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CASE-MATCHING ANALYSIS OF HEAD AND NECK SQUAMOUS CELL CARCINOMA IN RACIAL AND ETHNIC MINORITIES IN THE UNITED STATES—POSSIBLE ROLE FOR HUMAN PAPILLOMAVIRUS IN SURVIVAL DISPARITIES

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Abstract

Background—Several studies have documented disparities in head and neck cancer outcomes for black patients in the United States. Recent studies have found that differences in oropharyngeal tumor human papillomavirus (HPV) status may be a cause of this disparity.

Methods—In all, 76,817 cases of head and neck squamous cell carcinoma (HNSCC) recorded in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program were analyzed. Racial/ethnic groups were studied, for disease-specific survival in both case-matched and non-matched cohorts. Calculation of expected disparity magnitudes based on HPV status was performed using data reported in the literature.

Results—A disease-specific survival disparity was demonstrated for Hispanic patients. However, case matching eliminated this disparity. Conversely, the disparity for black patients persisted in matched cohorts. The oropharyngeal subsite was found to be the dominant contributor to this disparity.

Conclusions—The survival disparity for Hispanic patients in SEER with HNSCC is explained by differences in presentation and treatment. Also, HPV tumor status is likely a key determinant of the disparity for black patients.

Keywords

race; head and neck squamous cell carcinoma; survival; disparities; human papillomavirus

Many studies have documented survival disparities for black versus white patients from both national (United States) and regional populations with head and neck squamous cell carcinoma (HNSCC) of the upper aerodigestive tract. This disparity has also been demonstrated to persist when controlling for many important clinical variables, including stage at presentation, age, sex, smoking habits, alcohol consumption, course of treatment, and poverty.^{1,2} As national minority groups, the black and Hispanic populations face similar social and economic hardships, in terms of both poverty and health insurance status.^{3–5}

Although only a small number of studies have investigated survival outcomes for Hispanics in the United States with head and neck cancer, to date no study has demonstrated poorer survival for Hispanic versus non-Hispanic white patients.^{1,6} Considering the well-documented disparity between black and white patients, and the similar social pressures on the black and Hispanic populations, this is quite surprising.

Furthermore, although many studies demonstrate the existence of a racial disparity, currently no consensus on the cause of this disparity has been reached.^{1,2,7,8} Past hypotheses presented in the literature have emphasized socioeconomic status and differences in access to care.⁷ More recently, however, Settle et al⁹ recently demonstrated that racial variance in tumor human papillomavirus (HPV) status accounted for the survival disparity in black versus white patients with oropharyngeal squamous cell carcinoma (SCC) in 1 clinical trial.

Existing literature leaves at least 2 major areas of investigation to be addressed with regard to racial/ethnic disparities in HNSCC on a national scale. First, to determine whether a survival disparity exists for Hispanic versus white patients on a national scale, and, second, to examine whether HPV tumor status is a reasonable explanation for the well-documented black versus white survival disparity in HNSCC nationally.

To investigate the differences between outcomes for black, Hispanic, and white patients with HNSCC, we analyzed HNSCC cases reported in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. We demonstrated a small but statistically significant survival disparity for Hispanic versus white patients and a larger survival disparity for black versus white patients. We then used a case-matching strategy to analyze survival data. Although the Hispanic versus white disparity was completely reconciled by case matching, the black versus white disparity persisted in the case-matched cohorts. Our findings also indicate that SCC of the oropharyngeal subsite is the dominant contributor to the disparity in black patients. Furthermore, the latter is likely attributable to HPV-related cancer at this subsite.

MATERIALS AND METHODS

Data

Data from the National Cancer Institute's SEER program were acquired on limited-use terms, with completely de-identified data, including cases diagnosed from 1973 to 2005. Data for all cases of HNSCC were extracted for the period 1988 to 2002. Included primary sites as defined by the American Joint Committee on Cancer (AJCC) were identified by the following site codes: Glottic Larynx (C32.0), Supraglottic Larynx (C32.1), Subglottic Larynx (C32.2), Hypopharynx (C12.9–13.2, C138, C139), Oropharynx (C09.0, C09.1, C09.8–10.0, C10.2–10.4, C10.8, C10.9, C01.9, C02.4, C05.1, C05.2), Oral Cavity (C02.0–02.3, C02.8–03.1, C03.9–04.1, C04.8–05.0, C05.8–06.2, C06.8, C06.9). Histology codes defining SCC were: 8070, 8071, 8072, 8073, 8074, 8075, 8076, and 8078. Information for a unique patient identifier, sex, age at diagnosis, date of diagnosis, tumor size, tumor extension, lymph node involvement, surgical treatment, radiation use and method, race, Hispanic ethnicity, survival time, cause of death, vital status at last follow-up, and primary tumor site were extracted for each case. These parameters were determined by the following SEER variables: Patient ID number, Sex, Age at Diagnosis, Year of Diagnosis, EOD (Extent of Disease)–Tumor Size, EOD–Extension, EOD–Lymph Node Involv, RXSumm–Surg Prim Site, RXSumm–Surgery Type, RXSumm–Radiation, Race Recode (W, B, AI, API), Origin recode NAACCR Hispanic Identification Algorithm (NHIA) (Hispanic, Non-Hispanic), Survival Time Recode, Cause of Death to SEER Site Recode, Vital Status Recode, and Primary Site.

Analysis

Data extraction, preparation, and case matching were performed with in-house software written in Python (Python Software Foundation/Corporation for National Research Initiatives, Reston, VA). SEER Extent of Disease (EOD) variables were converted to the American Joint Committee on Cancer 5th Edition (AJCC5) stage, a previously utilized approach. The calculated stage should be considered an AJCC5 Pathological Stage because EOD variables from SEER include operative/pathological assessment. Cohorts of matching of temporal variables, age at diagnosis, and year of diagnosis were performed with a ± 3 -year matching window. All other variables, including sex, AJCC5 Stage (I, II, III, IVA, IVB, IVC), surgical treatment performed (yes/no), and radiation (yes/no), were identically matched between cases. Cases were matched 1 to 1, randomly choosing cases from the set of all possible matches. Hispanic/white and black/white case-matched pairs were identified. Additionally, black/white case-matched pairs were constructed for each anatomic subsite: oral cavity, oropharynx, hypopharynx, and larynx. Analysis of the Hispanic data by subsite was not possible because of the limited numbers of cases. Multiple rounds of randomized rematching were performed to verify the reproducibility of our matching analysis.

All statistical analyses and figure generation were performed using the R-project. Two-sample *t* tests were used to test for dissimilarity of the temporal variables in the matched cohorts. A chi-square test of homogeneity was used to test for differences in categorical variables between the subsite cohorts. The Survival package was used to analyze the survival data. Comparisons of Kaplan–Meier survival estimates for different populations were performed using the log-rank test, and confidence intervals were calculated using the log-transform method. Hazard ratios (HRs) and 95% confidence intervals were also calculated to indicate magnitude of differences in disease-specific survival between racial groups.

Numerical Simulations

Simulated survival curves were generated using the R-project Prodlm package. An identical arbitrary baseline hazard function (Weibull distribution) was used for all simulations. Simulations for each racial group were performed based on the expected rate of HPV+ tumors reported by Settle et al⁹ (34% of white patients and 4% of black patients) and the expected HR of HPV status reported in several studies (see Table 2 in the following text). The simulated datasets of 20,000 patients were combined and subjected to Cox regression by race, to estimate expected disparity (apparent hazard ratio) of race based on these values. Greatest- and least-case expected differences between the 2 groups, based on the experimental uncertainty of the rates of both HPV and HR associated with HPV status were also calculated. For example, the greatest possible difference ($HR_{\text{apparent, race}}$) observed by race was estimated by simulating the upper confidence limit of HPV+ in white patients, the lower confidence limit of HPV–in black patients, and the upper confidence limit of the HR of HPV. The converse simulation was performed to estimate the least-case difference observed by race.

RESULTS

Survival Analysis

All cases of HNSCC diagnosed from 1988 to 2002 were extracted from the SEER database and were separated into groups of non-Hispanic white, non-Hispanic black, and Hispanic patients. The majority of patients were men in all groups (71.8%, 77.1%, and 77.1%), and the male-to-female ratio was increased for both black and Hispanic populations compared with whites (77.1% and 77.1% vs 71.8%, $p < .01$). Black patients were found to have the most unfavorable distribution of stage at diagnosis, whereas Hispanics were intermediate to

black and white patients. For example, black, Hispanic, and white patients present with 38.6%, 34.0%, and 30.2% AJCC5 stage IV disease ($p < .01$). Both minority groups received less surgery and more radiation, but the difference from white patients is much greater for black than that for Hispanic patients. In all, 55.8% of white patients were treated with surgery, whereas only 44.8% and 53.4% of black and Hispanic patients, respectively, received surgery ($p < .01$ in both cases); 67.4% of white patients were treated with radiation, whereas 72.1% and 69.0% of black and Hispanic patients, respectively, received radiation ($p < .03$ in both cases). Furthermore, small but significant differences for both Hispanic and black patients were observable in age at diagnosis, distribution of subsite, and individual T/N/M classifications.

Using an unmatched analysis, disease-specific survival for Hispanic patients was found to be intermediate to white and black patients, and was significantly worse for both Hispanic and black patients than for white patients (see Figure 1). To further investigate the nature of the observed racial/ethnic disparities in disease-specific survival, a case-matching analysis was performed to control for the impact of variables recorded in SEER. Matched cases were selected to control for age, year of diagnosis, stage, site, and treatment (see Materials and Methods). In all, 2609 Hispanic/white and 4671 black/white case-matched pairs were identified. The Kaplan–Meier disease-specific survival curves of the case-matched groups are shown in Figure 2. There was no statistical difference in disease-specific survival distributions of the Hispanic and white patients in the matched analysis. See Table 1 for a summary of the hazard ratios between groups and 10-year survival rates. The difference between black and white patients, however, was found to be significant in the matched analysis (Table 1).

Case-Matching Analysis by Anatomic Subsite

These above-cited data were further subdivided by subsite of tumor: oral cavity, oropharynx, hypo-pharynx, and larynx. White and black patients with cancer of the same subsite were subsequently randomly matched, as described earlier. Comparison of survival of the matched cohorts for each subsite revealed the previously reported trend toward poorer outcomes for black patients in all cases. The statistical analysis of these comparisons is summarized in Table 2.

Qualitatively, the hypopharynx, oral cavity, and larynx sites all demonstrated small, but similar trends for poorer survival for black patients (HR: 1.22 to 1.28). The agreement of these data seems to bolster the importance of the (not statistically significant) trends observed for the hypopharyngeal and oral cavity sites.

The oropharyngeal SCC cohort, on the other hand, revealed comparatively dramatic differences between white and black patients (HR: 2.05). This difference between the 2 groups was highly significant. Figure 3 illustrates not only how strikingly different the survival curves are for the case of oropharyngeal SCC, but also the dissimilarity of the oropharynx to the other sub-sites in question.

Residual bias within the matched variables could potentially explain overall survival differences in the oropharyngeal subsite for black versus white patients. Such bias would be expected if disparities in parameters (in unmatched dataset) such as stage were far more severe for the oropharyngeal than that for other subsites. To explore this possibility, patient factors from unmatched cohorts were examined. Comparison reveals that oropharyngeal SCC does not appear to have especially large disparities with respect to patient factors. For example, 48.0% and 50.5% of white and black oropharyngeal SCC patients, respectively, presented with stage IV disease, compared with 37.4% versus 44.2% (white vs black) for oral cavity SCC. All patient features of presentation and other subsites were similarly

analyzed, with no remarkable differences. Therefore, residual bias in the matching is an unlikely explanation for the strong differences observed between the oropharynx and other sites.

Matched cohorts of Hispanic patients were also constructed and examined. However, with smaller numbers, case matching resulted in poorly reproducible HRs for different matched sets. Qualitatively, however, it appears that no consistent trends for poorer survival were revealed in the oropharynx subsite. This is consistent with our analysis of HNSCC as a whole (Figure 2 and Table 1).

Estimation of the Effect of HPV Status on Racial Groups

To this point the presented data agree with the results of Settle et al, who also found that the oropharynx was the predominant site associated with a racial survival disparity in HNSCC.⁵ Interestingly, this study also demonstrated that the survival benefit associated with HPV+ tumors drives the survival disparity between black and white patients.⁵ Accordingly, we hypothesize that differences in tumor HPV status among black and white patients can also explain the difference in survival seen in the national SEER data. However, from the analysis to this point it is unclear whether HPV status alone can explain the magnitude of the disparity for case-matched black patients in SEER or, alternately, if other unknown factors must also contribute to this disparity.

In principle, to estimate the expected difference in survival between black and white patients based on tumor HPV status, it is necessary to know 2 things: (1) the rate (or percentage) of tumors that are HPV positive in each racial group, and (2) the difference in survival between otherwise identical cases of HPV+ and HPV- tumors. Settle et al⁹ recently reported the rates of HPV+ HNSCC tumors in the TAX324 trial, thus providing the first evidence of differing rates of HPV+ tumors among black and white patients. Specifically, it was found that 4% of HNSCC cases were HPV+ among black patients, whereas 34% of cases were HPV+ among white patients.⁹ In addition, several studies have also reported the survival difference (HR) between HPV+ and HPV- HNSCC.⁹⁻¹²

To perform the desired calculation, we first generated simulated survival curves for each racial group, in accord with the reported rates of HPV+ tumors and the HR associated with HPV tumor status, assuming that the groups were otherwise identical (see Materials and Methods). The simulated datasets were then subjected to the identical Cox regression procedure (by race) applied to the SEER data. This regression yields the apparent difference in survival ($HR_{\text{apparent, race}}$) of black and white patients based on the tumor HPV status alone.

The results of these simulations are summarized in Table 3. Because available values of HR of HPV were generally for overall survival (OS) of oropharyngeal SCC, or OS of populations with a high percentage of oropharyngeal cases, the simulation results were compared with the OS difference of oropharyngeal SCC for black/white case-matched pairs from SEER. We note that the tumor HPV positivity rates reported for the TAX324 included nonoropharyngeal sites.⁹ However, these values are the only available estimates of such rates by race. The calculated values demonstrate that the magnitude of the HR of race observed for OS of oropharyngeal SCC in SEER is within range of what should be expected from values of HPV+ tumor prevalence and survival benefit reported in the literature.

The difference between greatest- and least- case estimates of the $HR_{\text{apparent, race}}$ (see Materials and Methods) was found to be quite large because of the large experimental error of both the reported HPV HRs and prevalence of HPV+ tumors by race. Therefore, the seemingly exact agreement of the observed and predicted HRs should be interpreted with

great caution. However, these simulations do suggest that the full magnitude of racial disparity seen in SEER could be explained by racial variation in the rates of HPV+ tumors. More specifically, the greatest-case scenario for the $HR_{\text{apparent, race}}$ is larger than the measured HR (OS) of race (Table 3).

DISCUSSION

A Survival Disparity for Hispanic Patients

The results presented here show that a disparity disease-specific survival of HNSCC, although modest, exists for Hispanic patients in the United States. Several other studies have reported contradictory results.^{1,6} The differences and similarities between these reports and the work reported herein are discussed in the following text.

In 1991, Harris et al⁶ reported a chart review of 49 Hispanic and 226 Anglo-American patients diagnosed with HNSCC. In this population, Hispanics presented with more advanced stage disease, lost more weight, and had lower serum albumin levels.⁶ However, Hispanic ethnicity was not a significant predictor of OS, using univariate analysis.⁶ Interestingly, in our dataset the nonmatched groups OS curves are quite similar for Hispanic and white patients (data not shown).

A similar, but much larger, study was recently reported by Molina et al,¹ using data from the Florida Cancer Data System (FCDS) and included 2217 Hispanic patients in a total study population of 20,915. Hispanics in this Florida-based population were more likely than white patients to live in communities characterized by high poverty rates.¹ Surprisingly, white Hispanic patients with head and neck cancer were found to have an increased median survival time compared with that of white non-Hispanics (univariate analysis).¹ Our results show no evidence of the increased OS of Hispanic patients seen in this study.

The differences between data from the FCDS and SEER may reflect significant differences in Hispanic population recorded in each database. Cuba is the country of origin of most Hispanic persons in the Southeastern United States (ie, Florida).¹³ Persons of Mexican and Puerto Rican origin, on the other hand, make up the majority of Hispanics in the South and West coast, and Northeast, respectively, where several SEER registries are located. In this sense, it is reasonable that the populations of Hispanic patients represented by SEER and the FCDS are fundamentally different groups.

With respect to multivariate analysis (or case-matching) the above-discussed studies, as well as a recent study by Chen et al, have also found results similar to ours.^{1,6,14} No evidence exists for outcomes that control for standard features of presentation and treatment. These results, together with ours, support the idea that delayed presentation is the main driver for the identified differences in disease-specific survival between Hispanic and white patients.

A Survival Disparity for Black Patients

The presented results are consistent with many other studies of HNSCC, which have reported severe disparities for black patients. Studies of both regional and national populations have indicated that black patients with HNSCC have worse overall and disease-specific survival compared with that of whites.^{1,2,7} However, disparities in treatment and stage at presentation only partially explain this difference. For instance, Nichols and Bhattacharyya² demonstrated that black patients with SCC of the larynx have poorer disease-specific outcomes in matched cohorts, controlling for stage and treatment. Molina et al¹ further analyzed this disparity, examining the impact of socioeconomic status and race, among other factors, including smoking, alcohol consumption, stage, grade, treatment, and sex. They reported that both poverty and race are independent predictors of OS in patients

with head and neck cancer.¹ Therefore, although recent data suggest that HPV infection rates play a predominant role in the black versus white disparity,⁹ socioeconomic factors must also be considered.

Modest Differences in Treatment by Race/Ethnicity

Previous studies have indicated that black patients with head and neck cancer generally receive less surgery and more radiation than do white patients.^{1,2} The presented analysis also demonstrates this trend. Although (in the presented analysis) the treatments received by Hispanic and white patients are practically very similar, it is noteworthy that the same trend noted above for black patients is also recognizable for Hispanics. This result is in contradiction with the result of Molina et al,¹ who found Hispanic and non-Hispanic patients in Florida have no statistically significant difference in treatment, either surgery or radiotherapy.

Environmental Exposure and Socioeconomic Status

Two differences stand out when comparing the disparities in survival for the 2 minority populations in question. First, the magnitude of the difference in survival is much greater for black patients. Second, matching for features of presentation and treatment completely eliminates the disparity for the Hispanic but not the black patients. The difference of the outcome of matching is particularly intriguing because it supports the notion that some factors not included in our matching analysis adversely affect outcomes for black but not for Hispanic patients. Obvious factors that could explain these findings include differences in tobacco and alcohol usage, agents well known to increase the risk for HNSCC and socioeconomic status.

Over the time period in question, data from the Centers for Disease Control and Prevention indicate that rates of smoking of the black and white populations are similar, whereas smoking rates are significantly less for the Hispanic population.^{15,16} In addition, Dikshit et al¹⁷ examined the effect of cigarette smoking and alcohol consumption on disease-specific survival in upper aerodigestive tract cancers, and found no evidence of a relationship.

As stated earlier, much evidence indicates a possible role for socioeconomic factors in health disparities.^{1,7,18} Accordingly, this issue merits more detailed discussion here. Although SEER does not provide socioeconomic data, an abundance of other data would suggest that the socioeconomic stress and lack of access to care are comparable for the black and Hispanic populations in the United States. Specifically, the average yearly poverty rate from 1988 to 2002 was 28%, 26%, and 7% for black, Hispanic, and white persons, respectively.⁴ Hispanics in the United States are currently less likely to have health insurance than are black Americans.⁵ Historically, this disparity has been steadily increasing.⁵ From 1988 to 2002, the uninsured rate has increased from approximately 30% to 40% in the Hispanic population, and decreased slightly in the black population, 25% to 22%.⁵ Over the same period, the uninsured rate for whites has remained close to 15%, decreasing slightly with time.⁵ Data from the National Survey of American Families (NSAF) report that in 2002, 44% of Hispanic and 38% of blacks persons had difficulty feeding their families, compared with 17% of whites. In 2002, the NASF also recorded that 24%, 20%, and 10% of persons experienced housing hardship, among the black, Hispanic, and white populations, respectively.¹⁹

Considering the above-cited data, the lack of disparity for Hispanics when matched with white controls seems irreconcilable with the relatively strong disparity observed in the black population. Therefore, it seems that an economic explanation for the poorer performance of black versus Hispanic patients is not clear from national trends.

The Relationship of HPV Tumor Status and HNSCC Subsite

HPV DNA has been repeatedly identified from SCC tumors of the oropharynx, oral cavity, and larynx.^{19,20} Tonsillar SCC seems to have the highest rates of infectivity, 51% on meta-analysis, with reported values ranging from 20% to 75%.^{21,22} Oropharynx sites (including the tonsil) have been found to be approximately 25% HPV positive.²³ Measured rates of HPV positivity for oral cavity and laryngeal tumors range from 4% to 31% and from 3% to 47%, respectively.^{22,24} Oropharyngeal SCC tumors, especially the tonsil and base of tongue,²⁵ have consistently been found to have higher rates of HPV positivity.²³ One study, for example, using internally identical methods for oropharyngeal and oral cavity tumors, reports much higher rates of HPV in the oropharynx, specifically 42% versus 11%.²⁶ Some have suggested that the increased rates of oropharyngeal/tonsillar tumor HPV positivity may be attributed to invaginations within the tonsillar crypts, providing a better environment for HPV infection.²⁰ Others have pointed out a notable similarity of the oropharyngeal mucosa to that of the cervix.²⁷ These results suggest that the tumor biology oropharyngeal sites, more than others in the upper aerodigestive tract, are influenced by HPV infection.

The results presented herein demonstrate that differences in survival of oropharyngeal SCC alone account for the preponderance of the survival disparity (previously reported) for black patients with HNSCC in the SEER database. This result confirms that this trend, also observed in 2 smaller populations, holds true for a national population.^{9,14} The most basic implication of this result is that some biologic rather than socioeconomic explanation for the disparity in oropharyngeal SCC may be most appropriate. In light of the above-discussed work, which demonstrates the special relationship between HPV and oropharyngeal SCC, identification of the oropharynx in particular as the subsite of primary dissimilarity is highly suggestive of the hypothesis that differences in HPV infection between the 2 groups may play a part in this disparity on a national level.

Rational for Prognostic Value of HPV Tumor Positivity

Several studies have confirmed that HPV+ tumors of the oropharynx are associated with increased survival.^{9–12,28,29} Most studies have examined patients receiving chemoradiotherapy for oropharyngeal SCC. However, a recent study has demonstrated that the survival benefit is present for patients treated with surgery as well.²⁸ The presence of viral proteins also seems to be key for a differential interaction of the host immune system with the HNSCC tumor.³⁰ Williams et al³⁰ demonstrated in a mouse model that the differential tumor growth, survival, and tumor clearance of mice challenged with model HPV positive or negative SCC tumors were eliminated in immunocompromised mice lacking B and T cells. Moreover, the splenocytes of mice able to repeatedly clear HPV+ tumors were found to confer the tumor-clearing phenotype to immunocompromised mice upon transfer.³⁰ Thus a difference between the immune response of the host to HPV positive and negative tumors should be expected. This finding does provide a strong rationale for the highly reported improved survival for patients with HPV+ HNSCC (see HRs in Table 3). These findings might otherwise be quite surprising because HPV+ HNSCC is clinically associated with more poorly differentiated cancer and positive lymph nodes.²⁵ In extension, these strong biological differences in survival for HPV+ tumors point to the possibility that disparities between groups with differing rates of HPV+ tumors could be easily detectable.

Oral Transmission of HPV+

Several studies have concluded that HPV is an etiological agent in a subset of HNSCC. Furthermore, oral HPV infection or HPV seropositivity is associated with increased risk of HNSCC independent of the well-established risk factors of tobacco and alcohol.^{25,27,31} For example, nonsmoker, nondrinker patients with HNSCC are more likely to have HPV+ tumors.²⁷ Sexual contact seems to be the primary route of transmission of oral HPV

infection. Higher numbers of lifetime vaginal-sex partners³¹ and the practice of oral–anal sex²⁵ and oral–genital sex^{25,31} are associated with increased risk of HPV+ HNSCC. Oral–vaginal sex as well as open-mouth kissing have been identified as risk factors for the development of oral HPV infection.³²

Interestingly, Wyatt et al^{33,34} have compared sexual practices of women, more recently interviewed, to the famous Kinsey study. The authors report that the practice of cunnilingus and fellatio are increasing from the time of the Kinsey research (1953) to that of the authors (1988).^{33,34} This increase would seem to give reasonability to the recent increase in the incidence of oropharyngeal SCC.²⁷ Interestingly, in both studies black women were found to be less likely to engage in cunnilingus or fellatio, although this difference appears to be decreasing with time.^{33,34} Other reports confirm that white males, also, are more likely than black males to have oral sex with a female, 2.7-fold, and were 1.4-fold more likely to receive oral sex from a female.³⁵ Other authors have suggested that initial genital HPV infection may enhance immune response and thus decrease the risk of oral HPV infection. Therefore, if more black patients are first exposed to HPV via genital/genital contact and more white patients through oral-sexual contact, the disparity could be reconciled independent of overall infection rates.³⁶ This hypothesis is consistent with reports of higher rates of cervical HPV infection among black women. These results agree with the possibility of a racial disparity in the prevalence of HPV+ oropharyngeal SCC. Such a difference could be the root cause of the black versus white survival disparity in question.

Limitations of Dataset

Although SEER data provide a great advantage in numbers and the generality of the population, we note several limitations of these data that should temper the interpretation of any SEER study—for this study, in particular: the lack of data on chemotherapy, limited description of surgical and radiation treatment, and unequal treatments/outcomes from various institutions. Therefore, in a disparities study results can be biased by different racial and ethnic groups attending different institutions and/or receiving differing types or qualities of treatment that may be coded as identical. SEER also contains no data on tobacco or alcohol use.

CONCLUSION

The reported work demonstrates a disease-specific survival disparity for both black and Hispanic patients with HNSCC. The Hispanic population under study demonstrates several of the trends, reported here and elsewhere, to be features of the black population, including later stage at presentation and decreased (disease-specific) survival. However, the magnitude of the disparity for black patients far exceeds that of the Hispanic patients. Furthermore, these disparities appear to be of a fundamentally different quality because case matching for stage, features of presentation, and treatment can eliminate the disparity for Hispanic, but not for black patients.

Furthermore, the presented data in the context of the literature convincingly demonstrate that differences in HPV status are a reasonable explanation for the preponderance of the nationwide disparity in outcomes for black patients with HNSCC. These results emphasize that HPV+ HNSCC is a clinically, biologically, and epidemiologically distinct disease. Further effort must be put into developing high-quality diagnostics for HPV tumor status and treatment strategies tailored to each distinct disease process.

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FIGURE 1.

Kaplan–Meier estimate of disease-specific survival for all available white, Hispanic, and black patients. Unmatched analysis. Solid lines: probability of survival; dashed lines: 95% confidence interval, estimated by the log-transform method; vertical hashes: right censoring. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FIGURE 2.

Kaplan–Meier estimate of disease-specific survival for case-matched cohorts. (A) Hispanic/White case matched pairs (n = 2609). (B) Black/White case matched pairs (n = 4671). Solid lines: probability of survival; dashed lines: 95% confidence interval, estimated by the log-transform method; vertical hashes: right censoring. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FIGURE 3.

Kaplan–Meier estimate of disease-specific survival of head and neck squamous cell carcinoma (HNSCC) for case-matched cohorts, by race and subsite. **(A)** Hypopharynx. **(B)** Oral cavity. **(C)** Larynx. **(D)** Oropharynx. Solid lines: probability of survival; dashed lines: 95% confidence interval, estimated by the log-transform method; vertical hashes: right censoring. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 1

Differences in survival of HNSCC for minority groups in case-matched and unmatched cohorts.

Analysis	No. of cases	10-year survival rate		5-year survival rate		HR (minority vs white)	
		Value	95% CI	Value	95% CI	Value	p value
Unmatched							
Hispanic	4,673	0.77	±0.02	0.80	±0.01	1.14	1.06–1.23
Black	9,619	0.71	±0.02	0.76	±0.01	1.39	1.32–1.47
White	62,252	0.789	±0.005	0.82	±0.003		
Matched							
Hispanic	2,609	0.79	±0.02	0.82	±0.02	0.98	0.85–1.12
White	2,609	0.79	±0.03	0.84	±0.02		.725
Matched							
Black	4,671	0.74	±0.02	0.79	±0.02	1.33	1.20–1.47
White	4,671	0.81	±0.02	0.84	±0.01		<.01

Abbreviations: HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; CI, confidence interval.

Table 2

Differences in survival of HNSCC for black patients by anatomic subsite.

Case-matched group	No. of cases	5-year survival rate		HR (minority vs white)		
		Value	95% CI	Value	95% CI	p value
Oral cavity						
Black	979	0.75	±0.03	1.22	0.99–1.50	.06
White	979	0.79	±0.03			
Oropharynx						
Black	1035	0.87	±0.03	2.05	1.47–2.86	<.01
White	1035	0.94	±0.02			
Hypopharynx						
Black	225	0.73	±0.08	1.23	0.77–1.95	.39
White	225	0.82	±0.07			
Larynx						
Black	2433	0.77	±0.02	1.28	1.12–1.47	<.01
White	2433	0.82	±0.02			

Abbreviations: HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; CI, confidence interval.

Table 3

Analysis of published oropharyngeal SCC survival data by HPV status

Reference (year)	Nonoropharyngeal sites included	HR _{OS} (HPV) * (95% CI) **	HR _{apparent, race} † (least/greatest case simulation value) ‡
Settle et al ⁹ (2009)	None	5.10 (NA)	1.65 (NA)
Fakhry et al ¹¹ (2008)	None	2.56 (−0.08 to 6.66)	1.34 (0.996 to 2.10)
Sedagat et al ¹⁰ (2009)	None	8.33 (1.47 to 50)	1.75 (1.06 to 2.98)
Klozar et al ¹² (2008)	12% Oral cavity	3.70 (1.64 to 8.33)	1.52 (1.06 to 2.24)
Average		4.92	1.63
SEER OS [§] (95% CI)		NA	1.60 (1.42–1.78)
SEER DS [¶] (95% CI)/		NA	2.05 (1.47–2.86)

Abbreviations: SCC, squamous cell carcinoma; HPV, human papillomavirus; HR, hazard ratio; CI, confidence interval; NA, not applicable; SEER, National Cancer Institute's Surveillance, Epidemiology and End Results database; OS, overall survival; DS, disease-specific survival; HNSCC, head and neck squamous cell carcinoma.

* HR of overall survival (reported for the corresponding reference) for the relationship between HPV+ and HPV− oropharyngeal SCC tumors.

** The reported 95% confidence interval of HR_{OS} (HPV).

† The apparent HR of race (black vs white) calculated by Cox regression of simulated data, based on HR_{OS} (HPV) and rates of HPV+ tumors in HNSCC by race, as reported by Settle et al.⁹

‡ The greatest- and least-case scenario difference (HR_{apparent}) based on the 95% CI of the HR (HPV) and %HPV+ reported in the literature (see Materials and Methods).

§ Observed values for OS from the present analysis of the SEER data

¶ Observed values for DS from the present analysis of the SEER data.

/ The 95% CI, reported herein, of HR_{OS} (Race)