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ORIGINAL ARTICLE

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Disparities and guideline adherence for HPV testing among patients with oropharyngeal squamous cell carcinoma, NCDB, and SEER

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Abstract

Background: Human papilloma virus testing for oropharyngeal squamous-cell carcinoma has been recommended by the National Comprehensive Cancer Network since 2012. We examine disparities, reported rates of human papillomavirus (HPV) testing, and the impact on these findings of limitations with the variable in database registries.

Methods: The HPV variable was queried for patients with oropharyngeal squamous carcinoma (OPSCC) from 2013 to 2016 in National Cancer Data Base (NCDB) and Surveillance, Epidemiology, and End Results (SEER). Multivariable regression was used to identify disparities based on sociodemographic variables. Sensitivity analyses were used to investigate limitations of the variable.

Results: Despite limitations in the HPV variable in the databases, there was less than 100% adherence to recommended testing, and there were significant disparities in multiple sociodemographic variables. For example, in NCDB 70% of white versus 60.4% of black patients were tested (odds ratio [OR] 0.75, confidence interval [CI] 0.66–0.85, $p \leq 0.0001$); in SEER 59.8% of white and 47.6% of black patients were tested (OR 0.73, CI 0.67–0.81; $p \leq 0.0001$).

Conclusions: Disparities exist among patients undergoing testing for HPV-associated OPSCC and adherence to guideline recommended HPV testing has been suboptimal. In addition, the HPV variable definition, especially as it relates to p16 positivity, and use in these two registries should be improved.

KEYWORDS
disparities, head and neck cancer, HPV, oropharynx, testing

IRB approval was obtained for this research study and the need for written consent was waived.

1 | INTRODUCTION

The incidence of human papillomavirus (HPV)-related oropharyngeal squamous carcinoma (OPSCC) is rapidly increasing, and has surpassed cervical cancer as the leading HPV-related malignancy in the United States.[1-3] HPV tumor status has important prognostic and staging implications,[4-6]

[4-6] guides eligibility for current and future clinical trials, and may impact management algorithms for OPSCC. Public health efforts at cancer prevention and control will ideally use information about HPV status to target interventions aimed at specific sociodemographic groups at risk for HPV-related OPSCC.[7] In 2008, National Comprehensive Cancer Network (NCCN) guidelines were updated to suggest HPV testing for patients with a new diagnosis of OPSCC. Specifically, the guidelines suggested testing for high risk HPV types either via polymerase chain reaction or in situ hybridization. The guidelines were further updated in 2012 and put forth a strong recommendation to perform HPV testing in newly diagnosed OPSCC.[8]

A recent investigation by Rotsides et al. utilizing the National Cancer Data Base (NCDB) found significantly higher rates of HPV negative cancer among patients who were black and had lower socioeconomic status (SES).[9] However, no data exist regarding potential sociodemographic disparities in testing or on how well the guideline recommendation to test for HPV status is followed. Two large secondary cancer databases in the United States have included a variable since 2010 describing both HPV testing and HPV positivity for OPSCC. The variable has not been used to examine trends or disparities in HPV testing, but has been used for analyses of HPV positivity in the NCDB.[10,11] The other database, Surveillance, Epidemiology, and End Results (SEER), has restricted access to the HPV variable due to the potential of underreporting and incorrect coding of HPV testing and status. The reliability of the SEER and NCDB data have not been assessed or compared in the literature. The National Cancer Institute granted access to the SEER database for this analysis.

We queried the NCDB and SEER registry with the primary goal of examining disparities among patients undergoing HPV testing for OPSCC according to sociodemographic, hospital, and clinical factors. Secondary and tertiary goals of this investigation included assessing changes in HPV testing trends over time and describing the HPV variable, including its components, limitations related to our findings, and consistency between the two databases. We queried both databases in order to assess the validity of our findings and evaluate SEER data that were heretofore not made available for publication.

2 | METHODS

2.1 | Data sources and study population

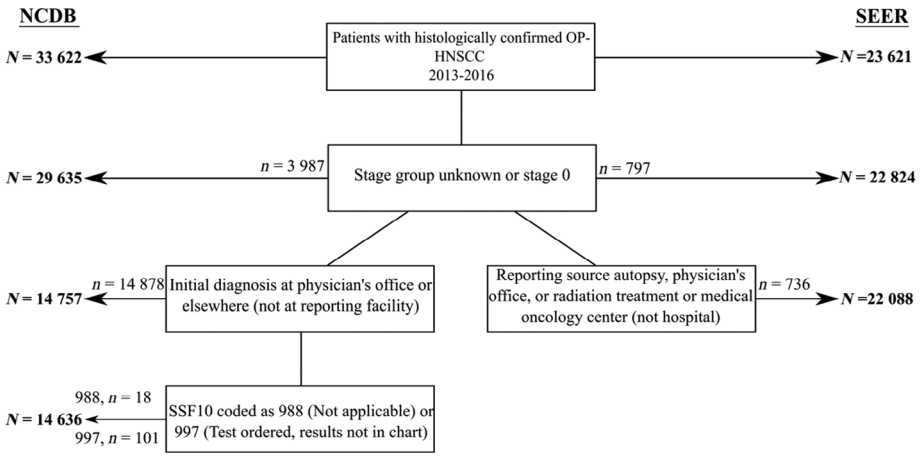
We used the NCDB and SEER databases to study patients diagnosed with OPSCC between 2013 and 2016 (International Classification of Disease for Oncology ICD-O C019, C090, C091, C098-C104, C108, C109, C142; histology codes 8073-8079 and 8083-8084). Registrars for both databases were required to enter HPV status beginning in 2010; data were not available beyond 2016 from either registry. The NCDB contains data from hospital-based registries at Commission on Cancer accredited hospitals, which collect data from over 70% of new cancer cases in the United States each year, and over 80% of cases from the oral cavity and pharynx.[12] The SEER database collects population-level data on approximately 28% of the US population from 18 registries with appropriate minority representation, each case included is unique.[13] SEER registry data are publicly available for research purposes; however, special access must be obtained for HPV-related variables through the use of a data user agreement. The NCDB and SEER databases are not mutually exclusive, and some patients are included in both.

Figure 1 shows a flow diagram of inclusion and exclusion criteria for the cohort. Within NCDB, patients 18 years or older with histologically confirmed OPSCC and documented stage were included. Within SEER, patients 20 years or older, with the same histological confirmation were included. In order to avoid falsely reporting that HPV testing was not performed when it might have been, we excluded patients for whom HPV status may have been checked, but may not have been available to the registrar entering data. For NCDB, this was defined as patients who were not diagnosed at the reporting facility, but rather at a doctor's office or other facility. We excluded patients for whom the HPV variable was coded 988 (not applicable: information not collected for this case). We excluded those coded 997 (test ordered, results not in chart). For NCDB, we excluded patients from hospitals that did not contribute cases for all 5 years of this study population. SEER now only reports cases as having been tested for HPV or not.

2.2 | Study variables

Patient demographics included age, sex, race, year of diagnosis, tumor classification, and zip-code level information derived from 2012 American Community Survey data about education (categorized as greater or less than 87% with high school diploma). Insurance status is coded slightly differently between the two databases, with an

FIGURE 1 CONSORT diagram



additional category of "insured NOS" for SEER. Income in the NCDB is based on 2012 American Community Survey data and was categorized as greater or less than $38 000. For SEER, the Yost socioeconomic index was used as a proxy for income, with patients categorized into quintiles (low, 2, 3, 4, and high).[14] The NCDB has additional variables not available in SEER, including the patient's Charlson-Deyo comorbidity index[15] (0, 1, or ≥2), urban/rural continuum, hospital characteristics including facility type, and hospital volume (categorized in quartiles).

The HPV variable for head and neck cancers in both databases is American Joint Committee on Cancer Collaborative Stage site-specific factor (SSF)-10. To calculate HPV testing rates, we coded patients as "tested" if they were documented HPV positive or negative, and not tested otherwise. For our primary analysis, the group apparently not tested included two codes, "998; test not done" as well as "999; unknown or no information." SEER does not include a "999; unknown or no information" code regarding the HPV variable—patients are either tested or not.

2.3 | Sensitivity analyses

We performed two sensitivity analyses to deal with uncertainty regarding the data. The first uncertainty related to the HPV variable: although we had already excluded patients whose records were likely to be unavailable to the registrar (at a physician's office, etc.), coding 999 still suggests a lower level of certainty than coding 998 that the registrar found the pathology report and ascertained that HPV status was not tested. Therefore, as a sensitivity analysis we excluded patients with a code of 999 (in which HPV testing may have been completed and not reported or not completed and not reported and therefore the status of which was unknown at recording) and reanalyzed the data to determine if the disparities in HPV testing rates were still significant. This was only performed for the NCDB data, as SEER does not include this code in relation to the HPV testing variable.

The second uncertainty related to the year of HPV testing, since HPV testing was only suggested by the NCCN prior to 2012, and then more firmly recommended starting in 2012. Furthermore, since the update, the literature has overwhelmingly demonstrated the importance of HPV positivity in determining outcomes for oropharyngeal disease. Therefore, we performed a second sensitivity analysis, excluding data from years prior to 2015 to assess for disparities in testing after the recommendation was strengthened and because no arguments can be made against HPV testing at this time point.

2.4 | Statistical analysis

We calculated the rates of HPV testing captured by the cancer registries overall and by patient subgroups. Bivariate logistic regression was performed to determine the unadjusted odds ratios of being tested by patient subgroup. Multivariable logistic regression was used to determine factors predictive of HPV testing. The two sensitivity analyses with exclusion of code 999, and with exclusion of years 2013–2014 used the same regression model. All available factors were used in these models. p-Values ≤0.05 were considered significant. Analyses were conducted using Stata Statistical Software (Release 12.1; Stata Inc, College Station, TX, USA).

3 | RESULTS

3.1 | Study population, overall testing rates, and the HPV variable

In all, 33 622 patients in the NCDB and 23 621 patients in SEER between 2013 and 2016 were diagnosed with

histologically confirmed OPSCC. After applying exclusion criteria, 14 636 patients in the NCDB and 22 088 in SEER who should have received HPV testing according to guideline recommendations were available for analysis (Figure 1). Table 1 shows the frequency of SSF-10 codes in the NCDB. Tables 2 and 3 describe the frequency of testing overall and by patient subgroups as reported in NCDB and SEER. The overall rate of testing was 68.9% in NCDB and 57.4% in the SEER registry, assuming that patients with a code of 999 (unknown or no information in the NCDB only) were not tested. Testing rates increased from 2013 to 2016; testing was as high as 74.4% and 65% in later years in the NCBD and SEER, respectively.

3.2 | Disparities in HPV testing by patient subgroup

Tables 2 and 3 describe the rates of HPV testing in patient subgroups for NCDB and SEER from 2013 to 2016, respectively, as well as the unadjusted odds that belong to a subgroup influences testing rates. Figure 2 shows forest plots of the adjusted odds of multivariable analysis of factors associated with HPV testing in the two databases. Controlling for other variables, significant disparities in testing were observed in patient subgroups. For example, in the NCDB 70% of white versus 60.4% of black patients were tested; in SEER 59.8% of white and 47.6% of black patients were tested (NCDB OR 0.75, CI 0.66–0.85; SEER OR 0.73, CI 0.67–0.81, $p \leq 0.0001$ for both). Patients were less likely to be tested for HPV if they were older compared to younger (e.g. <50 versus older than 80: NCDB OR 0.49, CI 0.39–0.61; SEER OR 0.57, CI 0.49–0.66, $p \leq 0.0001$ for both); if they had any insurance other than private (e.g. private versus Medicare/Medicaid/Other Govt insurance NCDB OR 0.66, CI 0.60–0.72; SEER OR 0.72, CI 0.66–0.78, $p \leq 0.0001$ for both); if they lived in zip-codes with lower educational attainment compared to higher (NCDB OR 0.86, CI 0.78–0.94, $p = 0.001$); and if they lived in areas with lower socioeconomic status (SEER SES-index high compared to low: OR 0.58, CI 0.52–0.63, $p \leq 0.0001$). Patients were less likely to receive HPV testing if they had a lower stage of disease compared to higher (Stage IV versus I: NCDB OR 1.49, CI 1.28–1.74, $p \leq 0.0001$).

3.3 | Hospital-level differences in HPV testing

Additional variables in the NCDB allowed comparison of HPV testing rates based on hospital and geographic characteristics. Patients were less likely to be tested for HPV if they received care at a community hospital or comprehensive community cancer center (NCDB only) compared to academic hospitals and NCI-designated comprehensive cancer centers. In addition, patients were less likely to be tested if they received care at hospitals seeing a lower volume of OPSCC compared to higher (NCDB only).

3.4 | Sensitivity analyses for HPV variable and for year

In the NCDB sensitivity analysis relating to the HPV variable, dropping patients with a code of 999 (unknown or no information) changed the rate of testing to 88.1% overall respectively, increasing to as high as 89.9% in later years within NCDB (Figure 3). Looking at disparities in testing with code 999 dropped, the NCDB ($n = 11\,442$ compared to 14 636 available for analysis) showed similar significant disparities in testing rates after multivariable regression compared to the primary analysis based on age, race, insurance status, income,

TABLE 1 Total patients tested and results

		NCDB Number of patients (%)	SEER Number of patients
Overall		14 636 (100.0)	22 088 (100.0)
Tested		10 081 (68.9)	12 685 (57.4)
	HPV negative	3051 (20.8)	3925 (17.8)
	HPV positive	7030 (48.0)	8760 (39.7)
Not apparently tested		4555 (31.1)	9403 (42.6)
998	Test not done	1361 (9.3)	N/A
999	Unknown or no information	3194 (21.8)	N/A

Abbreviations: HPV, human papillomavirus; NCDB, National Cancer Data Base; SEER, Surveillance, Epidemiology, and End Results.

TABLE 2 National Cancer Data Base (NCDB) unadjusted and adjusted odds ratios of human papillomavirus (HPV) testing

Patients with OPSCC Characteristic	Overall 14 636 (100%) Overall	Tested for HPV 10 081 (68.9%) Tested for HPV	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age at diagnosis						
<50 years	1720 (11.8%)	1306 (75.9%)	1 [Reference]		1 [Reference]	
50–64 years	8090 (55.3%)	5664 (70%)	0.74 (0.66–0.84)	≤0.0001	0.74 (0.64–0.84)	≤0.0001
65–79 years	4194 (28.7%)	2772 (66.1%)	0.62 (0.54–0.70)	≤0.0001	0.75 (0.64–0.87)	≤0.0001
80 years or more	632 (4.3%)	339 (53.6%)	0.37 (0.30–0.44)	≤0.0001	0.49 (0.39–0.61)	≤0.0001
Sex						
Male	11 847 (80.9%)	8274 (69.8%)	1 [Reference]		1 [Reference]	
Female	2789 (19.1%)	1807 (64.8%)	0.80 (0.73–0.87)	≤0.0001	0.91 (0.82–1.01)	0.062
Race						
White	12 596 (86.1%)	8821 (70%)	1 [Reference]		1 [Reference]	
Black	1617 (11%)	977 (60.4%)	0.65 (0.59–0.73)	≤0.0001	0.75 (0.66–0.85)	≤0.0001
Other	423 (2.9%)	283 (66.9%)	0.87 (0.70–1.06)	0.168	0.77 (0.61–0.97)	0.029
Insurance status						
Private	6458 (44.1%)	4868 (75.4%)	1 [Reference]		1 [Reference]	
Uninsured	853 (5.8%)	545 (63.9%)	0.58 (0.50–0.67)	≤0.0001	0.69 (0.59–0.82)	≤0.0001
Medicaid, Medicare, Other Govt	7043 (48.1%)	4503 (63.9%)	0.58 (0.54–0.62)	≤0.0001	0.66 (0.60–0.72)	≤0.0001
Unknown	282 (1.9%)	165 (58.5%)	0.46 (0.36–0.59)	≤0.0001	0.58 (0.44–0.76)	≤0.0001
Urban/rural continuum						
1 million or more	7271 (50.8%)	5078 (69.8%)	1 [Reference]		1 [Reference]	
Less than 1 million	7051 (49.2%)	4775 (67.7%)	0.91 (0.84–0.97)	0.006	0.97 (0.89–1.06)	0.512
Education						
>87% w/ HS degree	7959 (54.4%)	5758 (72.3%)	1 [Reference]		1 [Reference]	
≤87% w/ HS degree	6664 (45.6%)	4315 (64.8%)	0.70 (0.66–0.75)	≤0.0001	0.86 (0.78–0.94)	0.001
Income						
$38 000 or greater	11 577 (79.3%)	8153 (70.4%)	1 [Reference]		1 [Reference]	
<$38 000	3031 (20.7%)	1908 (62.9%)	0.71 (0.66–0.78)	≤0.0001	0.93 (0.83–1.04)	0.189
Year diagnosed						
2013	3563 (24.3%)	2283 (64.1%)	1 [Reference]	≤0.0001	1 [Reference]	
2014	3644 (24.9%)	2474 (67.9%)	1.35 (1.11–1.62)	0.002	1.21 (1.08–1.34)	0.001
2015	3642 (24.9%)	2507 (68.8%)	1.55 (1.31–1.83)	≤0.0001	1.25 (1.12–1.39)	≤0.0001

(Continues)

TABLE 2 (Continued)

Patients with OPSCC Characteristic	Overall 14 636 (100%) Overall	Tested for HPV 10 081 (68.9%) Tested for HPV	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
2016	3787 (25.9%)	2817 (74.4%)	1.56 (1.34–1.80)	≤0.0001	1.74 (1.55–1.95)	≤0.0001
Clinical characteristics						
AJCC stage						
I	847 (6.4%)	527 (62.2%)	1 [Reference]		1 [Reference]	
II	1125 (8.4%)	775 (68.9%)	1.27 (1.05–1.54)	0.013	1.37 (1.12–1.66)	0.002
III	2406 (18%)	1728 (71.8%)	1.69 (1.43–2.00)	≤0.0001	1.51 (1.27–1.80)	≤0.0001
IV	8957 (67.2%)	6443 (71.9%)	1.76 (1.51–2.04)	≤0.0001	1.49 (1.28–1.74)	≤0.0001
Charlson-Deyo Comorbidity Count (CCI)						
0	11 416 (78%)	7913 (69.3%)	1 [Reference]		1 [Reference]	
1	2289 (15.6%)	1529 (66.8%)	0.89 (0.81–0.98)	0.018	1.03 (0.92–1.15)	0.618
2	602 (4.1%)	406 (67.4%)	0.92 (0.77–1.09)	0.332	1.10 (0.90–1.33)	0.365
>3	329 (2.2%)	233 (70.8%)	1.07 (0.84–1.37)	0.559	1.24 (0.95–1.62)	0.121
Hospital characteristics						
Facility type						
Academic/NCI CCC	5755 (39.8%)	4018 (69.8%)	1 [Reference]		1 [Reference]	
Community	1408 (9.7%)	900 (63.9%)	0.77 (0.68–0.87)	≤0.0001	1.19 (1.00–1.41)	0.048
Comprehensive community	5486 (37.9%)	3768 (68.7%)	0.95 (0.88–1.03)	0.193	1.19 (1.07–1.33)	0.002
INCP	1810 (12.5%)	1265 (69.9%)	1.00 (0.89–1.13)	0.954	1.13 (0.98–1.30)	0.093
Hospital volume						
1–24 pts	3797 (25.9%)	2452 (64.6%)	1 [Reference]		1 [Reference]	
25–43 pts	3518 (24%)	2400 (68.2%)	1.18 (1.07–1.30)	0.001	1.22 (1.08–1.36)	0.001
44–76 pts	3754 (25.6%)	2604 (69.4%)	1.24 (1.13–1.37)	≤0.0001	1.40 (1.24–1.59)	≤0.0001
77–245 pts	3567 (24.4%)	2625 (73.6%)	1.53 (1.38–1.69)	≤0.0001	1.99 (1.72–2.29)	≤0.0001
Geographic region						
New England	888 (6.1%)	697 (78.5%)	1 [Reference]		1 [Reference]	
Middle Atlantic	1881 (13%)	1368 (72.7%)	0.73 (0.61–0.88)	0.0012	0.66 (0.53–0.81)	≤0.0001
South Atlantic	3485 (24.1%)	2418 (69.4%)	0.62 (0.52–0.74)	≤0.0001	0.57 (0.47–0.70)	≤0.0001
East North Central	2722 (18.8%)	1833 (67.3%)	0.57 (0.47–0.68)	≤0.0001	0.50 (0.41–0.61)	≤0.0001
East South Central	1153 (8%)	715 (62%)	0.45 (0.37–0.55)	≤0.0001	0.43 (0.34–0.54)	≤0.0001
West North Central	1216 (8.4%)	894 (73.5%)	0.76 (0.62–0.93)	0.009	0.66 (0.52–0.83)	≤0.0001

TABLE 2 (Continued)

Patients with OPSCC Characteristic	Overall 14 636 (100%) Overall	Tested for HPV 10 081 (68.9%) Tested for HPV	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
West South Central	1184 (8.2%)	627 (53%)	0.31 (0.25–0.38)	≤0.0001	0.30 (0.24–0.38)	≤0.0001
Mountain	521 (3.6%)	360 (69.1%)	0.61 (0.48–0.78)	≤0.0001	0.62 (0.47–0.82)	0.001
Pacific	1409 (9.7%)	1039 (73.7%)	0.77 (0.63–0.94)	0.010	0.72 (0.57–0.90)	0.004

Note: New England (CT, MA, ME, NH, RI, VT); Middle Atlantic (NJ, NY, PA); South Atlantic (DC, DE, FL, GA, MD, NC, SC, VA, WV); East North Central (IL, IN, MI, OH, WI); East South Central (AL, KY, MS, TN); West North Central (IA, KS, MN, MO, ND, NE, SD); West South Central (AR, LA, OK, TX); Mountain (AZ, CO, ID, MT, NM, NV, UT, WY); Pacific (AK, CA, HI, OR, WA).

clinical stage, hospital volume, and geographic region (see Appendix Table A1).

The second sensitivity analysis was performed to evaluate if disparities in testing existed and/or improved following changes in the strength of testing recommendations. Starting in 2008, the NCCN guidelines "suggested" HPV testing in new diagnoses of oropharyngeal OPSCC; this was later changed to "recommended" in 2012. In performing the sensitivity analysis, we hoped to assess the impact of the guideline strength on rates of HPV testing. From 2015 to 2016 (the most recent available data with the greatest strength of recommendation), there were still significant disparities in testing between the two databases. In the NCDB, patients were less likely to have undergone HPV testing if they were older (>80 years old), had government insurance, presented at higher clinical stage, or were treated in certain geographic regions (data not shown). Within the SEER database, there were disparities based on age, sex, race, type of insurance, and income (data not shown).

4 | DISCUSSION

Testing the tumors of newly diagnosed patients with OPSCC for HPV positivity was first suggested in the 2008 NCCN guidelines and recommended in 2012. While the HPV variable has been recorded in NCDB and SEER registries since 2010, it has not previously been used to assess disparities in HPV testing among different sociodemographic groups or to evaluate rates of testing among patients with newly diagnosed OPSCC. The HPV variable in the NCDB has been used for analysis according to HPV positivity.[10,11] SEER has not made the variable available in publicly released data because of possible reliability issues with variable coding. The issues of quality of the variable occur in both NCDB and SEER as the coding instructions and data collection practices are the same. The variable itself, including its limitations related to findings of testing rates and positivity, and consistency between the two databases, has not been evaluated. We sought to identify disparities in testing, evaluate trends in HPV testing from 2013 to 2016, and assess the limitations of the variable used to indicate the status of HPV testing and positivity within the two databases. Our purpose in including both databases in our analysis was to confirm the validity of our findings and to examine SEER data that were not made available for public use.

Despite limitations in the HPV variable, we found that HPV testing rates increased from 2013 to 2016 as reported in both NCDB and SEER, but remained below

TABLE 3 Surveillance, Epidemiology, and End Results (SEER) unadjusted and adjusted odds ratios of human papillomavirus (HPV) testing

Patients with OPSCC	**Overall 22 088 (100%)**	**Tested for HPV 12 685 (57.4%)**				
Characteristic	Overall	Tested for HPV	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age at diagnosis						
<50	2445 (11.1%)	1338 (54.7%)	1 [Reference]		1 [Reference]	
50–64	11 097 (50.3%)	6663 (60%)	1.24 (1.14–1.36)	≤0.0001	1.11 (1.01–1.22)	0.026
65–79	7201 (32.6%)	4080 (56.7%)	1.08 (0.99–1.19)	0.096	0.90 (0.81–0.99)	0.036
≥80	1336 (6.1%)	604 (45.2%)	0.68 (0.60–0.78)	≤0.0001	0.57 (0.49–0.66)	≤0.0001
Sex						
Male	17 961 (81.3%)	10 535 (58.7%)	1 [Reference]		1 [Reference]	
Female	4127 (18.7%)	2150 (52.1%)	0.77 (0.72–0.82)	≤0.0001	0.85 (0.79–0.91)	≤0.0001
Race						
White	18 218 (82.5%)	10 895 (59.8%)	1 [Reference]		1 [Reference]	
Black	2137 (9.7%)	1017 (47.6%)	0.61 (0.56–0.67)	≤0.0001	0.73 (0.67–0.81)	≤0.0001
Other	1733 (7.8%)	773 (44.6%)	0.54 (0.49–0.60)	≤0.0001	0.52 (0.47–0.58)	≤0.0001
Insurance status						
Insured	17 692 (80.1%)	10 555 (59.7%)	1 [Reference]		1 [Reference]	
Uninsured	660 (3%)	320 (48.5%)	0.64 (0.55–0.74)	≤0.0001	0.68 (0.57–0.80)	≤0.0001
Medicaid	3330 (15.1%)	1645 (49.4%)	0.66 (0.61–0.71)	≤0.0001	0.72 (0.66–0.78)	≤0.0001
Unknown	406 (1.8%)	165 (40.6%)	0.46 (0.38–0.57)	≤0.0001	0.43 (0.34–0.53)	≤0.0001
SES quintile						
High	4382 (21.1%)	2884 (65.8%)	1 [Reference]		1 [Reference]	
4	4304 (20.8%)	2569 (59.7%)	0.77 (0.71–0.84)	≤0.0001	0.78 (0.71–0.85)	≤0.0001
3	4199 (20.2%)	2398 (57.1%)	0.69 (0.63–0.76)	≤0.0001	0.70 (0.64–0.77)	≤0.0001
2	4023 (19.4%)	2161 (53.7%)	0.60 (0.55–0.66)	≤0.0001	0.61 (0.56–0.67)	≤0.0001
Low	3833 (18.5%)	1920 (50.1%)	0.52 (0.48–0.57)	≤0.0001	0.58 (0.52–0.63)	≤0.0001
Year diagnosed						
2013	5293 (24%)	2625 (49.6%)	1 [Reference]		1 [Reference]	
2014	5449 (24.7%)	3001 (55.1%)	1.25 (1.16–1.34)	≤0.0001	1.27 (1.17–1.38)	≤0.0001
2015	5481 (24.8%)	3243 (59.2%)	1.47 (1.37–1.59)	≤0.0001	1.50 (1.38–1.62)	≤0.0001
2016	5865 (26.6%)	3816 (65.1%)	1.89 (1.75–2.04)	≤0.0001	1.97 (1.82–2.14)	≤0.0001

100% adherence. Although the numbers cannot be known exactly due to the limitations with the variable, testing rates remained as low as 65%–74% in 2016, the last year of available data. With the most stringent exclusion criteria, maximal testing rates captured by the NCDB may have been as high as 90% in 2016; however, testing rates were unlikely to have been this high, given that this required exclusion of cases where the registrar marked "999: unknown or no information." Ultimately, regardless of what the true absolute numbers tested are, we found that improvements in testing rates across the United States over time have been modest at best. Additionally, significant disparities in testing were present in both databases. Specifically, we found that patients who were older, black, and without private insurance were significantly less likely to undergo HPV testing. The NCDB demonstrated differences in testing rates according to hospital characteristics, notably with less testing performed in hospitals with lower volumes of head and neck cancer. Regarding the variable itself, we found that registrars were consistent in their coding between the two databases, and that sensitivity analysis did not change the overall results.

We are not aware of any studies that have examined HPV testing rates and disparities in testing among patients with OPSCC. There is literature on disparities in HPV positivity, including a recent publication that

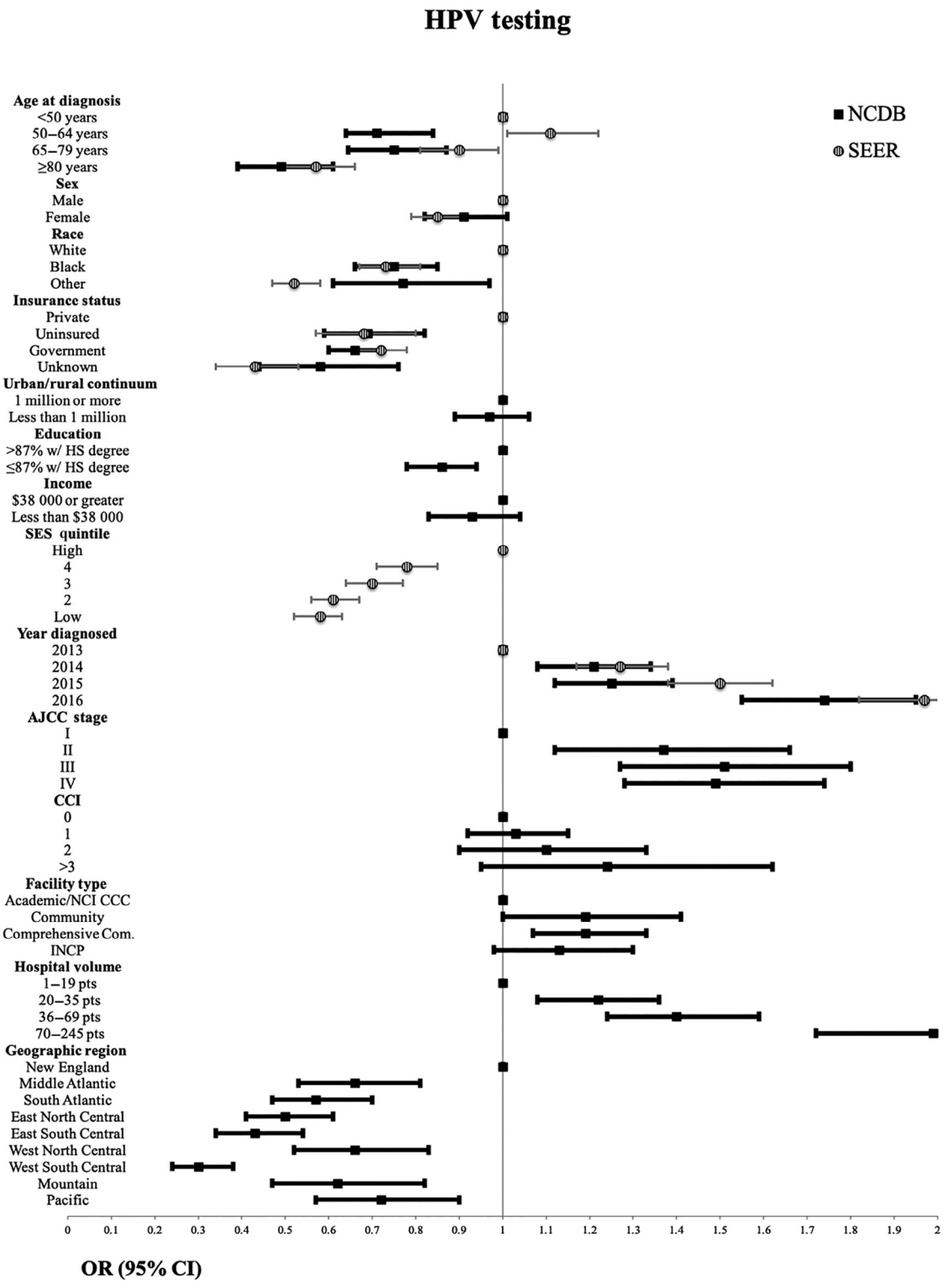


FIGURE 2 Odds of undergoing human papillomavirus (HPV) testing

describes significantly higher rates of HPV negative disease among black patients compared to white and the association of race and SES with poorer survival outcomes.[9] Regarding testing, one Canadian study described self-reported use of HPV testing in 2012 among primarily Canadian physicians to be 67%, with higher use among academic and higher oncologic-volume practices.[16] Those findings fit with our data of suboptimal adherence to the guideline recommendations, and lower rates of testing according to hospital characteristics.

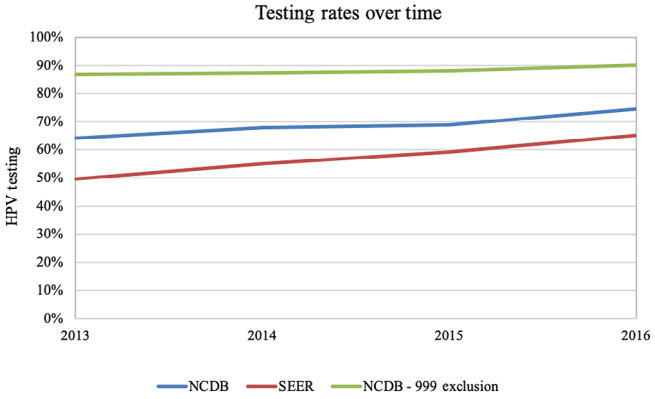


FIGURE 3 Human papillomavirus (HPV) testing rates over time [Color figure can be viewed at wileyonlinelibrary.com]

In our data set, disparities related to sociodemographic factors remained even after guidelines strongly recommending testing for OPSCC were published in 2012. Disparities in HPV testing may reflect differences in access to pathologists and pathology departments that perform the test. It has been shown that guideline changes are slowly adopted in the field of head and neck and thyroid cancer.[17,18] In addition, HPV testing can be expensive and the various methodologies are not yet standardized.[17,19] In the Canadian study, the most common reason given for not testing was the cost of the tests.[16] In addition, the finding of disparities in testing as relating to the type of insurance and patient income highlights the potential impact of heath care reimbursement and economics of HPV testing on cancer care. It may be that patients with lower income and nonprivate insurance type are unable to obtain care at higher volume or more experienced cancer centers with greater resources and access to HPV testing.

Yet access to a facility that performs the test, the year of diagnosis, implementation of guideline suggestions and recommendations, and strength of recommendations cannot entirely explain disparities based on age, sex, and race, since differences in testing still existed when all sociodemographic factors and years were controlled for. Instead, some of the disparities in HPV testing may reflect biases in presumed risk-related behaviors regarding the use of tobacco, alcohol, sexual habits, and presumed differences in HPV positivity, leading clinicians or pathologists to perform the test only in certain cases.

Prior to our current understanding of the differences in HPV positive versus HPV negative disease, it may be argued that HPV testing did not significantly alter treatment and, therefore, HPV testing did not offer additional value in disease management. This may also explain why the rate of testing continued to be low despite changes in guidelines, particularly in nonacademic centers. Of course, the difference in prognosis that HPV status infers on patients with OPSCC is now well described and this understanding has started to impact the treatment of HPV-related OPSCC. Updates in OPSCC staging systems reflect the differences in prognosis and survival between HPV-positive and HPV-negative diseases. Beyond adding important prognostic information, HPV status has now prompted efforts to assess oncologic outcomes following de-escalation therapy for HPV OPSCC. The results of these trials may significantly alter future therapies and management algorithms for HPV-positive OPSCC, which, in turn, may significantly impact both disease-specific and treatment-related outcomes. Given the potentially long-lasting impact of HPV status on treatments and outcomes, adequate testing for this factor becomes even more critical.

More widespread adoption of HPV testing will likely require a change in both access and standardization of testing as well as a mediation of whatever biases might prevent some patients from receiving testing, particularly in light of increasing incidence of HPV-associated OPSCC and its impact on treatment and outcomes.

Another important finding of this paper is that the HPV variable itself, including how it is defined in the coding dictionary, and how registrars are instructed to use it, could be improved. One limitation of the variable that impacts the analyses of testing rates and disparities is that a significant number of patients (22% in NCDB) are coded as 999 "unknown or no information." Even when excluding this group, a significant number of patients still apparently did not receive testing. Furthermore, sensitivity analyses excluding these patients from the group apparently not tested confirms that disparities in testing still exist.

Another important limitation of the variable, as currently defined, is that it does not distinguish between methods of testing. Diagnosis of the viral infection of the tumor tissue is performed with DNA in situ hybridization (ISH) or PCR HPV DNA detection, a method that also can provide the subtype of HPV.[20] An alternative and less expensive method is immunohistochemical (IHC) analysis for the presence of p16, a tumor suppressor protein shown to be present in most HPV-positive tumors and absent in HPV-negative tumors.[21] p16 status by IHC is similarly prognostic and p16 positivity is therefore often used interchangeably with HPV positivity. For instance, the summary of a pathology reports may state something to the effect of "p16 testing indicates that the tumor is HPV-related."

For registrars, there is no separate code for p16 IHC positivity. Faced with a p16 test alone, a registrar therefore is forced to make one of the following errors: The most common HPV subtypes using ISH or PCR are subtypes 16 and 18, and the registrars may incorrectly code

p16 positivity as HPV positive, type 16. By anecdotal report from officials of the SEER database, this is the most common error, and is reflected in the high number of HPV-positive patients coded as type 16 as seen in Appendix Table A2. Alternatively, as this test was not mentioned in the coding instructions as a valid test for ascertaining HPV status, someone may inappropriately mark as "test not done" for a patient who may in fact have undergone testing. Similarly, a tumor may be marked p16 positive without specifically articulating or referencing HPV status, which may be interpreted by an uneducated coder who is not aware of p16 status as a surrogate for HPV status as "test not done." Finally, they may mark "test performed but results not in the chart" (code 997, excluded in Figure 1) if there is ambiguous terminology according to registry definitions. For example, if the pathologist stated "p16 positive suggestive for HPV infection," this could have been coded as unknown HPV status because "suggestive" is considered an ambiguous term in cancer surveillance.

Two of the SEER registries performed evaluation of the quality of the HPV variable. The major findings revealed underreporting of HPV status (9% and 16%, respectively) mainly due to not coding HPV status if it was determined by p16 IHC. A second cause of underreporting resulted from not coding or miscoding of p16 overexpression as HPV type 16 in a very large number of cases. However, overall HPV status (positive or negative) had high degrees of accuracy in both quality studies. Unfortunately, there remain many pitfalls for coding of the HPV variable in both databases that may significantly impact the evaluation of HPV positivity differences among different demographic groups within the population.

This issue with the HPV variable should be addressed. As of this writing, SEER has begun to examine the quality of this data and is investigating correction of the variable. Until the variable is improved, it will be difficult to be confident about true HPV testing rates in the population, to distinguish between the methods of testing, or to draw any conclusions about HPV subtypes. These issues do not, however, affect the overall message of the results of this analysis, because patients are in fact mostly appropriately marked as tested for HPV even if marked in the wrong box because the test was done with p16 IHC, and because observed disparities were robust between databases and sensitivity analyses.

Some considerations in improving the HPV variable in both databases should be given to adding fields to help differentiate between p16 IHC, HPV ISH, and HPV PCR. Not only would these fields identify method of testing but may negate some of the mistakes associated with interpreting test results (such as coding p16 positivity as HPV type 16 positivity). These changes may also inform inexperienced coders of the validity and availability of multiple different testing methodologies and prevent inappropriate coding as "not tested" when faced with ambiguous results.

HPV positivity, rather than HPV testing, is another issue raised by this data. It would be valuable for researchers to be able to use national databases to examine sociodemographic differences in HPV positivity, survival, and treatment differences. Many cohort studies have examined sociodemographic differences in HPV positivity according to race, but they have used small and/or local samples and have come to different conclusions.[22-25] The current study raises questions about these types of analyses using national databases, because of the potential impact of variable limitations and testing disparities. These questions deserve further analysis examining HPV positivity rates in these databases.

In summary, our findings suggest that although the use of HPV testing has increased over time for patients with OPSCC, there was still significant underuse of testing up to 2016 despite changes in the strength of recommendations for HPV testing in national cancer guidelines. More important, however, is the finding of the existence of significant disparities in testing among patients within different demographic groups with potentially significant impacts on treatment and disease outcomes. Additional questions raised by these analyses, which are beyond the scope of this paper, include whether limitations with the variable or disparities in testing have implications for analyses of sociodemographic differences in HPV-positivity and HPV-associated OPSCC survival. Even with the limitations of the variable and changes in guideline adherence over time, these findings are robust and have important implications. HPV positivity offers important prognostic information and guides enrollment in current and future clinical trials for patients with OPSCC. Efforts to improve rates of testing in the population, decrease disparities among groups tested, and improve the coding of the HPV variable in national databases are important for the coming decades when HPV-associated OPSCC will be increasingly prevalent.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the National Cancer Data Base and the Surveillance, Epidemiology, and End Results Program.

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APPENDIX A.

TABLE A1 National Cancer Data Base (NCDB) unadjusted and adjusted odds ratios of human papillomavirus (HPV) testing, excluding SSF-10 "999"

Patients with OPSCC **Characteristic**	**Overall** **11 442** **Overall**	**Tested for HPV** **10 081 (88.1%)** **Tested for HPV**	**Unadjusted OR (95% CI)**	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**
Age at diagnosis						
<50 years	1431 (12.5%)	1306 (91.3%)	1 [Reference]		1 [Reference]	
50–64 years	6396 (55.9%)	5664 (88.6%)	0.74 (0.61–0.90)	0.003	0.69 (0.55–0.87)	0.002
65–79 years	3178 (27.8%)	2772 (87.2%)	0.65 (0.53–0.81)	≤0.0001	0.77 (0.60–1.00)	0.048
80 years or more	437 (3.8%)	339 (77.6%)	0.33 (0.25–0.44)	≤0.0001	0.36 (0.25–0.51)	≤0.0001
Sex						
Male	9355 (81.8%)	8274 (88.4%)	1 [Reference]		1 [Reference]	
Female	2087 (18.2%)	1807 (86.6%)	0.84 (0.73–0.97)	0.018	1.05 (0.89–1.23)	0.590
Race						
White	9942 (86.9%)	8821 (88.7%)	1 [Reference]		1 [Reference]	
Black	1173 (10.3%)	977 (83.3%)	0.63 (0.54–0.75)	≤0.0001	0.75 (0.62–0.92)	0.005
Other	327 (2.9%)	283 (86.5%)	0.82 (0.59–1.13)	0.222	0.73 (0.51–1.05)	0.089
Insurance status						
Private	5345 (46.7%)	4868 (91.1%)	1 [Reference]		1 [Reference]	
Uninsured	638 (5.6%)	545 (85.4%)	0.57 (0.45–0.73)	≤0.0001	0.60 (0.46–0.78)	≤0.0001
Medicaid, Medicare, Other Govt	5268 (46%)	4503 (85.5%)	0.58 (0.51–0.65)	≤0.0001	0.62 (0.53–0.73)	≤0.0001
Unknown	191 (1.7%)	165 (86.4%)	0.62 (0.41–0.95)	0.028	0.73 (0.46–1.16)	0.180
Urban/rural continuum						
1 million or more	5712 (51%)	5078 (88.9%)	1 [Reference]		1 [Reference]	
Less than 1 million	5479 (49%)	4775 (87.2%)	0.85 (0.76–0.95)	0.004	0.87 (0.76–1.00)	0.047
Education						
>87% w/ HS degree	6446 (56.4%)	5758 (89.3%)	1 [Reference]		1 [Reference]	
≤87% w/ HS degree	4987 (43.6%)	4315 (86.5%)	0.77 (0.69–0.86)	≤0.0001	0.98 (0.84–1.14)	0.760
Income						
$38 000 or greater	9148 (80.1%)	8153 (89.1%)	1 [Reference]		1 [Reference]	
<$38 000	2271 (19.9%)	1908 (84%)	0.64 (0.56–0.73)	≤0.0001	0.77 (0.64–0.91)	0.002
Year diagnosed						
2013	2629 (23%)	2283 (86.8%)	1 [Reference]	≤0.0001	1 [Reference]	
2014	2834 (24.8%)	2474 (87.3%)	1.04 (0.89–1.22)	0.614	1.02 (0.86–1.22)	0.809
2015	2845 (24.9%)	2507 (88.1%)	1.12 (0.96–1.32)	0.152	1.10 (0.93–1.32)	0.272
2016	3134 (27.4%)	2817 (89.9%)	1.35 (1.15–1.58)	0.000	1.46 (1.22–1.74)	≤0.0001
Clinical characteristics						
AJCC stage						
I	637 (6%)	527 (82.7%)	1 [Reference]		1 [Reference]	
II	897 (8.4%)	775 (86.4%)	1.33 (1.00–1.76)	0.049	1.46 (1.09–1.96)	0.011
III	1915 (18%)	1728 (90.2%)	1.93 (1.50–2.49)	≤0.0001	1.98 (1.53–2.58)	≤0.0001
IV	7200 (67.6%)	6443 (89.5%)	1.78 (1.43–2.21)	≤0.0001	1.82 (1.45–2.28)	≤0.0001
Charlson-Deyo Comorbidity Count (CCI)						
0	8952 (78.2%)	7913 (88.4%)	1 [Reference]		1 [Reference]	
1	1755 (15.3%)	1529 (87.1%)	0.89 (0.76–1.04)	0.132	1.08 (0.91–1.28)	0.399
2	470 (4.1%)	406 (86.4%)	0.83 (0.64–1.09)	0.187	1.01 (0.75–1.36)	0.964
>3	265 (2.3%)	233 (87.9%)	0.96 (0.66–1.39)	0.814	1.15 (0.76–1.73)	0.508

(Continues)

TABLE A1 (Continued)

Patients with OPSCC Characteristic	Overall 11 442 Overall	Tested for HPV 10 081 (88.1%) Tested for HPV	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Hospital characteristics						
Facility type						
Academic/ NCI CCC	4561 (40.4%)	4018 (88.1%)	1 [Reference]		1 [Reference]	
Community	1039 (9.2%)	900 (86.6%)	0.88 (0.72–1.07)	0.190	1.12 (0.85–1.47)	0.431
Comprehensive community	4243 (37.6%)	3768 (88.8%)	1.07 (0.94–1.22)	0.298	1.18 (0.98–1.41)	0.075
INCP	1451 (12.8%)	1265 (87.2%)	0.92 (0.77–1.10)	0.353	0.91 (0.74–1.13)	0.401
Hospital volume						
1–24 pts	2833 (24.8%)	2452 (86.6%)	1 [Reference]		1 [Reference]	
25–43 pts	2696 (23.6%)	2400 (89%)	1.26 (1.07–1.48)	0.005	1.27 (1.05–1.54)	0.013
44–76 pts	2956 (25.8%)	2604 (88.1%)	1.15 (0.98–1.34)	0.078	1.26 (1.03–1.54)	0.025
77–245 pts	2957 (25.8%)	2625 (88.8%)	1.23 (1.05–1.44)	0.010	1.55 (1.24–1.94)	≤0.0001
Geographic region						
New England	754 (6.7%)	697 (92.4%)	1 [Reference]		1 [Reference]	
Middle Atlantic	1557 (13.8%)	1368 (87.9%)	0.59 (0.43–0.81)	0.0009	0.55 (0.39–0.77)	0.001
South Atlantic	2713 (24%)	2418 (89.1%)	0.67 (0.50–0.90)	0.008	0.68 (0.49–0.94)	0.020
East North Central	2095 (18.5%)	1833 (87.5%)	0.57 (0.42–0.77)	≤0.0001	0.56 (0.40–0.78)	0.001
East South Central	839 (7.4%)	715 (85.2%)	0.47 (0.34–0.66)	≤0.0001	0.50 (0.34–0.73)	≤0.0001
West North Central	1011 (9%)	894 (88.4%)	0.63 (0.45–0.87)	0.005	0.62 (0.43–0.89)	0.010
West South Central	756 (6.7%)	627 (82.9%)	0.40 (0.29–0.55)	≤0.0001	0.41 (0.29–0.59)	≤0.0001
Mountain	445 (3.9%)	360 (80.9%)	0.35 (0.24–0.50)	≤0.0001	0.38 (0.26–0.58)	≤0.0001
Pacific	1124 (10%)	1039 (92.4%)	1.00 (0.71–1.42)	0.998	1.00 (0.68–1.48)	0.988

Note: New England (CT, MA, ME, NH, RI, VT); Middle Atlantic (NJ, NY, PA); South Atlantic (DC, DE, FL, GA, MD, NC, SC, VA, WV); East North Central (IL, IN, MI, OH, WI); East South Central (AL, KY, MS, TN); West North Central (IA, KS, MN, MO, ND, NE, SD); West South Central (AR, LA, OK, TX); Mountain (AZ, CO, ID, MT, NM, NV, UT, WY); Pacific (AK, CA, HI, OR, WA).

TABLE A2 SSF-10 frequencies, National Cancer Data Base (NCDB) and Surveillance, Epidemiology, and End Results (SEER)

Code	Code	Meaning	NCDB Number of patients (%)	SEER Number of patients (%)
Overall			14 636 (100.0)	22 088 (100.0)
Tested			10 081 (68.9)	12 685 (57.4)
	0	HPV negative	3051	N/A
	10	HPV positive, low-risk types only	285	N/A
	20	HPV positive, specified high risk types other than 16 and 18	444	N/A
	30	HPV positive, type 16	4630	N/A
	40	HPV positive, type 18	19	N/A
	50	HPV positive, types 16 and 18	468	N/A
	60	HPV positive, high risk NOS	344	N/A
	70	HPV positive, NOS	840	N/A
Not tested			4555 (31.1)	9403 (42.6)
	998	Test not done	1361	N/A
	999	Unknown or no information	3194	N/A