Systematic review and meta-analysis of racial survival disparities among oropharyngeal cancer cases by HPV status

Eva Stein MD | Nicholas R. Lenze BS | Wendell G. Yarbrough MD, MMHC
D. Neil Hayes MD, MPH | Angela Mazul PhD, MPH
Siddharth Sheth DO, MPH

1Department of Medicine, University of Colorado, Denver, Colorado
2Department of Otolaryngology/Head & Neck Surgery, University of North Carolina, Chapel Hill, North Carolina
3Department of Medicine, Division of Hematology-Oncology, University of Tennessee Health Science Center, Memphis, Tennessee
4Division of Head and Neck Surgical Oncology, Department of Otolaryngology, Washington University School of Medicine, St Louis, Missouri
5Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St Louis, Missouri
6Division of Hematology/Oncology, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina

Correspondence
Siddharth Sheth, UNC Division of Medical Oncology, Physicians Office Building, CB# 7305, 170 Manning Drive, 3rd Floor, Chapel Hill, NC 27599-7305.
Email: siddharth.sheth@med.unc.edu

Abstract

Background: There is a well documented racial disparity in overall survival for oropharyngeal squamous cell carcinoma (OPSCC); however, it is unknown to what extent this disparity varies by HPV-status.

Methods: A literature search was conducted through December 2019 using Ovid Medline, Cochrane Library, Embase, Scopus, and Clinicaltrials.gov. PRISMA guidelines were followed. A meta-analysis was conducted using random effects models to obtain pooled hazard ratios (HRs).

Results: Of 649 studies initially identified, 20 studies met criteria for the narrative review. There were four studies evaluating survival by race in HPV-positive OPSCC and five studies in HPV-negative OPSCC suitable for pooling. The pooled HR associated with black race was 1.10 (95% CI 0.96-1.23) among patients with HPV-positive (n = 23,608) and 1.50 (95% CI 1.12-1.88) among patients with HPV-negative (n = 12,112). There was notable heterogeneity (I² = 83%) and publication bias among the HPV-negative OPSCC studies.

Conclusions: The racial disparity in OPSCC survival persists for HPV-negative disease and is nonsignificant for HPV-positive disease. Unmeasured differences in socioeconomic status and access to care may contribute to this disparity.

Keywords
disparities, head and neck neoplasms, human papillomavirus, oropharyngeal neoplasms, race, survival

1 | INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the United States, affecting approximately 40,000 new patients each year. Traditional HNSCC risk factors include smoking and alcohol exposure.

However, over the last two decades, HNSCC epidemiology has changed significantly due to the rapidly increasing incidence of oropharyngeal squamous cell carcinoma (OPSCC), which is primarily driven by human papillomavirus (HPV) infection. HPV-associated OPSCC is a unique histopathological and clinical entity from HPV-negative HNSCC with distinct pathogenesis and response to therapy. HPV is a robust and independent predictor for overall survival (OS) in OPSCC. Patients with HPV-positive OPSCC have...
higher sensitivity to chemoradiation, enhanced immunogenecity, and superior survival regardless of the stage at diagnosis. The increase in HPV-associated cancer has driven an improvement in overall HNSCC mortality.

Racial disparities in OPSCC overall are well described, with black patients having worse OS compared to white patients. In contrast, there is limited evidence describing racial disparities in HPV-positive and HPV-negative OPSCC separately. Lower socioeconomic status and access to care in black patients may contribute to the differences in survival for overall OPSCC. Furthermore, a recent study of over 31,000 patients with OPSCC revealed higher HPV prevalence among whites (70.2%) compared to blacks (46.3%). Some propose this explains the difference in outcomes by race. Others postulate that HPV status alone cannot fully account for the survival difference observed by race in OPSCC.

We recently conducted a meta-analysis in which we concluded that HPV accounts for much of the observed racial disparity in survival for OPSCC. However, this conclusion was reached without directly measuring racial disparities by HPV status, but rather by adjusting for HPV status in the overall model. Our results suggested that unmeasured founders other than HPV status may contribute to the racial disparity in OS. Given that HPV-positive and HPV-negative OPSCC are considered distinct clinicopathological entities and studies are increasingly stratifying by HPV-status, we sought to perform an updated analysis taking into account these factors. Understanding the racial disparity in OPSCC will be important for developing targeted interventions aimed at prevention and early diagnosis.

In this study, we (a) examined the current literature on racial disparities in oropharyngeal cancer and (b) performed a meta-analysis to determine a pooled hazard ratio (HR) and 95% confidence interval (CI) comparing black race vs white race in HPV-positive and HPV-negative OPSCC survival, respectively.

2 METHODS

2.1 Literature search

A literature search was conducted through December 2019 using Ovid Medline, Cochrane Library, Embase, Scopus, and Clinicaltrials.gov to identify studies assessing the role of race and HPV status in OS for OPSCC. The following MESH terms and relevant keywords were used in the search: oropharyngeal cancer, health status disparities, racial disparities, health disparities, race, racial, African Americans, black, papillomavirus, and HPV. Reference lists were reviewed for additional articles. The PRISMA reporting guidelines were followed.

This study did not require Institutional Review Board approval or written informed consent because it was a systematic review that used de-identified, publicly available data.

Titles and abstracts of the studies retrieved using the search strategy were screened independently by two review authors (S.S., A.M.) to identify studies that potentially met the inclusion criteria. Each of the full texts of these identified studies was independently assessed for eligibility by three authors (E.S, SS, AM). Any disagreement over the eligibility of a particular study was resolved by discussion and adjudication between study authors.

2.2 Inclusion and exclusion criteria

The following inclusion criteria were applied for the narrative review: studies must (a) specify that patients were diagnosed with OPSCC, and (b) must assess survival differences by race (overall survival, relative survival, disease-free survival, disease-specific survival, etc.). Studies that were not available in English were excluded. Study design (retrospective cohort, prospective cohort, case-control, randomized control trial, etc.) was not used as an inclusion or exclusion criterion in order to capture all studies with potentially relevant data on racial disparities in OPSCC. For inclusion of studies into the pooled meta-analysis, the following additional inclusion criteria were applied: (a) must use a univariate or multivariable Cox regression model to obtain a HR and 95% confidence interval (CI) for OS; (b) the study must use an accepted method for HPV testing, including HPV DNA in situ hybridization (ISH), HPV DNA PCR, or p16 immunohistochemistry; and (c) the study must include black and white race as exposure variables in the survival model.

2.3 Data extraction and risk of bias assessment

Data from eligible studies were independently extracted into a table (E.S. and N.L.) and reviewed by two additional authors (S.S. and A.M.). Extracted information included study authors and year, journal of publication, type of study (hospital based or national database), location of study, sample size, HR with 95% CI for OS by race, other survival results by race (median or percent OS, relative survival, disease-specific survival, or disease-free survival), HPV status, follow-up time, and when applicable, adjustment set (covariates included in the multivariable model). For hospital-based studies, the city and state of the hospital location was recorded. For national database studies, the country of the database location was
recorded. Email correspondence was used to contact study authors with any relevant missing data.

Risk of bias was assessed using the validated Joanna Briggs Institute Critical Appraisal Tool Checklist for Cohort Studies. There were 11 items (coded as yes/no) on the critical appraisal checklist, so we used cut-off scores from 1 to 11 to estimate overall risk of bias. Scores 1 to 4 represented high risk of bias, scores 5 to 8 represented moderate risk of bias, and scores 9 to 11 represented low risk of bias.

2.4 | Statistical analysis

The pooled HR for OS based on race (black patients vs white patients) was calculated separately for patients with HPV-positive and HPV-negative OPSCC. The pooled HR was calculated based on the effect sizes from individual studies. For patients with HPV-positive, 3 of the 4 HRs came from studies with adjusted analyses. For patients with HPV-negative, 4 of the 5 HRs came from studies with adjusted analyses. A random-effects model was employed and forest plots were generated. Heterogeneity was assessed using the $I^2$ statistic, and publication bias was assessed using a funnel plot. All statistical analyses were conducted using the R statistical computing software (version 3.3.1) and meta package was used for the meta-analysis.

3 | RESULTS

3.1 | Search Results

The initial literature search yielded 649 articles, of which 310 were duplicates. After screening titles and abstracts for relevance and inclusion criteria, 208 were excluded (Figure 1). We reviewed 102 full-text articles, which yielded 20 publications that met the inclusion criteria for the narrative review. Fifteen of these studies assessed OS by race without stratifying into HPV-positive and HPV-negative groups. Four of the studies included survival

---

**FIGURE 1** Flow diagram describing the process of identifying and selecting studies for inclusion [Color figure can be viewed at wileyonlinelibrary.com]
<table>
<thead>
<tr>
<th>Manuscript (author, year)</th>
<th>Journal</th>
<th>Type of study</th>
<th>Location of study</th>
<th>No. of patients</th>
<th>Hazard ratio for OS (95% CI)</th>
<th>Other survival results by race</th>
<th>Primary conclusions</th>
<th>Follow-up</th>
<th>Risk of bias assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert et al, 2019</td>
<td>Laryngoscope</td>
<td>Hospital based</td>
<td>Jackson, Mississippi</td>
<td>80</td>
<td>Univariate: 3.17 (1.40-7.19) Multivariable: 4.81 (1.48-15.6)</td>
<td>3-year OS was 45.5% for black patients and 88.1% for white patients (P = .003)</td>
<td>Black race was associated with worse overall survival for OPSCC cancer in the unadjusted and adjusted analysis. Adjustment set included age, T and N classification, tumor crossing midline, nodal necrosis, multilevel nodal involvement, PEG tube, not-completed radiation or chemotherapy, and insurance status.</td>
<td>Median 3 years (range 1.5-10 years)</td>
<td>8 (moderate)</td>
</tr>
<tr>
<td>Amini A., et al, 2016</td>
<td>Oral Oncology</td>
<td>Database (National Cancer Database)</td>
<td>U.S.</td>
<td>3952</td>
<td>Univariate: 2.47 (1.92-3.19) Multivariable: 1.31 (1.00-1.72)</td>
<td>NR</td>
<td>Patients with HPV-positive in the National Cancer Database were more commonly white, young, and male. Black race was associated with worse OS overall in the HPV-negative subset. Adjustment set included age, sex, insurance status, rural/urban/metropolitan residence, Charlson-Deyo Comorbidity Score, facility type, primary tumor site, T and N classification, year of diagnosis, extracapsular extension or positive margins, and treatment modality.</td>
<td>Median 23.7 months (range 1.0-54.5)</td>
<td>8 (moderate)</td>
</tr>
<tr>
<td>Ang K.K., et al, 2010</td>
<td>NEJM</td>
<td>Hospital Based</td>
<td>U.S. (Multicenter RTOG 0129)</td>
<td>433</td>
<td>Multivariable: 2.13 (1.39-3.25)</td>
<td>NR</td>
<td>HPV status and smoking status are major independent prognostic factors for OPSCC. White race was a positive prognostic factor for survival in a combined HPV-positive and HPV-negative OPSCC group. Adjustment set included treatment modality, age, T and N classification, year of diagnosis, extracapsular extension or positive margins, and treatment modality.</td>
<td>Median 4.8 years (range 0.3 to 6.5 years)</td>
<td>8 (moderate)</td>
</tr>
<tr>
<td>Brown L.M., et al, 2011</td>
<td>Cancer Causes Control</td>
<td>Database (Surveillance, Epidemiology, and End Results)</td>
<td>U.S.</td>
<td>880</td>
<td>NR</td>
<td>5-year relative survival rate was 33.2% in African American men vs 60.3% in white men. 5-year relative survival rate was 35.1% in African American women vs 54.6% in white women</td>
<td>Overall OPSCC incidence and mortality were higher in men than women and in African Americans than whites. Relative survival rates took into account the expected mortality for a comparable race-, sex-, age-, and time period-specific cohort</td>
<td>NR</td>
<td>8 (moderate)</td>
</tr>
<tr>
<td>Manuscript (author, year)</td>
<td>Journal</td>
<td>Type of study</td>
<td>Location of study</td>
<td>No. of patients</td>
<td>Hazard ratio for OS (95% CI)</td>
<td>Other survival results by race</td>
<td>Primary conclusions</td>
<td>Follow-up</td>
<td>Risk of bias assessment*</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>-------------------</td>
<td>----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Chen K.M., et al, 2015</td>
<td>JAMA Otolaryngol Head Neck Surg</td>
<td>Hospital based</td>
<td>Detroit, Michigan</td>
<td>121</td>
<td>Multivariable: 0.8 (0.3-1.7) for whites vs blacks</td>
<td>Median OS was 2.5 years (95% CI 1.2-5.2) for black patients and 7.0 years (95% CI 4.2-16.2) for white patients (P = .008)</td>
<td>White race was an independent predictor for HPV-positive status. In univariate analysis, black patients had decreased median OS vs white patients. In a multivariate model, race was not an independent predictor for survival. Adjustment set included sex, age, smoking, treatment, stage, HPV status, and methylation status (IGSF4, DAPK1, ESR1)</td>
<td>NR</td>
<td>6 (moderate)</td>
</tr>
<tr>
<td>Chernock R.D., et al, 2011</td>
<td>Arch. Otolaryngol Head Neck Surg</td>
<td>Hospital based</td>
<td>St. Louis, Missouri</td>
<td>174</td>
<td>NR</td>
<td>Log-rank P-value = .20 comparing Kaplan Meier curves for OS between African American and white patients</td>
<td>The difference in OS was not significant between African American and white patients in an unadjusted Kaplan Meier analysis</td>
<td>Median 28 months (range 2-106 months)</td>
<td>9 (low)</td>
</tr>
<tr>
<td>Fakhry C., et al, 2017</td>
<td>Cancer</td>
<td>Hospital based</td>
<td>Baltimore, MD and San Francisco, CA</td>
<td>239</td>
<td>Univariate: 1.55 (1.01-2.37)</td>
<td>NR</td>
<td>In univariate analysis, survival was significantly worse for black patients compared to white patients; however this effect no longer persisted with statistical significance in the multivariable model. Adjustment set included age, sex, T and N classification, tobacco use, alcohol use, and HPV status</td>
<td>Median 3.5 years (interquartile range, 1.3-6.9 years)</td>
<td>10 (low)</td>
</tr>
<tr>
<td>Faraji F., et al, 2018</td>
<td>Cancer</td>
<td>Database (National Cancer Database)</td>
<td>U.S.</td>
<td>42 024</td>
<td>Univariate: 2.21 (2.06-2.37)</td>
<td>NR</td>
<td>In multivariate analysis, adjustment for socioeconomic factors mitigated, though did not completely erase, racial disparities in survival. Race-based survival differences detected in the overall OPSCC population persisted in the HPV-negative subset (see Table 2). Adjustment set included age, sex, race, year of diagnosis, insurance payer, income, education, metro/urban/rural residence, facility region, T category, N category, M category, Charlson-Deyo score, and treatment</td>
<td>Median 35.7 months (interquartile range 24.3-50.1)</td>
<td>6 (moderate)</td>
</tr>
<tr>
<td>Manuscript (author, year)</td>
<td>Journal</td>
<td>Type of study</td>
<td>Location of study</td>
<td>No. of patients</td>
<td>Hazard ratio for OS (95% CI)</td>
<td>Other survival results by race</td>
<td>Primary conclusions</td>
<td>Follow-up</td>
<td>Risk of bias assessment*</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>------------------------------</td>
<td>------------------------------</td>
<td>----------------------</td>
<td>-----------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Goodman M.T., et al, 2015</td>
<td><em>European Journal of Cancer</em></td>
<td>Database (multiple state-based cancer registries)</td>
<td>U.S. (Florida, Kentucky, Louisiana, Michigan, Hawaii, and Iowa)</td>
<td>529</td>
<td>Multivariable: 2.57 (1.78–3.72)</td>
<td>5-year OS was 15.2% among black patients and 56.6% among white patients (log rank test P-value&lt;0.0001)</td>
<td>Most OPSCC patients were white, and these patients were more likely than black patients to have HPV-positive tumors. Black OPSCC patients had a 2.6-fold greater risk of death after 5 years compared to white patients after adjustment for other prognostic variables. Adjustment set included age, sex, stage, grade, treatment, and HPV status</td>
<td>NR</td>
<td>8 (moderate)</td>
</tr>
<tr>
<td>Isayeva T., et al, 2014</td>
<td>Human Pathology</td>
<td>Hospital based</td>
<td>Birmingham, AL</td>
<td>102</td>
<td>NR</td>
<td>White patients had better disease-specific survival compared to black patients: HR 0.27 (95% CI 0.10-0.75) White patients had better disease-free survival than black patients in the univariate (HR 0.29, 95% CI 0.12-0.71) analysis but the effect was nonsignificant in the multivariable (HR 0.43, 95% CI 0.11-1.63) analysis</td>
<td>African Americans had significantly poorer outcomes compared with whites. This difference was not attributed to differences in HPV activity, but rather to increased p16(INK4a) silencing among African Americans. This tumor suppressor gene is an important positive prognosticator and validated surrogate HPV biomarker. The poorer survival among African Americans was also attributed to higher T classification and nonsurgical management. Adjustment set for disease-free survival analysis included age, T and N classification, tobacco use, treatment, HPV status; disease-specific survival analysis was unadjusted</td>
<td>NR</td>
<td>8 (moderate)</td>
</tr>
<tr>
<td>Jiron J., et al, 2014</td>
<td><em>American Journal of Otolaryngology</em></td>
<td>Hospital based</td>
<td>Detroit, MI</td>
<td>81</td>
<td>Univariate: 2.55 (1.42-4.59)</td>
<td>Median OS was 3.11 years for black patients and 10.94 years for white patients (P = 0.0012)</td>
<td>Black patients with OPSCC had significantly worse overall survival than white patients. Adjustment for smoking alone had little effect on this difference, but adjustment for HPV status drastically reduced the HR. Adjustment set included marital status, smoking, and HPV status</td>
<td>NR</td>
<td>7 (moderate)</td>
</tr>
<tr>
<td>Manuscript (author, year)</td>
<td>Journal</td>
<td>Type of study</td>
<td>Location of study</td>
<td>No. of patients</td>
<td>Hazard ratio for OS (95% CI)</td>
<td>Other survival results by race</td>
<td>Primary conclusions</td>
<td>Follow-up</td>
<td>Risk of bias assessment*</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>--------------------</td>
<td>-----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Razzaghi H. et al, 2018</td>
<td>Cancer</td>
<td>Database (National Program of Cancer Registries)</td>
<td>U.S.</td>
<td>80 151</td>
<td>NR</td>
<td>5-year relative survival rate was 32.4% (95% CI 30.6-34.1) among black patients and 53.5% (95% CI 52.9-54.1) among white patients</td>
<td>African Americans with OPSCC had significantly worse relative survival at 5 years than whites in a large population-based cancer registry. Relative survival rates took into account the expected mortality for a comparable group of age-standardized individuals in the general population</td>
<td>NR</td>
<td>5 (moderate)</td>
</tr>
<tr>
<td>Saha N.F. et al, 2011</td>
<td>Oncology</td>
<td>Database (Surveillance, Epidemiology, and End Results)</td>
<td>U.S.</td>
<td>51 092</td>
<td>Localized disease, Multivariable: 1.59 (1.43-1.77) Advanced disease, Multivariable: 1.92 (1.83-2.0)</td>
<td>5-year OS was 29.3% for black patients and 51.3% for white patients</td>
<td>Black patients with OPSCC had significantly increased mortality for both localized and advanced cancers of the oral tongue, base of the tongue, and tonsils when compared to white patients. The survival difference by race was more pronounced among those with advanced disease compared to localized disease. Adjustment set included age, sex, tumor subsite, and time period</td>
<td>NR</td>
<td>7 (moderate)</td>
</tr>
<tr>
<td>Schrank T.P. et al, 2011</td>
<td>Head and Neck</td>
<td>Database (Surveillance, Epidemiology, and End Results)</td>
<td>U.S.</td>
<td>2070</td>
<td>NR</td>
<td>HR 2.05 (1.47-2.86) for disease-specific survival in black vs white patients</td>
<td>Black patients with OPSCC had significantly worse disease-specific survival than matched white counterparts. Based on the unique relationship between HPV status and oropharyngeal survival, these data may support the hypothesis that differences in HPV infection between blacks and whites play a role in the racial survival disparities. Analysis used case-matching based on age, year of diagnosis, stage, site, and treatment</td>
<td>NR</td>
<td>5 (moderate)</td>
</tr>
<tr>
<td>Manuscript (author, year)</td>
<td>Journal</td>
<td>Type of study</td>
<td>Location of study</td>
<td>No. of patients</td>
<td>Hazard ratio for OS (95% CI)</td>
<td>Other survival results by race</td>
<td>Primary conclusions</td>
<td>Follow-up</td>
<td>Risk of bias assessment*</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>-------------------</td>
<td>-----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Settle K. et al, 2009</td>
<td>Cancer Prevention Research</td>
<td>Hospital based</td>
<td>Baltimore, Maryland</td>
<td>124</td>
<td>NR</td>
<td>Median OS was 25.2 months (95% CI 18.4-36.0) among black patients and 69.4 months (95% CI 52.1-127.3) among white patients ($P = .0006$)</td>
<td>Worse OS for patients with African American HNSCC was driven by oropharyngeal cancer outcomes. The authors conclude that worse OS among black patients with oropharyngeal cancer was driven by a lower prevalence of HPV. The proportion of HPV-positive tumors was nearly 9-fold higher in white patients than in black patients.</td>
<td>Median 67 months</td>
<td>7 (moderate)</td>
</tr>
<tr>
<td>Worsham M.J. et al, 2013</td>
<td>Clinical Cancer Research</td>
<td>Hospital based</td>
<td>Detroit, Michigan</td>
<td>121</td>
<td>Multivariable: 1.15 (0.64-2.07)</td>
<td>NR</td>
<td>Black race was not independently associated with worse outcome in multivariate analysis</td>
<td>Adjustment set included age, gender, HPV status, stage, smoking, treatment, marital status, and year of diagnosis.</td>
<td>Median 46.8 months (range 0.1 to 194 months)</td>
</tr>
<tr>
<td>Yin L.X. et al, 2018</td>
<td>The Laryngoscope</td>
<td>Hospital based</td>
<td>Baltimore, MD and San Francisco, CA</td>
<td>192</td>
<td>HPV-positive, multivariable: 1.09 (0.44-2.72) HPV Negative, Multivariable: 0.80 (0.41-1.57)</td>
<td>NR</td>
<td>Black race was not significantly associated with worse overall survival for HPV-positive OPSCC or HPV-negative OPSCC</td>
<td>Adjustment set included age, sex, stage, alcohol use, and tobacco use</td>
<td>Median 3.5 years (interquartile range 1.3-6.9 years)</td>
</tr>
<tr>
<td>Zandberg D.P. et al, 2016</td>
<td>Head and Neck</td>
<td>Hospital based</td>
<td>Baltimore, MD</td>
<td>331</td>
<td>Multivariable: 1.6 (1.2-2.2)</td>
<td>Median OS was 2.1 years (95% CI 1.5-2.9) for black patients and 4.9 years (95% CI 3.7-8.1) for white patients ($P &lt; 0.0001$)</td>
<td>Black race was associated with worse survival outcomes, with a 1.6-fold increased risk of death among black patients</td>
<td>Adjustment set included sex, age, smoking, alcohol use, and stage.</td>
<td>NR</td>
</tr>
<tr>
<td>Zandberg D.P. et al, 2015</td>
<td>Cancer Prevention Research</td>
<td>Hospital based</td>
<td>Baltimore, MD</td>
<td>194</td>
<td>Univariate: 1.9 (1.4-2.7) Multivariable: 1.9 (1.25-2.90)</td>
<td>Among patients with HPV-positive, median OS was 8.1 years for both black and white patients; $P = .68$ Among patients with HPV-negative, median OS was 0.9 years among blacks and 2.3 years among whites; $P = .02$</td>
<td>There was a significant increase in HPV-positive OPSCC over time, with an emergence of HPV-positive OPSCC in black patients increasing from no cases in 1992 to 1995 to 17.7% of black OPSCC cases in 2004 to 2007. HPV positivity was found to be a positive prognostic factor for OPSCC.</td>
<td>Adjustment set included age, sex, smoking, alcohol use, and HPV status</td>
<td>NR</td>
</tr>
</tbody>
</table>
outcomes by race specifically for HPV-positive OPSCC and five studies reported survival outcomes by race specifically for HPV-negative OPSCC. Table 1 presents the primary findings of the studies included in the review.

### 3.2 Risk of bias assessment

All of the studies that met the criteria for inclusion in the narrative review and meta-analysis had low to moderate risk of bias according to the Joanna Briggs Institute Critical Appraisal Tool Checklist for Cohort Studies. Common sources of bias included incomplete information on follow-up, failure to control for confounding variables such as tobacco use, and lack of reporting about how race categories were obtained (ie, self-report vs chart review).

### 3.3 Narrative review of racial disparities in oropharyngeal cancer not stratified by HPV-status

There were 15 studies that assessed racial disparities in OPSCC without stratifying by HPV status. Among the studies that reported a univariate analysis, HRs associated with black race ranged from 1.55 to 3.17 (Table 1). There were 13 publications that used a multivariable analysis, with HRs for OS in black patients ranging from 1.17 to 4.81 (Table 1). Of the 13 studies that used a multivariable model, 8 showed significantly worse OS for black patients in the adjusted analysis. In a survival model evaluating independent predictors of 5-year survival in OPSCC, for example, black race was associated with a HR of 2.57 (95% CI 1.78-3.72) after adjusting for age, sex, stage, grade, tumor subsite, HPV status, and treatment modality.

### 3.4 Racial disparities among HPV-positive oropharyngeal cancer: Meta-analysis

Four studies assessed OS by race in HPV-positive OPSCC and had sufficient data for pooling into a meta-analysis (n = 23 503). The meta-analysis yielded a pooled HR of 1.10 (95% CI: 0.96 to 1.23; Figure 2A), suggesting that black patients with OPSCC have a nonsignificant hazard of death compared to white patients with OPSCC. The precision funnel plot (Figure 3A) suggests minimal publication bias. Heterogeneity was estimated at 0%, as calculated by the $I^2$ statistic, suggesting that there was very little statistical variation among the studies.
Five studies assessed OS by race in HPV-negative OPSCC and had sufficient data for pooling into a meta-analysis (n = 12,112). The meta-analysis yielded a pooled HR of 1.50 (95% CI: 1.12, 1.88; Figure 2B), suggesting that black patients with HPV-negative OPSCC have a significantly increased hazard of death compared to white patients. Publication bias was illustrated using a precision funnel plot (Figure 3B), which suggests some publication bias in the included studies. The $I^2$ was estimated at 83%, suggesting significant heterogeneity among the included studies.

### 3.5 Racial disparities among HPV-negative oropharyngeal cancer: Meta-analysis

Five studies compared OS in OPSCC by race stratified by HPV status (Table 2). Amini et al used National Cancer Database data on 3952 patients with OPSCC to evaluate the relationship between race and OS in HPV-positive, HPV-negative, and combined subsets. Black race was associated with worse OS in the combined...
<table>
<thead>
<tr>
<th>Manuscript (author, year)</th>
<th>Journal</th>
<th>Type of study</th>
<th>Location of study</th>
<th>No. of patients in model</th>
<th>Hazard ratio: HPV+ (95% CI)</th>
<th>Hazard Ratio: HPV- (95% CI)</th>
<th>Primary conclusions</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amini A. et al, 2016</td>
<td>Oral Oncology</td>
<td>Database (National Cancer Database)</td>
<td>U.S.</td>
<td>2454 (HPV+) 1498 (HPV-)</td>
<td>Multivariable: 1.01 (0.50-2.03)</td>
<td>Multivariable: 1.38 (1.00-1.89)</td>
<td>Patients with HPV-positive in the National Cancer Database were more commonly white, young, and male. Black race was associated with worse OS overall and in the HPV-negative subset. Adjustment set included age, sex, insurance status, rural/urban/metropolitan residence, Charlson-Deyo Comorbidity Score, facility type, primary tumor site, T and N classification, year of diagnosis, extracapsular extension or positive margins, and treatment modality</td>
<td>Median 23.7 months (range 1.0-54.5)</td>
</tr>
<tr>
<td>Faraiji F. et al, 2018</td>
<td>Cancer</td>
<td>Database (National Cancer Database)</td>
<td>U.S.</td>
<td>20,886 (HPV+) 10,364 (HPV-)</td>
<td>Multivariable: 1.10 (0.95-1.27)</td>
<td>Multivariable: 1.21 (1.10-1.33)</td>
<td>In this large population study, race predicted worse survival among black patients with HPV-negative compared to patients with white HPV-negative. Among patients with</td>
<td>Median 35.7 months (interquartile range 24.3-50.1)</td>
</tr>
<tr>
<td>Manuscript (author, year)</td>
<td>Journal</td>
<td>Type of study</td>
<td>Location of study</td>
<td>No. of patients in model</td>
<td>Hazard ratio: HPV+ (95% CI)</td>
<td>Hazard Ratio: HPV- (95% CI)</td>
<td>Primary conclusions</td>
<td>Follow-up</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------------</td>
<td>-------------------</td>
<td>-------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>---------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Worsham M.J. et al, 2013</td>
<td>Clinical Cancer Research</td>
<td>Hospital based</td>
<td>Detroit, MI</td>
<td>51 (HPV+) 67 (HPV-)</td>
<td>Univariate: 1.10 (0.42-2.88)</td>
<td>Univariate: 2.21 (1.19-4.08)</td>
<td>HPV-positive, there was a trend toward worse survival among black patients compared to white patients that did not reach significance. Adjusted set included age, sex, race, year of diagnosis, insurance payor, income, education, metro/urban/rural residence, facility region, T category, N category, M category, Charlson-Deyo score, and treatment</td>
<td>Median 46.8 months (range 0.1 to 194 months)</td>
</tr>
<tr>
<td>Yin L.X. et al, 2018</td>
<td>The Laryngoscope</td>
<td>Hospital-based</td>
<td>Baltimore, MD and San Francisco, CA</td>
<td>113 (HPV+) 79 (HPV-)</td>
<td>Multivariable: 1.09 (0.44-2.72)</td>
<td>Multivariable: 0.80 (0.41-1.57)</td>
<td>In this retrospective case series, race did not play a prognostic role among either patients with HPV-positive or -negative. The authors conclude that</td>
<td>Median 3.5 years (interquartile range 1.3-6.9 years)</td>
</tr>
<tr>
<td>Manuscript (author, year)</td>
<td>Journal</td>
<td>Type of study</td>
<td>Location of study</td>
<td>No. of patients in model</td>
<td>Hazard ratio: HPV+ (95% CI)</td>
<td>Hazard Ratio: HPV- (95% CI)</td>
<td>Primary conclusions</td>
<td>Follow-up</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>--------------</td>
<td>-------------------</td>
<td>-------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>---------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Zandberg D.P., et al 2015</td>
<td><em>Cancer Prevention Research</em></td>
<td>Hospital based</td>
<td>Baltimore, MD</td>
<td>104 (HPV-)</td>
<td>None reported</td>
<td>Multivariable: 2.0 (1.28–3.14)</td>
<td>Black race predicted poorer survival among an HPV-negative subset. Median OS was the same in black and white patients who were HPV-positive (8.1 years from time of diagnosis). Adjustment set included age, sex, smoking, alcohol use, and overall stage</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported; OS, overall survival.
group (regardless of HPV status) and the HPV-negative group, with HRs of 1.31 (95% CI 1.00-1.72) and 1.38 (95% CI 1.00-1.89), respectively. In the HPV-positive group, the relationship was nonsignificant (HR 1.01, 95% CI 0.95-2.03). The multivariable model included age, gender, race, insurance status, residence (metropolitan, rural, or urban), Charlson-Deyo comorbidity score, facility type, T and N classification, diagnosis year, and primary treatment.

Another cohort study of 20,866 patients with HPV-positive and 10,364 HPV-negative OPSCC from the National Cancer Database showed a temporally increasing HPV prevalence among all racial groups but at a faster rate among blacks and Hispanics. Among patients with HPV-negative, black patients had a higher risk of death compared to white patients (HR 1.21, CI 1.10-1.33). However, the adjusted HR among patients with HPV-positive was nonsignificant (HR 1.10 (95% CI 0.95-1.27). This model included age, sex, year of diagnosis, insurance payor, income, education, residence (metropolitan, rural, or urban), facility region, T category, N category, M category, Charlson-Deyo comorbidity score, and treatment in the adjustment set.

In a cohort study of 121 patients, HPV-positive status correlated with improved OS, with a 2.7 higher risk of death among patients with HPV-negative (HR 2.70, 95% CI 1.37-5.31) after adjusting for age, race, sex, tumor stage, treatment, smoking status, marital status, and year of diagnosis. In the combined HPV-positive and -negative cohort, black race was not independently associated with worse OS after adjusting for age, race, sex, tumor stage, treatment, smoking status, marital status, and year of diagnosis. Among patients with HPV-negative, black race predicted decreased OS with an HR of 2.21 (95% CI 1.00-1.89) in the univariate analysis. Among patients with HPV-positive, there were no differences in OS by race (P = .84) in the univariate analysis. Of note, this study did not report adjusted HRs for the HPV-stratified models.

Yin et al conducted a retrospective case series of 239 patients with OPSCC at Johns Hopkins and University of California-San Francisco with survival analyses stratified by HPV status. This analysis revealed a nonsignificant relationship between black race and OS among patient cohorts with HPV-positive and HPV-negative. The adjusted model included sex, age, stage, alcohol use, and tobacco use. The authors concluded that HPV status may explain the racial disparities in survival that have been documented in other studies not accounting for HPV status.

In a retrospective study of 467 patients with OPSCC, black race negatively predicted OS in a combined HPV-positive and HPV-negative group. Among the HPV-positive subset, there was no significant difference in OS by race (median OS 8.1 years in both groups). However, HPV-negative black patients had significantly worse survival than HPV-negative white patients, with an HR of 2.0 (95% CI 1.28-3.14), after adjusting for age, gender, smoking, alcohol, and overall stage.

4 | DISCUSSION

Racial disparities have been identified in survival outcomes in many different cancers. In oropharyngeal cancer, there are multiple potential contributors to this disparity, including variation in HPV prevalence, access to care, and provision of treatment. To fully understand racial disparities in OPSCC, evaluation by HPV status is imperative, as these are distinct cancer entities with unique pathogenesis, treatment approach, and survival outcomes. In this study, review of the literature reveals a paucity of evidence examining survival outcomes by HPV status. Nevertheless, the data suggest that survival disparities by race exist among patients with HPV-negative OPSCC and are not statistically significant among patients with HPV-positive OPSCC.

In most OPSCC studies, black Americans have worse overall and disease specific survival compared to white Americans. Our review of the literature confirmed this consensus. In our meta-analysis, black race was a predictor for worse survival compared to white race among patients with HPV-negative OPSCC, with a pooled HR of 1.50 (95% CI 1.12-1.88). Among patients with HPV-positive, the pooled HR 1.10 (95% CI 0.96-1.23) was not statistically significant, suggesting no difference in OS by race.

There are several likely contributors to survival disparity among patients with OPSCC. Known contributors to racial disparities in cancer include variation in tumor biology, access to care, biased provision of care, and differences in environmental exposures including but not limited to tobacco and alcohol. There is supporting evidence for these variables playing a role across cancer types, including but not limited to breast, urologic, lung, and hematologic malignancies. With regards to OPSCC in particular, household residence in a county with a low socioeconomic index (defined based on educational, poverty level, and unemployment of the residents) compared to a county with high socioeconomic index has been associated with worse OS outcomes in the United States. Black individuals remain far more likely to live below the poverty line, with 20% of black individuals in poverty compared to 8% of white individuals in 2017. In a Veterans Affairs population, where access to care and socioeconomic status are considered to be relatively
homogenous, there were no differences in survival based on race. Together these findings suggest that worse socioeconomic status among black patients is an important driver of the survival differences observed in OPSCC.

With respect to the differential provision of care, a retrospective analysis of Surveillance, Epidemiology, and End Results (SEER) found that black patients with oral and oropharyngeal cancer were less likely than white patients to be referred for surgery regardless of cancer stage and socioeconomic status. Similar patterns have been identified in other cancers. In breast cancer, lack of medical insurance, lower socioeconomic status, and barriers to screening have been linked to worse survival outcomes in black women. Differences in OPSCC tumor pathogenesis, independent of HPV status, may further widen racial disparities in survival. Isayeva et al found that the silencing of p16INK4, a well-validated prognosticator for worse survival in OPSCC, was far more common among black patients regardless of HPV infection. This may reflect differences in smoking prevalence and duration in addition to other unidentified differences in tumor pathogenesis.

A recent INHANCE analysis found that black patients with head and neck squamous carcinoma had higher rates of smoking history than white patients (90.4% of 880 black patients vs 81.8% of 5395 white patients). Furthermore, the adjusted OR for incidence of oropharyngeal cancer was greater among black ever smokers than white ever smokers (OR 2.70, 95% CI 1.66-4.39) vs [OR 1.49, 95% CI 1.32-1.68], respectively) after adjusting for age, sex, study center, educational level, alcohol use, and duration of smoking. These findings suggest that the effect of tobacco use on head and neck cancer outcomes is modified by race, which some authors hypothesize could be secondary to genetic differences in tobacco-related metabolism and pathogenesis. Of note, only 2 of the 5 studies in our pooled analysis adjusted for tobacco use, which is a limitation that could potentially bias our results toward the observed racial disparity.

It is important to evaluate why racial disparities were nonsignificant in the HPV-positive cohorts identified in our narrative review and pooled meta-analysis. The two large-scale, population-based studies that stratified analysis by HPV status employed models that accounted for indirect measures of socioeconomic status. Amini et al included insurance status and residence location (metropolitan, rural, or urban), and Faraji et al included insurance payor, income, education, and residence location. In both of these studies, the racial disparity may have been driven by differences in socioeconomic status, which could explain the nonsignificant HRs in the adjusted models. These two large-scale studies support the notion that the racial disparity in HPV-positive OPSCC may be mediated by socioeconomic variables or access to care.

The small size of the HPV-positive study samples may have limited the detection of survival disparities by race. Three studies were conducted in single-institutions with small HPV-positive samples. In a single system, insurance and treatment options may be relatively homogenous, limiting generalizability of the study. Moreover, given the lower prevalence of HPV among black patients, studies may be underpowered to detect a difference based on race. In three separate studies of OPSCC, the percentage of patients with black race and HPV-positive tumor status in the sample was 5% (10/200), 12.7%, (15/118) patients, and 14.2% (34/239), respectively.

The primary limitation of this meta-analysis is the small number of published studies in literature meeting our inclusion criteria. This highlights the need for more research that evaluates the racial disparities in HPV-positive and HPV-negative OPSCC. Our meta-analysis was also limited by significant heterogeneity among the HPV-negative OPSCC studies ($I^2 = 83\%$). This may be attributable to underlying differences in the study populations or adjustment sets. For example, the studies varied considerably in sample size (2 were national database studies and 3 were small hospital-based studies). Additionally, there were only 2 studies that adjusted for tobacco use and 2 that adjusted for indicators of socioeconomic status. We used a random effects model to help account for this heterogeneity, but we still recognize this as a potential limitation. Future studies should ideally adjust for tobacco use and measures of socioeconomic status when examining racial disparities in head and neck cancer to improve consistency and provide more accurate survival estimates.

Another limitation we encountered in the meta-analysis was the potential for overlapping populations between Amini et al and Faraji et al. Both used the National Cancer Database, with Amini et al using patients diagnosed from 2009 to 2011 and Faraji et al from 2010 to 2015. To examine the influence of these studies on the pooled effect size, we conducted a sensitivity analysis excluding Amini et al. The pooled effect size and confidence interval did not significantly change for the patients with HPV-positive (HR 1.10 95% CI 0.94-1.26), but for patients with HPV-negative, the effect became nonsignificant (HR 1.34 95% CI 0.82-1.86). Given that there was only 1 year of potentially overlapping patients (2010-2011), we elected to keep both of the studies. However, we recognize that this could bias our results in the direction of a disparity for patients with HPV-negative, and therefore we must interpret the results for the pooled analysis with caution. More
research is needed to improve the precision of these estimates.

Finally, it is important to note that there was substantial publication bias among the studies in our pooled analysis for HPV-negative OPSCC. The funnel plot demonstrates that the majority of studies had a significant and positive effect size for the racial disparity in HPV-negative OPSCC. The two studies with the greatest effect sizes also had relatively large standard errors. This finding supports the notion that small studies may be more likely to be published if they demonstrate significant findings. Given the evidence of publication bias, we expect that our pooled analysis may slightly overestimate the effect for the racial disparity in HPV-negative OPSCC. Journals are increasingly addressing publication bias by encouraging authors to submit negative or nonsignificant findings appropriately, and this will be especially relevant for fully understanding racial disparities in OPSCC.

There are well-documented racial disparities in survival in OPSCC, and these were confirmed by our review of the literature. There is a marked lack of published literature evaluating racial disparities in OPSCC stratified by HPV status. Among studies that are published, the persistence of a racial survival disparity among HPV-negative OPSCC suggests that HPV alone does not account for the entirety of survival disparities.

5 CONCLUSIONS

Racial disparities in OS for OPSCC persist when stratified by HPV-status. Black patients have worse OS compared to white patients for HPV-negative OPSCC. The association between race and OS for HPV-positive OPSCC was not statistically significant in any of the individual studies or the pooled analysis. More research is needed to better understand these findings and elucidate underlying mechanisms for this racial disparity in patients with HPV-negative OPSCC.

ORCID

Nicholas R. Lenze https://orcid.org/0000-0002-2126-6663
Siddharth Sheth https://orcid.org/0000-0002-1923-2309

REFERENCES


How to cite this article: E Stein, NR Lenze, WG Yarbrough, DN Hayes, A Mazul, S Sheth. Systematic review and meta-analysis of racial survival disparities among oropharyngeal cancer cases by HPV status. Head & Neck. 2020;42:2985–3001. https://doi.org/10.1002/hed.26328