oropharynx (n = 12,857)		Nonoropharynx (n = 952)	
	No. of Patients	%	No. of Patients	%
Facility type				
Community cancer program	786	6.2	45	5
Comprehensive community cancer program	4,023	31.8	259	28.8
Academic/research program	6,405	50.6	519	57.7
Integrated network cancer program	1,447	11.4	77	8.6
Missing	196	—	52	—
Facility location				
Northeast	2,710	21.4	201	22.3
South	4,149	32.8	306	34
Midwest	3,629	28.7	239	26.6
West	2,173	17.2	154	17.1
Missing	196	—	52	—
Sex				
Male	11,122	86.5	708	74.4
Female	1,735	13.5	244	25.6
Race				
White	11,943	93.7	852	90.2
Black	589	4.6	59	6.2
Other	212	1.7	34	3.6
Missing	113	—	7	—
Hispanic ethnicity				
No	12,220	97.2	894	96.2
Yes	350	2.8	35	3.8
Missing	287	—	23	—
Insurance				
Not insured	485	3.8	59	6.3
Private	8,085	63.5	445	47.1
Medicaid/Medicare/other government	4,157	32.7	440	46.6
Missing	130	—	8	—
Median income quartiles (2000)				
< \$30,000	1,128	9.1	111	11.8
\$30,000-\$34,999	1,891	15.2	150	16
\$35,000-\$45,999	3,412	27.5	292	31.1
≥ \$46,000	5,984	48.2	385	41
Missing	442	—	14	—
No high school education quartiles (2000), %				
≥ 29%	1,398	11.3	126	13.4
20%-28.9%	2,645	21.3	240	25.6
14%-19.9%	2,998	24.1	237	25.3
< 14%	5,374	43.3	335	35.7
Missing	442	—	14	—

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TABLE 2. Demographic and Patient and Tumor Characteristics for Oropharynx and Nonoropharynx Sites (continued)

Characteristic	Oropharynx (n = 12,857)		Nonoropharynx (n = 952)	
	No. of Patients	%	No. of Patients	%
Urban or rural (2003)				
Metro	10,466	83.2	793	85
Urban	1,880	15	121	13
Rural	226	1.8	19	2
Missing	285	—	19	—
HPV status				
High-risk HPV, not type 16 or 18	914	7.1	60	6.3
HPV type 16 only	9,422	73.3	747	78.5
HPV type 18 only	55	0.4	4	0.4
HPV types 16 and 18	1,252	9.7	78	8.2
HPV high-risk type(s), NOS	1,214	9.4	63	6.6
Clinical T stage				
T1	3,380	29.6	219	26.4
T2	4,874	42.6	278	33.5
T3/4	3,177	27.8	334	40.2
Missing	1,426	—	121	—
Clinical N stage				
N0/1	3,690	29.3	559	63.6
N2/3	8,886	70.7	320	36.4
Missing	281	—	73	—
Surgery				
No	7,267	56.6	350	36.8
Yes	5,580	43.4	602	63.2
Missing	10	—	—	—
Radiation				
No	1,401	10.9	324	34.3
Yes	11,422	89.1	621	65.7
Missing	34	—	7	—
Chemotherapy				
No	3,155	24.9	479	51.2
Yes	9,507	75.1	456	48.8
Missing	195	—	17	—
Age at diagnosis, years				
Mean	58.09		59.4	
Median	58		59	
Minimum	21		23	
Maximum	90		90	
Standard deviation	9.13		11.71	
Missing	0		0	

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TABLE 2. Demographic and Patient and Tumor Characteristics for Oropharynx and Nonoropharynx Sites (continued)

Characteristic	Oropharynx (n = 12,857)		Nonoropharynx (n = 952)	
	No. of Patients	%	No. of Patients	%
Primary site				
Tongue: base NOS	4,726	36.8		
Lingual tonsil	126	1.0		
Tonsil	7,235	56.3		
Vallecula/epiglottis	90	0.7		
Lateral wall of oropharynx	51	0.4		
Posterior wall of oropharynx	37	0.3		
Branchial cleft	5	0.0		
Oropharynx NOS	587	4.6		
Lip			7	0.7
Tongue			247	26
Gum			65	6.9
Floor of mouth			163	17.1
Hard palate/uvula			27	2.9
Cheek/mouth			137	14.4
Pyriform sinus			134	14.1
Hypopharynx/pharynx			172	18

Abbreviations: HPV, human papillomavirus; NOS, not otherwise specified.

characteristics in patients with HPV-related tumors presenting with metastasis.

For patients with HPVOPCA, our findings suggest that presentation with metastasis tends to occur in patients who are living in census tracts with a lower percentage of high school graduation. This finding needs to be evaluated within the context of the overall demographic characteristics of HPVOPCA as reported by Peterson et al,¹⁹ because patients with HPV-related SCCHN tend to live predominantly in zip code areas with higher median income and higher levels of educational attainment and are less likely to have a history of tobacco use compared with patients with HPV-negative tumors. Our findings indicate that private insurance is associated with a decreased likelihood of presenting with distant metastasis in patients with HPVOPCA.

To further elucidate the association between education and metastasis outcomes, we compared our results with studies evaluating metastasis at presentation in different tumor types. The Centers for Disease Control and Prevention has shown that, for breast, cervical, and colorectal cancer, education, availability and use of health care, and length of residence in the United States are associated with higher uptake of screening.²⁰ Higher screening rates would increase early diagnosis and yield a lower proportion of patients presenting with distant metastasis. Because education affects screening rates, we propose that in HPV-associated

HPVOPCA, patients with a higher level of education may seek medical attention for early symptoms, improving the chances of early detection. However, patients with a lower education level may have lower health literacy, face barriers to health care access, and have a lower chance of early detection. This is in contrast to the finding that, in HPVNOPCA, there was no association found between education and presentation with distant metastasis. In addition, there was no association between higher T or N stage and presentation with distant metastasis in this tumor type. These findings are concerning because patients may not have any outward signs of disease, such as lymphadenopathy, which could trigger a patient to see a physician more readily.

Several studies have shown that lower socioeconomic status predicts more advanced stage at presentation in other tumor types, including breast, colorectal, prostate, lung, and cervical cancer.²¹ For breast cancer, the socioeconomic contributions to stage at presentation have been well studied. Wang et al²² found that people living in areas with a high concentration of low-income groups and racial minorities are more likely to be diagnosed with late-stage breast cancer compared with those in more socioeconomically privileged areas. In a study of the SEER database, Clegg et al²³ demonstrated that, in lung cancer, men had 3 times and women 2 times the risk of advanced presentation with lung cancer relative to their college-educated counterparts, and lower income was associated

TABLE 3. Univariable Analysis for Oropharynx and Nonoropharynx Sites

Variable	Patients With Oropharyngeal Carcinoma			Patients With Nonoropharyngeal Carcinoma		
	No. (%) Without Distant Metastasis (M0; n = 12,577)	No. (%) With Distant Metastasis (M1; n = 280)	Parametric <i>P</i> ^a	No. (%) Without Distant Metastasis (M0; n = 878)	No. (%) With Distant Metastasis (M1; n = 74)	Parametric <i>P</i> ^a
Facility type			.086			.168
Community cancer program	762 (96.95)	24 (3.05)		41 (91.11)	4 (8.89)	
Comprehensive community cancer program	3,924 (97.54)	99 (2.46)		230 (88.8)	29 (11.2)	
Academic/research program	6,283 (98.1)	122 (1.9)		485 (93.45)	34 (6.55)	
Integrated network cancer program	1,416 (97.86)	31 (2.14)		71 (92.21)	6 (7.79)	
Facility location			.61			.542
Northeast	2,647 (97.68)	63 (2.32)		180 (89.55)	21 (10.45)	
South	4,060 (97.85)	89 (2.15)		282 (92.16)	24 (7.84)	
Midwest	3,558 (98.04)	71 (1.96)		221 (92.47)	18 (7.53)	
West	2,120 (97.56)	53 (2.44)		144 (93.51)	10 (6.49)	
Sex			.306			.027
Male	10,874 (97.77)	248 (2.23)		645 (91.1)	63 (8.9)	
Female	1,703 (98.16)	32 (1.84)		233 (95.49)	11 (4.51)	
Race			.486			.292
White	11,686 (97.85)	257 (2.15)		786 (92.25)	66 (7.75)	
Black	572 (97.11)	17 (2.89)		52 (88.14)	7 (11.86)	
Other	207 (97.64)	5 (2.36)		33 (97.06)	1 (2.94)	
Hispanic ethnicity			.611			.255
No	11,955 (97.83)	265 (2.17)		821 (91.83)	73 (8.17)	
Yes	341 (97.43)	9 (2.57)		34 (97.14)	1 (2.86)	
Insurance			< .001			.471
Not insured	458 (94.43)	27 (5.57)		52 (88.14)	7 (11.86)	
Private insurance	7,979 (98.69)	106 (1.31)		412 (92.58)	33 (7.42)	
Medicaid/Medicare/ other government	4,011 (96.49)	146 (3.51)		407 (92.5)	33 (7.5)	
Median income quartiles (2000)			< .001			.746
< \$30,000	1,080 (95.74)	48 (4.26)		103 (92.79)	8 (7.21)	
\$30,000-\$34,999	1,844 (97.51)	47 (2.49)		141 (94)	9 (6)	
\$35,000-\$45,999	3,348 (98.12)	64 (1.88)		266 (91.1)	26 (8.9)	
≥ \$46,000	5,871 (98.11)	113 (1.89)		355 (92.21)	30 (7.79)	
No high school education quartiles (2000), %			< .001			.374
≥ 29%	1,345 (96.21)	53 (3.79)		120 (95.24)	6 (4.76)	
20%-28.9%	2,581 (97.58)	64 (2.42)		224 (93.33)	16 (6.67)	
14%-19.9%	2,933 (97.83)	65 (2.17)		215 (90.72)	22 (9.28)	
< 14%	5,284 (98.33)	90 (1.67)		306 (91.34)	29 (8.66)	

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TABLE 3. Univariable Analysis for Oropharynx and Nonoropharynx Sites (continued)

Variable	Patients With Oropharyngeal Carcinoma			Patients With Nonoropharyngeal Carcinoma		
	No. (%) Without Distant Metastasis (M0; n = 12,577)	No. (%) With Distant Metastasis (M1; n = 280)	Parametric <i>P</i> ^a	No. (%) Without Distant Metastasis (M0; n = 878)	No. (%) With Distant Metastasis (M1; n = 74)	Parametric <i>P</i> ^a
Urban or rural (2003)			.982			.38
Metro	10,236 (97.8)	230 (2.2)		729 (91.93)	64 (8.07)	
Urban	1,840 (97.87)	40 (2.13)		113 (93.39)	8 (6.61)	
Rural	221 (97.79)	5 (2.21)		19 (100)	0 (0)	
HPV status			.86			.345
High-risk HPV, not type 16 or 18	897 (98.14)	17 (1.86)		54 (90)	6 (10)	
HPV type 16 only	9,214 (97.79)	208 (2.21)		695 (93.04)	52 (6.96)	
HPV type 18 only	53 (96.36)	2 (3.64)		4 (100)	0 (0)	
HPV types 16 and 18	1,227 (98)	25 (2)		68 (87.18)	10 (12.82)	
HPV high-risk type(s), NOS	1,186 (97.69)	28 (2.31)		57 (90.48)	6 (9.52)	
T stage			< .001			.022
T1	3353 (99.2)	27 (0.8)		216 (98.63)	3 (1.37)	
T2	4795 (98.38)	79 (1.62)		275 (98.92)	3 (1.08)	
T3/4	3037 (95.59)	140 (4.41)		320 (95.81)	14 (4.19)	
N stage			< .001			< .001
N0/1	3653 (99)	37 (1)		551 (98.57)	8 (1.43)	
N2/3	8650 (97.34)	236 (2.66)		303 (94.69)	17 (5.31)	
Age at diagnosis	12,577	280	.007	878	74	.674
Mean, years	58.06	59.55		59.45	58.85	
Median, years	58	58.5		59	58	

Abbreviations: HPV, human papillomavirus; NOS, not otherwise specified.

^aThe parametric *P* value is calculated by analysis of variance for numerical covariates.

with a higher risk of late-stage breast cancer in women and late-stage prostate cancer in men. Inverso et al²⁴ showed that patients who were uninsured or had Medicaid were more likely to present with metastatic head and neck cancer and were more likely to die of head and neck cancer than privately insured patients.

Regarding T and N stage, it is not surprising that patients with HPVOPCA with higher T and N stage are more likely to present with metastasis. However, our finding that higher T and N stage in HPVNOPCA was not related to distant metastasis is interesting. It is in keeping with the pattern noted that metastasis in these tumor types does not seem to fit any demographic pattern, as demonstrated in HPVOPCA.

Because head and neck cancer with metastatic presentation is a devastating diagnosis, it is imperative that possible interventions be undertaken to catch cancer as early as possible. Studies have shown that both hospital-based and community-based head and neck screening campaigns have been effective at raising awareness of head and neck cancer. Harris et al²⁵ found that motorsports

events captured patients who had higher rates of risk factors that are useful to diagnose early-stage head and neck cancers and that hospital-based campaigns captured patients with concerning signs, symptoms, and findings useful to diagnose head and neck cancer. Logan et al²⁶ conducted a study revealing that posters, flyers, and magnets on the side of trucks were effective in increasing intention to seek free oral cancer screening and that this effect was more pronounced in people with lower education and less financial security. We believe that all of these strategies may be effective at increasing screening. However, because of the lack of readily identifiable demographic patterns in HPVNOPCA, we recommend that community-based head and neck screening campaigns aimed to target a wide audience of men who are at higher risk of metastasis are conducted.

There are limitations to our study. Because the NCDB was used, there were substantial missing data and likely inaccurate data related to HPV. HPV status is collected as a site-specific factor, meaning that it is not required to be

TABLE 4. Multivariable Analysis for Oropharynx and Nonoropharynx Sites

Variable	Presence of Distant Metastasis (M1)			
	Oropharynx ^a		Nonoropharynx ^b	
	OR (95% CI)	OR <i>P</i>	OR (95% CI)	OR <i>P</i>
Facility type				
Community cancer program	1.62 (0.85 to 3.07)	.141	1.07 (0.07 to 15.62)	.96
Comprehensive community cancer program	1.15 (0.71 to 1.85)	.579	1.66 (0.25 to 11.12)	.604
Academic/research program	0.81 (0.51 to 1.30)	.389	1.02 (0.17 to 6.08)	.981
Integrated network cancer program	—	—	—	—
Facility location				
Northeast	0.98 (0.62 to 1.54)	.932	1.67 (0.32 to 8.71)	.543
South	0.66 (0.43 to 1.00)	.05	0.80 (0.14 to 4.53)	.803
Midwest	0.79 (0.51 to 1.22)	.285	0.85 (0.15 to 4.64)	.848
West	—	—	—	—
Sex				
Male	1.30 (0.81 to 2.09)	.274	3.13 (0.60 to 16.38)	.176
Female	—	—	—	—
Race				
Other	0.62 (0.18 to 2.12)	.442	2.72 (0.25 to 29.24)	.409
Black	0.63 (0.34 to 1.16)	.137	3.95 (0.76 to 20.40)	.101
White	—	—	—	—
Hispanic ethnicity				
Yes	0.62 (0.26 to 1.49)	.286	1.68 (0.17 to 16.31)	.654
No	—	—	—	—
Insurance				
Medicaid/Medicare/other government	0.89 (0.51 to 1.55)	.671	0.47 (0.07 to 3.26)	.444
Private insurance	0.37 (0.21 to 0.64)	< .001	0.65 (0.09 to 4.78)	.676
Not insured	—	—	—	—
Median income quartiles (2000)				
< \$30,000	1.20 (0.68 to 2.15)	.528	2.51 (0.30 to 21.13)	.397
\$30,000-\$34,999	0.84 (0.51 to 1.39)	.505	5.03 (0.76 to 33.53)	.095
\$35,000-\$45,999	0.73 (0.48 to 1.10)	.135	1.83 (0.42 to 7.94)	.419
≥ \$46,000	—	—	—	—
No high school education quartiles (2000), %				
≥ 29%	1.81 (1.02 to 3.19)	.041	0.16 (0.02 to 1.50)	.109
20%-28.9%	1.41 (0.89 to 2.23)	.145	0.17 (0.02 to 1.33)	.092
14%-19.9%	1.20 (0.79 to 1.82)	.383	1.16 (0.32 to 4.24)	.825
< 14%	—	—	—	—
T stage				
T3/4	3.67 (2.25 to 5.99)	< .001	1.29 (0.29 to 5.74)	.737
T2	1.98 (1.21 to 3.24)	.007	0.32 (0.05 to 1.87)	.205
T1	—	—	—	—
N stage				
N2/3	3.34 (2.11 to 5.29)	< .001	2.60 (0.73 to 9.30)	.141
N0/1	—	—	—	—
Age at diagnosis	1.00 (0.98 to 1.01)	.703	0.96 (0.90 to 1.03)	.25

Abbreviation: OR, odds ratio.

^aNo. of observations in the original data set was 12,857. No. of observations used was 10,083.^bNo. of observations in the original data set was 952. No. of observations used was 728.

collected or submitted to the NCDB. For each patient who had HPV status assigned in the database, there were > 2 patients who had unknown, unrecorded, or otherwise missing data. This introduces selection bias into the data set used in this study. Unfortunately, there is no way of knowing whether certain demographic groups are over- or underrepresented in this population. In addition, the missing HPV status data considerably lowered the sample size of patients with HPV-positive metastatic disease. An important strength of a large observational database such as the NCDB lies in its sample size. The relatively small number of patients we were able to include in subgroups was another limitation to this study. Furthermore, for many of the demographic features we were interested in, it was not possible to apply characteristics to individual patients. Rather, for factors such as education and income, we relied on averages based on zip codes linked to census tract data. Although the NCDB is an excellent resource

and census tract measures are fairly accurate, they do not fully capture the true demographic features of each patient with cancer.^{27,28}

With HPVOPCA surpassing cervical cancer as the most common HPV-related malignancy in the United States and with the expected aging of this population, it is important to evaluate risks that portend a worse presentation and prognosis for this growing population of patients. Better understanding of the demographic characteristics could help improve patient counseling, encouraging patients to report symptoms for further diagnostic workup earlier, while making a strong case for improving public educational approaches and focusing advocacy in this at-risk population. As the epidemiology of HPV-related SCCHN continues to evolve, it is important to understand the various factors conferring increased risks of worsened outcome in this growing population.

AFFILIATIONS

¹Emory School of Medicine, Atlanta, GA

²Biostatistics and Bioinformatics, Winship Cancer Institute, Emory University, Atlanta, GA

³Department of Hematology and Medical Oncology, Emory University, Atlanta, GA

⁴Department of Otolaryngology, Emory University, Atlanta, GA

⁵Department of Radiation Oncology, Emory University, Atlanta, GA

⁶Department of Surgery, Emory University, Atlanta, GA

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CORRESPONDING AUTHOR

Nabil F. Saba, MD, Emory University Winship Cancer Institute, 1365 Clifton Rd, Building C, Atlanta, GA 30322; e-mail: nfsaba@emory.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Marta B. Bean, Georgia Z. Chen, Theresa Gillespie, Nabil F. Saba

Administrative support: Dong M. Shin, Theresa Gillespie

Provision of study materials or patients: Mihir Patel, Theresa Gillespie

Collection and assembly of data: Mihir Patel, Nabil F. Saba

Data analysis and interpretation: Marta B. Bean, Jeffrey M. Switchenko, Conor Ernst Steuer, Kristin Higgins, Mark McDonald, Jonathan J. Beitler, Dong M. Shin, Theresa Gillespie, Nabil F. Saba

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Demographic and Socioeconomic Factors Associated With Metastases at Presentation in HPV-Related Squamous Cell Carcinoma of the Head and Neck: An NCDB Analysis**

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Conor Ernst Steuer

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Kristin Higgins

Consulting or Advisory Role: AstraZeneca, Genentech, Varian Medical Systems

Speakers' Bureau: AstraZeneca

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Nabil F. Saba

Honoraria: Merck, Eli Lilly, Pfizer, Bristol-Myers Squibb, Cue, GlaxoSmithKline, Aduro Biotech, Kura, Genentech

Consulting or Advisory Role: Pfizer, Bristol-Myers Squibb, Merck, Eli Lilly

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