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Measures of economic advantage associated with HPV-positive head and neck cancers among non-Hispanic black and white males identified through the National Cancer Database

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Conflicts of interest

None.

Abstract

Background—National trends show dramatic increases in the incidence of HPV-related head and neck squamous cell carcinomas (HNSCCs) among black and white males. Using cases identified through the National Cancer Data Base, we assessed factors associated with HPV 16- or 16/18 positive HNSCCs among non-Hispanic black and white males diagnosed in the U.S. between 2009 and 2013.

Methods—This sample included 21,524 HNSCCs with known HPV status. Adjusted relative risks (RRs) and 95% confidence intervals (CIs) were estimated using log-binomial regression.

Results—Compared to those with HPV-negative tumors, male patients diagnosed with HPV-positive HNSCCs were non-Hispanic white, younger at diagnosis, lived in zip-code areas with higher median household income and higher educational attainment, had private health insurance and no reported comorbidities at diagnosis. Although the risk of HPV-positive HNSCCs increased with measures of higher area-level socioeconomic status, the effect was stronger for non-Hispanic black males ($RR_{Adjusted}$ = 1.76, 95% CI 1.49–2.09) than for whites ($RR_{Adjusted}$ = 1.12, 95% CI 1.08–1.16). The peak age for diagnosis of HPV-positive HNSCCs occurred in those diagnosed at 45–49 years ($RR_{Adjusted}$ = 1.57, 95% CI 1.42–1.73). Oropharyngeal tumors were strongly associated with HPV-positivity ($RR_{Adjusted}$ = 4.32, 95% CI 4.03–4.63). In the analysis restricted to oropharyngeal anatomic sites, similar patterns persisted.

Conclusion—In our analysis, measures of economic advantage were associated with an increased risk of HPV-positive HNSCCs. In order to develop effective interventions, greater understanding of the risk factors for HPV-positive HNSCCs is needed among both high-risk males and their healthcare providers.

Keywords

Head and neck cancer; Socioeconomic status; Economic advantage; Human papillomavirus; HPV

1. Introduction

Head and neck squamous cell carcinomas (HNSCCs) include tumors of the oral cavity, or mouth (i.e., lip, oral tongue, gingiva, retromolar trigone area, hard palate, buccal mucosa, floor of mouth), pharynx (i.e., oropharynx, nasopharynx, hypopharynx), and larynx [1]. In 2016, an estimated 48,330 new HNSCC cases will be diagnosed in the U.S., with more than 70% occurring in males [2]. Tobacco, heavy alcohol consumption [3], and infection with human papillomavirus (HPV) type 16 [4,5] are the major known risk factors for HNSCCs in the U.S. However, these risk factors differ in their associations with anatomical sites and prognoses [6,7]. HPV-related HNSCCs typically arise in the oropharynx, particularly the base of the tongue or the tonsil [8]. Although these tumors have a better prognosis than those attributed to tobacco and alcohol [9], the morbidity associated with their treatment is costly in terms of care and quality of life [10,11]. In recent decades, the incidence of tobacco-related HNSCCs in the U.S. has decreased due to a decline in the prevalence of smoking [12]. Yet meanwhile, national trends show significant increases in HPV-related HNSCCs [13,14], particularly among non-Hispanic white and black males [15]. These trends correlate

with increases in sexual behaviors associated with oral HPV infection [16,17], with the strongest associations among men [18].

Evidence suggests that HPV-positive HNSCCs could potentially be treated less aggressively than HPV-negative tumors [19], yet HPV status is not currently part of the tumor-staging system [20]. Thus, identifying those at greatest risk for developing HPV-positive tumors is needed. Using cases from the National Cancer Data Base (NCDB), we assessed individual- and area-level factors associated with HPV16- or 16/18-positive HNSCCs among non-Hispanic black and white males diagnosed in the U.S. between 2009 and 2013 in order to identify those at greatest risk for developing these HNSCC sub-types.

2. Materials and methods

2.1. National cancer data base (NCDB) study population

The NCDB is a joint project of the Commission on Cancer (CoC) and the American Cancer Society[1]. Cases reported to the NCDB are collected from over 1500 hospitals with CoC-accredited cancer programs and represent approximately 70% of all newly diagnosed cancer cases in the U.S. and Puerto Rico [21]. Reporting centers consist of community hospitals, academic medical centers, and NCI-designated Comprehensive Cancer Centers [22]. The NCDB included 11,189 non-Hispanic black and 85,992 non-Hispanic white males diagnosed with HNSCCs between 2009 and 2013. We sequentially eliminated individuals with unknown[2] HPV status (n = 70,582), missing data[3] (n = 70), and cases that were positive for low-risk (n = 3060) or high-risk HPV types other than 16 or 16/18 (n = 1945). The final analytical sample included 21,524 cases of which 39% (n = 8418) were HPV-positive for type 16 or 16/18 and 61% (n = 13,106) were HPV-negative.

2.2. Demographic variables

Age at diagnosis was categorized as <40, 40–49, 50–59, 60–69, 70–79, and >80 years in bivariate analysis and further broken down in multivariable analysis to examine the effect of age at diagnosis on HPV positivity [17]. Comorbid conditions using the Charlson/Deyo Score were categorized as 0 (no comorbid conditions recorded), or 1 (1 comorbid condition), or 2 (greater than 1 comorbid condition) [23]. Primary payer was categorized as not insured, private insurance, Medicaid, Medicare, other government, and insurance status unknown.

2.3. Area-level variables

A composite variable representing area-level socioeconomic status was created using two variables, education and income, which were based on the 2000 U.S. Census percentage of adults in the patient's zip code without a high school diploma and median household income in the patient's zip code, respectively. Tertiles of education and income were summed to create the final composite variable representing area-level socioeconomic status, and

[1]The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not been verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.
[2]Unknown HPV status are those cases in which HPV tests were ordered but results were not noted, or tests were not ordered/performed, or test documentation was not found in the patient record.
[3]Missing data are those cases in which no information on HPV tests are recorded.

analyzed in tertiles [24]. The Rural–Urban continuum describes the patient's county at time of diagnosis and was estimated by matching the state and county FIPS code against the 2013 U.S. Department of Agriculture's classification scheme [25].

2.4. Anatomical sites and HNSCC site groups

Using ICD-0-3 site codes [26] anatomical sites were based on the SEER Primary Site Grouping classification [27] and analyzed as lip, anterior tongue, gum (including front of mouth and other mouth), base of tongue, tonsil, oropharynx, nasopharynx, hypo-pharynx, other pharynx, and larynx. Anatomical sites were collapsed and further analyzed in three HNSCC site groups: Oral cavity, including lip, anterior tongue, gum, front of mouth, other mouth; oropharyngeal, including base of tongue, tonsil, and oropharynx; and non-oropharyngeal/laryngeal (including nasopharynx, hypopharynx, other pharynx, and larynx) [28].

2.5. Outcome variable: HPV status

HPV status is collected as part of the Collaborative Stage Data Collection System [29] and was categorized as negative or positive as detected by type16 or 16/18 analysis [30].

2.6. Statistical analysis

Differences in the distribution of demographic and clinical characteristics by HPV status were tested using Chi-square and *t*-test statistics for categorical and continuous variables, respectively. Adjusted relative risks (RR) and 95% confidence intervals (CIs) were estimated using log-binomial regression. Multivariable analysis was conducted to identify predictors of HPV-positive HNSCCs, as well as HPV-positive oropharyngeal anatomic sites. Potential interactions were assessed using single factor stratified analysis and log binomial models. Significance was assessed using Type 3 p values. A liberal cutoff ($p < 0.20$) was used to explore potential interactions with race. Ordinal year of diagnosis ($p = 0.12$) and area-level socioeconomic status ($p < 0.0001$) were selected as interactions to be further tested in multivariable models. Variables retained in the final models were selected if they were significantly ($p < 0.05$) associated with HPV-positivity in bivariate analysis or known to be associated with HPV-positive HNSCCs. All analyses were performed using SAS (v9.4, Cary, NC).

3. Results

3.1. Study population characteristics

Of the 21,524 HNSCC cases diagnosed between January 1, 2009 and December 31, 2013, 8418 (39%) were HPV-positive for types 16 or 16/18 and 13,106 (61%) were HPV-negative (Table 1). The mean age at diagnosis was 59.9 years (SD = 10.6), the majority (90%) of cases were non-Hispanic white, and of the 8418 HPV-positive HNSCCs, 95% were non-Hispanic white.

3.2. Factors associated with HPV-positive HNSCCs

Demographic and clinical characteristics were significantly different between HPV-positive and HPV-negative cases for all variables (Table 1). HPV-positive cases were younger at diagnosis (58.1 vs. 61.1 years), lived in zip-code areas with higher median household income and educational attainment (41% vs. 31%), and had private insurance (62% vs. 41%), $p < 0.0001$ for all variables. Compared to HPV-negative cases, a greater proportion of HPV-positive cases had no reported comorbidities at the time of diagnosis (84% vs. 77%, $p < 0.0001$), were diagnosed with oropharyngeal tumors (base of tongue, 34% vs. 13%; tonsil, 46% vs. 15%, $p < 0.0001$), while a significantly smaller proportion of HPV-positive cases were diagnosed with oral cavity tumors (6% vs. 27%, $p < 0.0001$) and non-oropharyngeal/laryngeal tumors (9% vs. 40%, $p < 0.0001$).

In the multivariable model using the full analytic sample, age, primary payer, and geographic area (i.e., rural-urban continuum), HNSCC site groups, and year of diagnosis were statistically significantly associated with HPV-positive tumors (Table 2). A significant interaction ($p < 0.0001$) was observed between race and area-level socioeconomic status, and although the risk of HPV-positive HNSCCs increased with higher area-level socioeconomic status for both groups, this effect was stronger for non-Hispanic black males ($RR_{Adjusted} = 1.76$, 95% CI 1.49–2.09) than for whites ($RR_{Adjusted} = 1.12$, 95% CI 1.08–1.16). There was an inverse association between patients who were either uninsured at diagnosis ($RR_{Adjusted} = 0.77$, 95% CI 0.72–0.83), had Medicaid ($RR_{Adjusted} = 0.73$, 95% CI 0.68–0.78), or with unknown insurance status ($RR_{Adjusted} = 0.70$, 95% CI 0.59–0.83). After adjusting for other factors, the risk of HPV-positive HNSCCs peaked in those diagnosed at ages 45–49 ($RR_{Adjusted} = 1.57$, 95% CI 1.42–1.73), and decreased, but remained statistically significant, at older ages. There was an increased risk of HPV-positive HNSCC with each increasing year of diagnosis ($RR_{Adjusted} = 1.10$, 95% CI 1.06–1.09). Oropharyngeal tumors were the only HNSCC site group associated with HPV-positivity ($RR_{Adjusted} = 4.32$, 95% CI 4.03–4.63).

These results persisted in the model restricted to oropharyngeal anatomic sites (Table 3). Compared to tumors located in the oropharynx, those at the base of the tongue ($RR_{Adjusted} = 1.34$, 95% CI 1.25–1.45) and tonsil ($RR_{Adjusted} = 1.41$, 95% CI 1.31–1.51) were significantly associated with HPV-positivity.

4. Discussion

In this analysis of non-Hispanic white and black males identified through the NCDB, we found that the risk of HPV-positive HNSCCs was highest in non-Hispanic white males, those who were younger at diagnosis, and had no reported comorbidities at diagnosis.

Notably, measures of economic advantage, specifically zip-code areas with higher median household income and higher educational attainment, and private health insurance were associated with HPV-positive HNSCCs. Higher area-level income and education [31], as well as private health insurance [32], are measures of economic advantage at the contextual- and the individual-level, respectively [33,34]. Although the risk of HPV-positive HNSCCs increased with higher area-level socioeconomic status, the effect was stronger for non-

Hispanic black males than for whites. Higher socioeconomic status, in particular higher individual-level income and education [35], as well as higher education at the county-level [36] has been associated with increased incidence of the HNSCC sub-types most commonly related to HPV.

We observed a peak in risk in those diagnosed at ages 45–49 years. There was also an increased risk of HPV-positive HNSCCs with each increasing year of diagnosis. These results suggest an “age cohort effect” due to a higher prevalence of oral sexual behavior in younger age cohorts [37].

An important limitation of this analysis is the lack of information on behavioral risk factors for HPV infection. Oral HPV infection is strongly associated with a number of sexual behaviors, most especially a higher number of lifetime partners engaging in oral sexual activities [18,38,39]. Another significant limitation is the absence of information on important HNSCC risk factors, most notably the use of both tobacco and alcohol. These limitations reduce our ability to assess the importance of these factors in HPV-positive HNSCCs, as well as the potential interaction between smoking and oral HPV infection [40].

Nevertheless, this analysis has several notable strengths. First, HPV status was captured for more than 20,000 patients, enabling HPV-positivity to be assessed directly rather than through the proxies of HPV-related HNSCC sub-types. Second, cases are derived from the NCDB, which collects approximately 70% of all new cancer diagnoses in the U.S., including Puerto Rico, [41]. Third, this large sample spans five years and includes cases from all regions of the U.S., allowing for an assessment of predictors of HPV-positive HNSCCs among non-Hispanic white and black males on a nationwide scale. Fourth, measures of economic advantage were assessed at both the contextual- and the individual-level.

In summary, we found that characteristics of economic advantage, in particular higher area-level socioeconomic status and private health insurance, were associated with an increased risk of HPV-positive HNSCCs. Individuals with private health insurance are more likely to have both “usual sources of care” and more frequent healthcare visits [42]. These features of routine healthcare present opportunities to increase awareness of the risk factors for these HNSCC sub-types, and to increase earlier diagnoses. Future studies need to assess knowledge of risk factors for HPV-positive HNSCCs among high-risk males and their healthcare providers in an effort to develop effective educational and clinical interventions.

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Table 1

Number and Percentage Distribution of Demographic and Clinical Characteristics among non-Hispanic black and white Males (N = 21,524), by HPV Status National Cancer Database, 2009–2013.

Characteristic	Total n = 21,524	HPV+ n = 8418 (39%)	HPV− n = 13,106 (61%)	*P*
Age, mean years [SD]	59.9 (10.6)	58.1 (9.1)	61.1 (11.3)	<0.0001
Race				
Non-Hispanic white	19,428 (90)	7993 (95)	11,435 (87)	<0.0001
Non-Hispanic black	2096 (10)	425 (5)	1671 (13)	
Age Group				
<40	459 (2)	135 (2)	324 (3)	<0.0001
40–49	2698 (13)	1248 (15)	1450 (11)	
50–59	7803 (36)	3487 (41)	4316 (33)	
60–69	6825 (32)	2710 (32)	4115 (31)	
70–79	2777 (13)	700 (8)	2077 (16)	
80+	962 (4)	138 (2)	824 (6)	
Charlson/Deyo comorbidity score[a]				
0	17104 (80)	7029 (84)	10075 (77)	<0.0001
1	3435 (16)	1115 (13)	2320 (18)	
2	985 (4)	274 (3)	711 (5)	
Primary payer at diagnosis				
Not insured	1242 (6)	391 (5)	851 (7)	<0.0001
Private insurance	10626 (49)	5201 (62)	5425 (41)	
Medicaid	2058 (10)	539 (6)	1519 (12)	
Medicare	6818 (32)	1998 (24)	4820 (37)	
Other government	478 (2)	209 (2)	269 (2)	
Insurance status unknown	302 (1)	80 (1)	222 (2)	
Socioeconomic status (area-level) tertiles[b]				
1st Tertile (Lowest)	7025 (33)	2200 (26)	4825 (37)	<0.0001
2nd	6934 (32)	2763 (33)	4171 (32)	
3rd Tertile (Highest)	7473 (35)	3419 (44)	4054 (31)	
Missing	92	36	56	
Rural–Urban continuum, 2003[c]				
Rural[d]	1095 (5)	467 (6)	628 (5)	0.014
Urban[e]	19913 (95)	7752 (94)	12161 (95)	
Missing	516	199	317	
Anatomical site				
Lip	244 (1)	13 (<1)	231 (2)	<0.0001
Tongue (anterior)	1801 (9)	248 (3)	1553 (12)	
Gum, Front of Mouth, Other Mouth	1951 (9)	224 (3)	1727 (13)	
Tongue (base)	4604 (21)	2840 (34)	1764 (13)	
Tonsil	5896 (27)	3896 (46)	2000 (15)	

Characteristic	Total n = 21,524	HPV+ n = 8418 (39%)	HPV− n = 13,106 (61%)	*P*
Oropharynx	1058 (5)	444 (5)	614 (5)	
Nasopharynx	506 (2)	138 (2)	368 (3)	
Hypopharynx	977 (5)	146 (2)	831 (6)	
Other pharynx	311 (1)	108 (1)	203 (2)	
Larynx	4176 (19)	361 (4)	3815 (29)	
HNSCC site group				
Oral Cavity[f]	3996 (18)	485 (6)	3511 (27)	<0.0001
Oropharyngeal[g]	11558 (54)	7180 (85)	4378 (33)	
Non-Oropharyngeal/laryngeal[h]	5970 (28)	753 (9)	5217 (40)	
Year of diagnosis				
2009	130 (1)	38 (<1)	92 (<1)	<0.0001
2010	2672 (12)	949 (11)	1723 (13)	
2011	4968 (23)	1746 (21)	3222 (25)	
2012	6316 (29)	2519 (30)	3797 (29)	
2013	7438 (35)	3166 (38)	4272 (33)	

[a] Charlson/Deyo Score with values 0 (no comorbid conditions recorded), 1 and 2 (greater than 1).

[b] Area-level composite measure of SES divided into thirds at the tertiles of the sample distribution.

[c] Area-based measure of rurality and urban influence estimated by matching the state and county FIPS code of the patient recorded at the time of diagnosis against the 2013 typology published by the United States Department of Agriculture Economic Research Service.

[d] Rural designation includes: Urban population of ≥ 20000 and not adjacent to a metro area, or completely rural/<2500 urban population and adjacent to a metro area, or completely rural/<2500 urban population and not adjacent to a metro area.

[e] Urban designation includes: Counties in metro areas of ≥1 million population, or counties in metro areas of 250,000–1 million, or counties in metro areas of <250,000, or urban population of ≥20,000 and adjacent to a metro area, or urban population of 2500–19,999 and adjacent to a metro area, or completely rural/<2500 urban population and adjacent to a metro area.

[f] Oral cavity includes lip, anterior tongue, gum, front of mouth, and other mouth.

[g] Oropharyngeal includes base of tongue, tonsil oropharynx.

[h] Non-oropharyngeal/laryngeal includes nasopharynx, hypopharynx, other pharynx, larynx.

Table 2

Multivariable model predicting HPV-positive HNSCCs among non-Hispanic black and non-Hispanic white Males (n = 20,983), by HPV Status. National Cancer Database, 2009–2013.

	Adjusted Relative Risk (95% Confidence Interval)	P value
Among non-Hispanic white males		<0.0001
Socioeconomic Status (area-level) tertiles[a]		
1 st Tertile (Lowest)	1.00 (reference)	
2nd Tertile	1.07 (1.03–1.11)	
3rd Tertile (Highest)	1.12 (1.08–1.16)	
Among non-Hispanic black males		<0.0001
Socioeconomic Status (area-level) tertiles[a]		
1st Tertile (Lowest)	1.00 (reference)	
2nd Tertile	1.42 (1.18–1.71)	
3rd Tertile (Highest)	1.76 (1.49–2.09)	
Age		<0.0001
<30	1.22 (0.83–1.80)	
30–34	1.39 (1.03–1.89)	
35–39	1.55 (1.34–1.79)	
40–44	1.53 (1.38–1.71)	
45–49	1.57 (1.42–1.73)	
50–54	1.50 (1.37–1.65)	
55–59	1.49 (1.35–1.64)	
60–64	1.46 (1.33–1.60)	
65–69	1.41 (1.29–1.55)	
70–74	1.24 (1.11–1.38)	
75 and above	1.00 (reference)	
Charlson/Deyo comorbidity score[b]		0.09
0	1.00 (reference)	
1–2	0.97 (0.93–1.01)	
Primary payer at diagnosis		<0.0001
Private insurance	1.00 (reference)	
Other government	0.96 (0.88–1.04)	
Medicare	0.90 (0.86–0.94)	
Medicaid	0.73 (0.68–0.78)	
Not insured	0.77 (0.72–0.83)	
Insurance status unknown	0.70 (0.59–0.83)	
Rural-Urban continuum, 2003[c]		0.0004
Rural[d]	1.00 (reference)	
Urban[e]	0.90 (0.86–0.95)	
HNSCC site group		<0.0001
Non-Oropharyngeal/laryngeal[f]	1.00 (reference)	

	Adjusted Relative Risk (95% Confidence Interval)	P value
Oral Cavity[g]	0.91 (0.81–1.00)	
Oropharyngeal[h]	4.33 (4.03–4.63)	
Year of diagnosis[i]	1.10 (1.06–1.09)	<0.0001

[a] Area-level composite measure of socioeconomic status divided into thirds at the tertiles of the sample distribution.

[b] Charlson/Deyo Score with values 0 (no comorbid conditions recorded), 1 and 2 (greater than 1).

[c] Area-based measure of rurality and urban influence estimated by matching the state and county FIPS code of the patient recorded at the time of diagnosis against the 2013 typology published by the United States Department of Agriculture Economic Research Service.

[d] Rural designation includes: Urban population of ≥20000 and not adjacent to a metro area, or completely rural/<2500 urban population and adjacent to a metro area, or completely rural/<2500 urban population and not adjacent to a metro area.

[e] Urban designation includes: Counties in metro areas of ≥1 million population, or counties in metro areas of 250,000–1 million, or counties in metro areas of <250,000, or urban population of ≥20,000 and adjacent to a metro area, or urban population of 2500–19,999 and adjacent to a metro area, or completely rural/<2500 urban population and adjacent to a metro area.

[f] Oral cavity includes lip, anterior tongue, gum, front of mouth, and other mouth.

[g] Oropharyngeal includes base of tongue, tonsil oropharynx.

[h] Non-oropharyngeal/laryngeal includes nasopharynx, hypopharynx, other pharynx, larynx.

[i] Year of diagnosis modeled continuously.

Table 3

Multivariable model predicting HPV-positive oropharyngeal anatomic sites among non-Hispanic black and non-Hispanic white Males (n = 11,267), by HPV Status. National Cancer Database, 2009–2013.

	Adjusted Relative Risk (95%Confidence Interval)	P value
Among non-Hispanic white males		<0.0001
Socioeconomic Status (area-level) tertiles[a]		
1st Tertile (Lowest)	1.00 (reference)	
2nd Tertile	1.05 (1.01–1.10)	
3rd Tertile (Highest)	1.11 (1.07–1.15)	
Among non-Hispanic black males		<0.0001
Socioeconomic Status (area-level) tertiles[a]		
1st Tertile (Lowest)	1.00 (reference)	
2nd Tertile	1.44 (1.18–1.77)	
3rd Tertile (Highest)	1.76 (1.46–2.12)	
Age		<0.0001
<30	0.97 (0.53–1.80)	
30–34	1.11 (0.73–1.69)	
35–39	1.32 (1.12–1.56)	
40–44	1.34 (1.20–1.50)	
45–49	1.37 (1.24–1.52)	
50–54	1.31 (1.19–1.45)	
55–59	1.31 (1.18–1.44)	
60–64	1.30 (1.18–1.43)	
65–69	1.27 (1.15–1.40)	
70–74	1.18 (1.06–1.31)	
75 and above	1.00 (reference)	
Charlson/Deyo comorbidity score[b]		0.1157
0	1.00 (reference)	
1–2	0.97 (0.93–1.01)	
Primary payer at diagnosis		<0.0001
Private insurance	1.00 (reference)	
Other government	0.94 (0.86–1.03)	
Medicare	0.89 (0.85–0.94)	
Medicaid	0.75 (0.70–0.80)	
Not insured	0.77 (0.71–0.83)	
Insurance status unknown	0.72 (0.60–0.86)	
Rural-Urban continuum, 2003[c]		0.0016
Rural[d]	1.00 (reference)	
Urban[e]	0.91 (0.86–0.96)	
Oropharyngeal		<0.0001
Oropharynx	1.00 (reference)	

	Adjusted Relative Risk (95%Confidence Interval)	P value
Tongue (base)	1.34 (1.25–1.45)	
Tonsil	1.41 (1.31–1.51)	
Year of diagnosis[f]	1.07 (1.05–1.08)	<0.0001

[a] Area-level composite measure of socioeconomic status divided into thirds at the tertiles of the sample distribution.

[b] Charlson/Deyo Score with values 0 (no comorbid conditions recorded), 1 and 2 (greater than 1).

[c] Area-based measure of rurality and urban influence estimated by matching the state and county FIPS code of the patient recorded at the time of diagnosis against the 2013 typology published by the United States Department of Agriculture Economic Research Service.

[d] Rural designation includes: Urban population of ≥20,000 and not adjacent to a metro area, or completely rural/<2500 urban population and adjacent to a metro area, or completely rural/<2500 urban population and not adjacent to a metro area.

[e] Urban designation includes: Counties in metro areas of ≥1 million population, or counties in metro areas of 250,000–1 million, or counties in metro areas of <250,000, or urban population of ≥20,000 and adjacent to a metro area, or urban population of 2500–19,999 and adjacent to a metro area, or completely rural/<2500 urban population and adjacent to a metro area.

[f] Year of diagnosis modeled continuously.