Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature: _____

Shruthi Rereddy Date: 4/8/2015

Oropharyngeal Squamous Cell Carcinoma and Human Papillomavirus in African American Populations

By

Shruthi Rereddy

Master of Science

Clinical Research

_____

Georgia Z. Chen, Ph.D.
Advisor

_____

Charles E. Moore, M.D.
Advisor

_____

Beau Bruce, M.D., Ph.D.
Committee Member

_____

Mitchel Klein, Ph.D.
Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____

Date

# Oropharyngeal Squamous Cell Carcinoma and Human Papillomavirus in African American Populations

By

Shruthi Rereddy
B.A, Dartmouth College, 2009

Advisor: Georgia Z. Chen, Ph.D.
Advisor: Charles E. Moore, M.D.

An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Clinical Research
2015

Abstract

Oropharyngeal Squamous Cell Carcinoma and Human Papillomavirus in African American Populations

By

Shruthi Rereddy

Purpose: Oropharyngeal squamous cell carcinoma (OPSCC) mortality in the U.S. is higher among African American patients compared to Caucasians. Tumors positive for human papillomavirus (HPV) are associated with decreased OPSCC mortality risk. Variation in tumor HPV status may explain the OPSCC mortality difference by race. This study examines overall survival in African American and Caucasian patients with HPV-positive and HPV-negative OPSCC.

Study Design: A retrospective cohort of 223 patients with biopsy-proven squamous cell carcinoma of the oropharynx was identified from tumor board registries and surgical logs. Patient demographics, risk factors, tumor characteristics, treatment modality, and comorbid disease were abstracted from medical records. Tumor HPV status was determined by p16 immunohistochemistry (IHC). Prevalence of p16-positive disease was compared between races using Chi square tests. Associations between p16-positive disease and race were analyzed using univariate and multivariate logistic regression models. Survival was analyzed using Kaplan-Meier plots and Cox proportional hazards models.

Results: The prevalence of p16-positive disease varied by race with 77.7% of Caucasian patients testing positive compared to 56.3% of African American patients ($p=0.003$). African American patients had significantly poorer survival compared to Caucasian patients both overall and when stratified by p16-negative and p16-positive groups ($p<0.0001$, $p=0.0253$, $p=0.0024$, respectively). African American patients had decreased survival compared to Caucasian patients even after adjusting for p16 status, tumor stage, alcohol and tobacco use, and socioeconomic factors (HR=2.10, $p=0.0244$).

Conclusions: Caucasian OPSCC patients were more likely to have p16-positive tumors compared to African American patients, however this difference did not fully explain the mortality risk difference between the two races even after adjusting for socioeconomic and behavioral factors. This study contributes to the growing evidence that tumor HPV status varies by race and may contribute to racial disparities in outcomes for OPSCC.

# Oropharyngeal Squamous Cell Carcinoma and Human Papillomavirus in African American Populations

By

Shruthi Rereddy
B.A, Dartmouth College, 2009

Advisor: Georgia Z. Chen, Ph.D.
Advisor: Charles E. Moore, M.D.

A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Clinical Research
2015

Table of Contents

List of Tables and Figures

# INTRODUCTION

Head and neck cancer refers to cancers arising from the nasal cavity, sinuses, mouth, salivary glands, cervical soft tissues, oropharynx, pharynx or larynx. The vast majority of these cancers are squamous cell carcinoma. The American Cancer Society estimates that 59,340 people will be diagnosed with head and neck cancer in 2015. Approximately 12,290 people will die of these cancers this year (1). Although this disease is relatively uncommon, it is a devastating diagnosis for patients and families due to its significant morbidity and associated impact on speech, swallowing, and appearance.

Tobacco and alcohol use have traditionally been the primary etiologic factors for head and neck cancer (2). However, sexually acquired oral infection with human papillomavirus (HPV) has emerged as a major risk factor for a specific subset of head and neck cancers – those arising from the oropharynx (3, 4, and 5). While the incidence of most head and neck cancers has declined over the past two decades, there has been a rise in the incidence of oropharyngeal squamous cell carcinoma (OPSCC), leading many to classify this disease as an "epidemic" due to its causal relationship with a virus (3, 6, and 7).

It has also been shown that HPV-positive OPSCC has a distinct clinical phenotype from HPV-negative OPSCC. Although patients with HPV-positive cancers tend to present at a more advanced clinical stage, they have a significantly improved prognosis compared to patients with HPV-negative OPSCC (3 and 5). A landmark 2010 trial estimated a 3-year survival of 82.4% for HPV-positive OPSCC compared to 57.1% for HPV-negative disease (8).

However, much of the research involving HPV and OPSCC is based on Caucasian populations. This is a significant shortcoming, as large health disparities exist between African American and Caucasian patients with respect to OPSCC. Three-year disease-free survival for OPSCC is 57% in Caucasian patients compared to 28% in African American patients (9). There is no consensus as to the cause of these disparities. Socioeconomic status, differential access to care, and insurance status are thought to play a role (10 and 11). It is unclear whether biological factors such as HPV status contribute to the racial disparity in outcome.

Therefore, the goal of this research is to further examine the relationship between race, HPV status and survival among patients with OPSCC. Our hypothesis is that the prevalence of HPV-positive disease among patients with OPSCC varies by race, and African American patients have a lower prevalence of HPV-positive tumors. Consistent with the existing literature, we anticipate that race is associated with survival among patients with OPSCC, and African American patients have poorer survival than Caucasian patients. We also expect that HPV status is associated with survival; patients with HPV-positive OPSCC disease have improved survival compared to patients with HPV-negative disease. Moreover, we hypothesize that the effect of HPV status on survival among OPSCC patients is modified by race.

# BACKGROUND

The association between HPV and OPSCC has emerged over the past two decades. A 2010 study of 743 patients reported that HPV DNA was detected in 74.6% of oropharyngeal cancers, with HPV type 16 accounting for 96.1% of HPV-positive cancer cases (8). In addition to epidemiologic data, a growing body of molecular evidence has demonstrated specificity of HPV to oropharyngeal tumor cell nuclei (12), integration of HPV DNA into the genome of neoplastic oropharyngeal cells (12 and 13), and overexpression of HPV oncogenes E6 and E7 in oropharyngeal tumor cells (14 and 15). These studies establish HPV as a causative agent in oropharyngeal cancers.

A cross-sectional study conducted as a part of the 2009 National Health and Nutrition Examination Survey estimated the overall prevalence of oral HPV infection as 6.9%, with a higher prevalence among men compared to women (16). The oncogenic pathway from oral infection with HPV to HPV-positive OPSCC has not been well defined. However, it is apparent that the majority of oral HPV infections are cleared by the immune system, while a small proportion progress to OPSCC.

## Clinical aspects of HPV-positive OPSCC

The clinical features of HPV-positive OPSCC are distinct from those of HPV-negative cancers. Patients with HPV-positive tumors present at an advanced clinical stage characterized by smaller tumor size but greater nodal involvement (3). Despite this advanced presentation, numerous retrospective and prospective studies have demonstrated that patients with HPV-positive OPSCC have better locoregional control

(17), improved disease-specific survival (17 and 18), and better overall survival compared to those with HPV-negative OPSCC (8, 17, and 18).

The RTOG 0129 trial, a prospective study designed to evaluate standard versus accelerated radiotherapy for head and neck cancer, found that HPV-positive tumor status was independently associated with a 58% reduction in overall risk of death (HR 0.42, 95% CI 0.27–0.66) (8). The ECOG 2399 trial, a multi-institutional prospective study, determined that patients with HPV-positive OPSCC had a significantly improved response to induction chemotherapy (82% vs. 55%, $p = 0.01$) and concomitant chemoradiotherapy (84% vs. 57%, $p = 0.007$) compared to those with HPV-negative tumors (18).

The exact mechanism behind the improved survival is unclear; however, these favorable outcomes are independent of treatment modality. Patients treated with surgery, radiotherapy, chemotherapy, or a combination of the three appear to do equally well (8, 17, 18, and 19).

**Determination of Tumor HPV Status**

Despite the prognostic significance of tumor HPV status, there is no standardized test for the determination of tumor HPV status. The two methods commonly utilized in a clinical setting are detection of HPV16 by in situ hybridization (ISH) or detection of p16 by immunohistochemistry (IHC) as a surrogate marker for the high-risk HPV E7 protein (20). The gold standard test for determination of tumor HPV status is expression of high-risk HPV E6/E7 oncogenes as detected by reverse transcription PCR, however this is generally deemed unfeasible in a clinical laboratory setting (21).

A 2012 study comparing these methods of HPV status determination found high agreement between results for HPV16 ISH and p16 IHC ($\kappa = 0.70$). The sensitivity for p16 IHC was 96.8% (95% CI 92.8-99.0%) and the specificity was 83.8% (95% CI 73.4-91.3%); the sensitivity for HPV16 ISH was 88.0% (95% CI 81.9-92.6%) and the specificity was 94.7% (95% CI 86.9-98.5%) (22). The sensitivity of HPV16 ISH is limited by an inability to detect the presence of high-risk HPV types other than HPV16 in tumors, although this is a very small proportion of HPV-positive tumors. The specificity of p16 IHC is limited by the presence of p16-positive tumors that do not have evidence of HPV DNA or E6/7 expression.

**Racial disparities in OPSCC**

There are large health disparities between African Americans and Caucasians, both with respect to head and neck cancer in general and OPSCC specifically. From 2003-2007, mortality from head and neck cancers in the white population was 3.7 per 100,000 men compared to 6.3 per 100,000 men in the African American population (23). On average, African American patients develop head and neck cancers at an earlier age, present with more advanced disease, and have a significantly poorer prognosis compared to their white counterparts (10, 11). These disparities are particularly apparent in OPSCC (9, 10, 24, and 25).

While socioeconomic status, health literacy, and access to care contribute to these disparities (10), several studies have demonstrated that poorer outcomes for African American patients persist even after adjusting for socioeconomic factors (11 and 26). In 2009, Settle et al proposed that a lower prevalence of HPV-positive OPSCC among

African American patients was responsible for racial disparities in survival observed in a prospective trial for advanced stage head and neck cancer patients treated with primary chemoradiotherapy (27). The two major limitations of this study are that it included patients with tumors from all sites in the head and neck, and that only 28 African American patients were tested for tumor HPV status. However, this study raised the interesting possibility of a biological explanation for racial disparities in OPSCC outcomes.

# METHODS

There are four hypotheses in this study. First, African American patients with OPSCC have a lower prevalence of HPV-positive disease than Caucasian patients. Second, race is associated with survival among patients with OPSCC, and African American patients with OPSCC have poorer survival than Caucasian patients. Third, OPSCC patients with HPV-positive disease have improved survival compared to patients with HPV-negative disease. Finally, the effect of HPV status on survival of OPSCC patients is modified by race.

The study was a retrospective cohort of African American and Caucasian patients diagnosed with biopsy-proven squamous cell carcinoma of the oropharynx (defined as base and dorsal surface of the tongue, soft palate, uvula, tonsils, and all other oropharynx sites except branchial cleft) at Emory Healthcare or Grady Health System from 1/1/10 to 12/31/12. Time zero for the cohort was defined as the date of diagnosis via biopsy. Within this larger study, a cross-sectional design was used to determine the prevalence of HPV-positive OPSCC by race at time of diagnosis. The Institutional Review Board of Emory University and the Research Oversight Committee of Grady Health System approved this study (Emory IRB#15670 and Grady ROC#63974).

## Patient population

The patients were drawn from Emory Healthcare, a tertiary referral medical center, and Grady Health System, a large public hospital system serving DeKalb and Fulton Counties. Patients diagnosed with OPSCC within the study period (1/1/10-

12/31/12) were identified though surgical logs and tumor board registries. Patients under the age of 18 were excluded from the analysis, as were those with a previous diagnosis of head and neck cancer, those without histologic confirmation of disease, and those who identified as a race other than African American or Caucasian. Finally, patients who had not previously undergone tumor HPV status determination and lacked sufficient banked tumor specimen for testing were also excluded from the analysis.

**Data collection and measurements**

Demographic, pathologic, treatment, and outcome data were collected. Race, gender, employment, and marital status were self-reported on patient intake forms at the time of diagnosis. Age, primary tumor site, date of diagnosis, TNM stage, tobacco and alcohol exposure, comorbid disease, treatment, recurrence, and date of last contact were extracted from the medical record in June 2014, two years following the study period.

TNM stage is defined by the American Joint Committee on Cancer and assigned based on the size of the untreated primary tumor (T), regional lymph node involvement (N), and distant metastasis (M) as determined by clinical examination and imaging findings (28). For analytic purposes, the TNM stage was further categorized as early (stage 1 or 2), stage 3, and stage 4.

Tobacco exposure was categorized as “never smoker,” “former smoker” if the patient reported no tobacco use at least 1 month prior to diagnosis of OPSCC, or “current smoker” if the patient reported tobacco use in the month prior to diagnosis. Alcohol exposure was categorized as “none/minimal” if the patient reported $\leq 2$ eight-ounce

alcoholic beverages per week, “moderate” if 3-8 drinks per week, or “heavy” if >8 drinks per week.

Comorbidity was graded using the Charlson Comorbidity Index, a numerical score that summarizes age and various comorbid conditions (29). The Charlson Index was chosen as it has been widely validated in the head and neck cancer population (30-33). The comorbid conditions included in the Charlson score are myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes mellitus, chronic kidney disease, hemiplegia, leukemia, lymphoma, solid tumor (other than OPSCC), liver disease, and AIDS.

Treatment was categorized as surgery alone, surgery with post-operative chemotherapy, surgery with post-operative radiation therapy, surgery with post-operative chemoradiation, radiation therapy alone, chemotherapy alone, and chemoradiation. Patients were considered disease free if physical exam and imaging findings revealed no evidence of disease at six weeks post-treatment. Recurrence of disease was determined clinically via physical exam, flexible fiberoptic endoscopy, and surveillance imaging with computed tomography and/or magnetic resonance imaging.

The primary outcome for the prevalence hypothesis was tumor HPV status as determined by p16 immunohistochemistry. Tumor p16 status was determined from the medical record or by testing banked tumor specimen if p16 status was previously unrecorded and there was enough specimen to test. Briefly, formalin-fixed, paraffin-embedded tumor tissue sections were stained using prediluted monoclonal mouse anti-human $p16^{INK4a}$ from the CINtec histology kit (Ventana, Tuscan, AZ) according to the

manufacturer's protocol. Board-certified pathologists from Emory University interpreted all slides.

The primary outcome for the survival analyses was overall survival from date of diagnosis via biopsy to date of death from any cause or date of last contact if censored. Death data was compiled from the medical record and confirmed by cross-referencing with the Social Security Death Index.

**Power calculations**

A power analysis was conducted using the sample size obtained from preliminary data collection, as the sample was fixed for this retrospective study. Power was estimated for Fisher's exact test comparing the proportion of p16 positive disease by race. The proportion of p16 positive disease was estimated at 0.7 in Caucasians and 0.35 in African Americans based on a review of current literature (7, 8, 34, 35). The projected power for this analysis using our sample size was 0.999. Power was also estimated for the log rank test for Kaplan-Meier analysis comparing overall survival by race. The three-year survival for OPSCC was estimated as 0.70 in Caucasians and 0.45 in African Americans according to American Cancer Society Facts & Figures 2014 (ACS). The projected power for the Kaplan-Meier analysis using our sample size was 0.946. A retrospective power analysis was performed for the Cox proportional hazards model testing for interaction between race and p16 status using results obtained from the statistical analysis. All power calculations were performed using R version 3.1.2.

**Statistical Analysis**

All analyses were performed using SAS 9.4. Statistical significance was set at $p<0.05$. Descriptive statistics were calculated with categorical data presented as counts (percent) and continuous data as mean (standard deviation). Patient characteristics were compared by race and tumor p16 status using Student t-tests for continuous variables and $\chi^2$ analyses for categorical variables; Fisher's exact test was used for categorical variables with one or more cell counts below 10. Univariate and multivariate logistic regression analyses were utilized to test associations between p16 positive disease and other covariates. Kaplan-Meier survival curves and log-rank tests were used to analyze overall survival by race and p16 status.

Cox proportional hazards models were utilized to estimate hazard ratios (HRs) of death and corresponding 95% confidence intervals (CIs). The proportional hazards assumption was tested for race and p16 by plotting log-negative-log curves. Crude HRs for race and p16 status were estimated in univariate Cox regression models. Adjusted HRs for race and p16 status were estimated in a Cox model that included both variables. Interaction between race and p16 status was tested using an interaction term in a Cox model and estimating stratum-specific HRs of death. Finally, multivariable HRs of death were estimated for race and p16 status adjusting for disease stage, smoking and alcohol history, employment, and marital status.

# RESULTS

## Population Characteristics

We identified 262 patients diagnosed with OPSCC at Emory Healthcare and Grady Health System from 1/1/10 to 12/31/12. There were 13 patients who were Asian or Hispanic, 3 with a previous diagnosis of head and neck cancer, 4 with no histologic confirmation of disease, and 19 with no p16 result in the medical record and insufficient banked tumor specimen for testing. This resulted in 223 patients who met study criteria.

African American patients comprised 22.2% of the subjects. The mean age at diagnosis was 58.5 years with a standard deviation of 8.8 years. The patients were predominately male, with men comprising 87% of the population. Tobacco use varied among patients; 35.4% were never smokers, 39.5% were former smokers, and 25.1% were current smokers. The majority of patients reported limited alcohol consumption; 65.0% did not drink or drank minimally, 24.2% were moderate drinkers, and 10.8% were heavy drinkers. The mean comorbidity score was 2.8 with a standard deviation of 1.7. The majority of patients had advanced disease with 84.8% presenting with Stage 4 cancer. Patients also had predominantly p16 positive disease with 73.1% of the tumors testing positive. The median length of follow up was 31 months with an interquartile range of 20 months; 55 patients died.

## Associations with Race and Tumor p16 Status

Patient characteristics are compared by race in Table 1. The prevalence of p16 positive disease varied by race – 77.7% of Caucasian patients had p16 positive tumors

versus 56.3% of African American patients (p=0.003). The age at diagnosis also varied by race, as did tobacco and alcohol use. African American patients were diagnosed at a younger age and had higher exposure to tobacco and alcohol. Employment and marital status also varied by race. African American patients had a markedly higher prevalence of disability/unemployment and lower prevalence of marriage. Patient characteristics are compared by tumor p16 status in Table 2. There was a higher prevalence of tobacco and alcohol use in patients with p16 negative disease, as well as a lower prevalence of marriage.

Univariate associations with p16 positive disease are summarized in Table 3. African American patients had lower odds of p16 positive OPSCC compared to Caucasian patients (OR = 0.369, p=0.0036). Tobacco and alcohol use were negatively associated with p16 positive disease. Marriage was positively associated with p16 positive disease, as was employment versus unemployment/disability. Multivariate associations with p16 positive disease are summarized in Table 4. In the multivariate logistic regression model, only tobacco use and moderate versus none/minimal alcohol use were significantly associated with tumor p16 status.

**Kaplan-Meier Survival Analysis**

We initially compared overall survival by race using Kaplan-Meier survival curves (Figure 1). The number of patients at risk at each time point is presented along the bottom of all Kaplan-Meier plots. The mean survival for Caucasian patients was 38.6 months with a standard error of 0.9 months, while the mean survival for African American patients was 29.5 months with a standard error of 2.4 months. Overall survival

varied significantly by race ($p<0.0001$). We also compared overall survival by tumor p16 status (Figure 2). The mean survival for patients with p16 positive OPSCC was 31.7 months with a standard error of 0.7 months, while the mean survival for patients with p16 negative OPSCC was 30.6 months with a standard error of 2.2 months. Overall survival varied significantly by tumor p16 status ($p<0.0001$).

We then compared overall survival for Caucasian patients by tumor p16 status (Figure 3). The mean survival for Caucasian patients with p16 positive disease was 32.4 months with a standard error of 0.7 months, while the mean survival for Caucasian patients with p16 negative disease was 33.9 months with a standard error of 2.4 months. Within Caucasian patients, overall survival varied significantly by p16 status ($p=0.0005$). We also compared overall survival for African American patients by tumor p16 status (Figure 4). The mean survival for African American patients with p16 positive disease was 23.2 months with a standard error of 1.3 months, while the mean survival for African American patients with p16 negative disease was 24.2 months with a standard error of 4.0 months. The overall survival also varied significantly by tumor p16 status within African American patients ($p=0.0243$).

The final set of Kaplan-Meier plots compared overall survival for patients with p16 positive and p16 negative disease by race (Figures 5 and 6). African American patients with p16 positive OPSCC had significantly poorer survival compared to Caucasian patients with p16 positive disease ($p=0.0024$). African American patients with p16 negative OPSCC also had significantly poorer survival compared to Caucasian patients with p16 negative disease ($p=0.0253$).

**Cox Proportional Hazards Analysis**

The proportional hazards assumption was met for race and tumor p16 status as demonstrated by the largely parallel log-negative-log curves (Figures 7 and 8). The first set of Cox models tested for confounding by comparing the HR for death by race and tumor p16 status in two separate models to obtain crude HRs and a single model to obtain adjusted HRs for each predictor (Table 5). The HR for death comparing African American versus Caucasian patients was 3.10 in the model with race alone, and 2.64 in the model adjusting for p16 status. The HR for death comparing patients with p16 positive tumors versus those with p16 negative tumors was 0.30 in the model with p16 status alone, and 0.35 in the model adjusting for race.

We tested for interaction between race and tumor p16 status by incorporating an interaction term into the Cox model with race and p16 status. The HR for the interaction was 1.306 (p=0.6283). The retrospective power analysis for this model testing the interaction between race and p16 status using the obtained HR and sample size resulted in a power of 0.14.

Finally, we analyzed the effect of multiple covariates on overall survival (Table 6). The HR of death for African American versus Caucasian patients was still significant at 2.10 (p=0.0244). The HR of death for patients with p16 positive tumors versus those with p16 negative tumors was also significant at 0.45 (p=0.0091). The HR of death for former smokers versus non-smokers was significant at 2.51 (p=0.0391) as was the HR for heavy drinkers versus those who drank minimally or not at all (p=0.0180).

# DISCUSSION

We found that the prevalence of p16 positive OPSCC varied by race, with African American patients having a markedly lower prevalence compared to Caucasian patients. There was a negative association between African American race and p16 positive disease even after controlling for tobacco and alcohol use, disease stage, and socioeconomic indicators, although this association was not statistically significant. The lower prevalence of p16-positive OPSCC in African Americans in our sample is consistent with several published studies, as summarized in Table 7.

There is an established theory as to why African American patients have a lower prevalence of HPV-related OPSCC. Studies have demonstrated a strong association between oral sexual behaviors and the risk of oral HPV infection and OPSCC (36 and 37). There is also evidence of racial variation in sexual practices, suggesting a higher proportion of Caucasians engage in oral sex (38 and 39). In 2012, Gillison et al found a lower prevalence of oral HPV infection in African Americans compared to Caucasians (16), and this appears to be explained by racial difference in oral sexual behavior (40).

Our study found improved overall survival for patients with p16-positive OPSCC compared to those with p16-negative disease. This clinical significance of tumor HPV and p16 status in OPSCC has been well established (5, 8, and 41). In fact, tumor HPV status has emerged as one of the most important prognostic factors for patients with OPSCC, and there is growing debate as to whether HPV status should guide treatment of OPSCC (42).

We also found that African Americans with OPSCC have decreased survival compared to Caucasian patients. This racial disparity in survival corroborates what is published in the literature (9-11, 43). There are several potential explanations for this result. African American patients in our cohort had higher prevalence of tobacco and alcohol use; they also had decreased prevalence of employment and marriage, indicating a lower socioeconomic status compared to Caucasian patients. Alcohol and tobacco use, particularly smoking and drinking at the time of diagnosis, have been associated with decreased survival for OPSCC (2). Unemployment is a poor prognostic factor for all head and neck cancer (44). Being single or living alone has been associated with poorer outcomes for cancers across various sites including the head and neck (45). Interestingly, there was no racial variation in disease stage at diagnosis or treatment modality.

The novel contribution of this study was the analysis of OPSCC survival by race and tumor p16 status. We found that patients with p16-positive OPSCC have improved survival compared to patients with p16-negative disease, regardless of race. This indicates that there are improved outcomes for African American patients with HPV-positive OPSCC compared to those with HPV-negative OPSCC. The HPV survival benefit has not been firmly established in African American populations, presumably due to lack of multi-ethnic cohorts and the limited number of African American patients with OPSCC. Our study contributes to the emerging literature confirming that African American patients do demonstrate a survival benefit with HPV-positive OPSCC (46 and 47).

In our survival analyses, we also found that African American patients have poorer survival compared to Caucasian patients regardless of tumor p16 status. It has been previously reported that African Americans with HPV-negative OPSCC have poorer outcomes compared to Caucasians with HPV-negative disease (46 and 47). This is the first study that identified racial disparities in survival for p16 positive OPSCC.

There are two potential explanations for this finding. The first is that the racial disparity in survival is due to socioeconomic factors that have not been fully addressed in the analysis. Although income and insurance data were not included in the analysis, the socioeconomic variables we included varied greatly by race and therefore likely captured a reasonable portion of the socioeconomic effect. However, disparities in access to care and health literacy are multifaceted and function on an individual, community, and systems level. They are difficult to adjust for in a survival analysis, and quite possibly account for the racial disparities in outcome identified in this study.

The second potential explanation is that the racial disparity in survival for p16 positive OPSCC is biologic. It is possible that the prevalence of oral HPV serotypes vary by race, either due to host genetics that increase susceptibility to particular HPV serotypes, viral genetics, or differences in HPV serotypes harbored by different sexual networks. This is highly relevant as the different HPV serotypes have different biology and carcinogenic potential. The cervical cancer literature has noted racial differences in the prevalence of high-risk HPV serotypes with African American women having a lower prevalence of the most common oncogenic serotypes (48 and 49). There may also be racial differences in host immune response to viral infection or the oral oncogenic potential of HPV infection in general.

Finally, we did not find interaction between race and HPV status. Interaction effects are much more difficult to detect than main effects, and our study was markedly underpowered to detect an interaction effect if it did exist. However, in comparing the Kaplan-Meier curves and the very similar effect sizes in the Cox models, we deemed that there is likely no interaction between the effect of race and HPV status on survival for OPSCC, indicating that HPV-status was associated with survival in similar ways in both African American and Caucasian patients.

The strengths of this study include the relatively large sample of African Americans with OPSCC compared to the existing literature, the broad inclusion criteria, and the use of the tumor board registry to identify patients, which allowed access to all patients diagnosed with head and neck cancer at Grady Health System and Emory Healthcare. The study patients received rather uniform care by a single academic otolaryngology faculty, which is apparent in the lack of racial variation in treatment modalities. In addition, the inclusion of medical comorbidities in the survival analysis controls for the variation in baseline health status of the study patients, which is especially important in this population as head and neck cancer patients often have multiple medical problems.

The limitations of the study are the retrospective design, which limits our ability to control for confounding and identify causal associations. In addition, the use of p16 immunohistochemistry in lieu of an HPV DNA detection method introduces measurement error to one of our primary variables of interest. The lack of insurance data limits our ability to control for socioeconomic status and access to care. In addition,

detailed tobacco and alcohol exposure information as well data on patient sexual practices was not available in the medical record.

This study raises several questions regarding the effect of socioeconomic, behavioral, and biological factors on the prevalence and outcome of HPV positive OPSCC in African American patients. Future work on this subject should include a thorough sexual history on all subjects, which can contribute valuable information on the racial variation in sexual practices and the determinants of HPV-positive OPSCC. Another important follow up investigation would be HPV genotyping of tumors in African American patients with p16 positive OPSCC to determine if HPV serotypes vary by race.

This work has contributed to the emerging literature on the effect of tumor HPV status on survival for African American patients with OPSCC. We conclude that the prevalence of p16 positive OPSCC is lower in African American patients compared to Caucasian patients in this population. We also found that African American patients with p16 positive disease have poorer survival compared to their Caucasian counterparts. Socioeconomic and behavioral factors appear to only partially explain this difference in survival, and there may be a biological component to this disparity.

**References**


1. American Cancer Society. Cancer Facts & Figures 2015. Atlanta, GA: American Cancer Society, 2015.
2. Olshan AF. Epidemiology, pathogenesis, and prevention of head and neck cancer. New York, NY: Springer; 2010.
3. Marur S, D'Souza G, Westra WH, et al. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol.* 2010;11(8):781–789.
4. Mork J, Lie AK, Glattre E, et al. Human papillomavirus infection as a risk factor for squamous cell carcinoma of the head and neck. *New Engl J Med.* 2001;344(15):1125–1131.
5. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. *Semin Oncol.* 2004;31(6):744–754.
6. Pytynia KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. *Oral Oncol.* 2014;50(5):380-386.
7. Chaturvedi AK. Epidemiology and clinical aspects of HPV in head and neck cancers. *Head Neck Pathol.* 2012;6:S16-S24.
8. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *New Engl J Med.* 2010;363(1):24-35.
9. Settle K, Taylor R, Wolf J, et al. Race impacts outcome in stage III/IV squamous cell carcinomas of the head and neck after concurrent chemoradiation therapy. *Cancer.* 2009;115(8):1744-1752.
10. Goodwin WJ, Thomas GR, Parker DF, et al. Unequal burden of head and neck cancer in the United States. *Head Neck.* 2008;30(3):358–371.
11. Molina MA, Cheung MC, Perez EA, et al. African American and poor patients have a dramatically worse prognosis for head and neck cancer: an examination of 20,915 patients. *Cancer.* 2008;113(10):2797–2806.
12. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst*. 2000;92(9):709-720.
13. Begum S, Cao D, Gillison ML, et al. Tissue distribution of human papillomavirus 16 DNA integration in patients with tonsillar carcinoma. *Clin Cancer Res.* 2005;11(16):5694–5699.
14. Braakhuis BJ, Snijders PJ, Keune WJ, et al. Genetic patterns in head and neck cancers that contain or lack transcriptionally active human papillomavirus. *J Natl Cancer Inst*. 2004;96(13):998–1006.
15. Ke LD, Adler-Storthz K, Chen Z, et al. Expression of human papillomavirus E7 mRNA in human oral and cervical neoplasia and cell lines. *Oral Oncol.* 1999;35(4):415-420.
16. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009-2010. *JAMA.* 2012;307(7):693-703.
17. Lassen P, Eriksen JG, Hamilton-Dutoit S, et al. Effect of HPV-associated p16INK4A expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2009;27(12):1992-1998.

18. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst.* 2008;100(4):261–269.
19. Posner MR, Lorch JH, Goloubeva O, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. *Ann Oncol.* 2011;22(5):1071–1077.
20. Cantley RL, Gabrielli E, Montebelli F, et al. Ancillary studies in determining human papillomavirus status of squamous cell carcinoma of the oropharynx: a review. *Patholog Res Int.* 2011;1–7.
21. Ahmed A, Cascarini L, Sandison A, et al. Survey of the use of tests for human papilloma virus and epidermal growth factor receptor for squamous cell carcinoma of the head and neck in UK head and neck multidisciplinary teams. *Br J Oral Maxillofac Surg*. 2012;50(2):119–121.
22. Jordan RC, Lingen MW, Perez-Ordonez B, et al. Validation of methods for oropharyngeal cancer HPV status determination in the US Cooperative Group Trials. *Am J Surg Pathol.* 2012;36(7):945-954.
23. American Cancer Society. Cancer Facts & Figures 2011. Atlanta, GA: American Cancer Society, 2011.
24. Shiboski CH, Schmidt BL, Jordan RC. Racial disparity in stage at diagnosis and survival among adults with oral cancer in the US. *Community Dent Oral Epidemiol.* 2007;35(3):233-240.
25. Morse DE, Kerr AR. Disparities in oral and pharyngeal cancer incidence, mortality and survival among black and white Americans. *J Am Dent Assoc.* 2006;137(2):203-212.
26. Ragin CC, Langevin SM, Marzouk M, et al. Determinants of head and neck cancer survival according to race. *Head Neck.* 2011;33(8):1092-1098.
27. Settle K, Posner MR, Schumaker LM, et al. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. *Cancer Prev Res.* 2009;2(9):776-781.
28. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.
29. Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47(11):1245-1251.
30. Singh B, Bhaya M, Stern J, et al. Validation of the Charlson Comorbidity Index in patients with head and neck cancer: A multi-institutional study. *Laryngoscope.* 1997;107(11):1469-1475.
31. Hall SF, Rochon PA, Streiner DL, et al. Measuring comorbidity in patients with head and neck cancer. *Laryngoscope*. 2002;112(11):1988 -1996.
32. Reid BC, Alberg AJ, Klassen AC, et al. A comparison of three comorbidity indexes in a head and neck cancer population. Oral Oncol. 2002;38(2):187-194.
33. Piccirillo JF, Spitznagel EL, Vermani N, et al. Comparison of comorbidity indices for patients with head and neck cancer. *Med Care*. 2004;42(5):482-486.
34. Chernock RD, Zhang Q, El-Mofty SK, et al. Human papillomavirus-related squamous cell carcinoma of the oropharynx: A comparative study in whites and African Americans. *Arch Otolaryngol Head Neck Surg*. 2011;137(2):163-169.

35. Isayeva T, Xu J, Dai Q, et al. African Americans with oropharyngeal carcinoma have significantly poorer outcomes despite similar rates of human papillomavirus-mediated carcinogenesis. *Hum Pathol*. 2014;45(2):310-319.
36. D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *J Infect Dis.* 2009;199(9):1263-1269.
37. Smith EM, Ritchie JM, Summersgill KF, et al. Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. *Int J Cancer*. 2004;108(5):766-772.
38. Billy JO, Tanfer K, Grady WR, et al. The sexual behavior of men in the United States. *Fam Plann Perspect*. 1993;25(2):52-60.
39. Gates GJ, Sonenstein FL. Heterosexual genital sexual activity among adolescent males: 1988 and 1995. *Fam Plann Perspect*. 2000;32(6):295-297.
40. D'Souza G, Cullen K, Bowie J, et al. Difference in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. *PLoS One*. 2014;9(1):e86023.
41. Lewis JS Jr, Thorstad WL, Chernock RD, et al. p16 positive oropharyngeal squamous cell carcinoma: An entity with a favorable prognosis regardless of tumor HPV status. *Am J Surg Pathol*. 2010;34(8):1088-1896.
42. Mirghani H, Amen F, Blanchard P, et al. Treatment de-escalation in HPV-positive oropharyngeal carcinoma: Ongoing trials, critical issues and perspectives. *Int J Cancer*. 2015;136(7):1494-1503.
43. Gourin CG, Podolsky RH. Racial disparities in patients with head and neck squamous cell carcinoma. *Laryngoscope*. 2006;116(7):1093-1106.
44. Andersen ZJ, Lassen CF, Clemmensen IH. Social inequality and incidence of and survival from cancers of the mouth, pharynx and larynx in a population-based study in Denmark, 1994-2003. *Eur J Cancer*. 2008;44(14):1950-1961.
45. Pinquart M, Duberstein PR. Associations of social networks with cancer mortality: a meta-analysis. *Crit Rev Oncol Hematol*. 2010 Aug;75(2):122-137.
46. Worsham MJ, Stephen JK, Chen KM, et al. Improved survival with HPV among African Americans with oropharyngeal cancer. *Clin Cancer Res*. 2013;19(9):2486-2492.
47. Zandberg DP, Liu S, Goloubeva OG, et al. Emergence of HPV16-positive oropharyngeal cancer in Black patients over time: University of Maryland 1992-2007. *Cancer Prev Res*. 2015;8(1):12-19.
48. Niccolai LM, Russ C, Julian PJ, et al. Individual and geographic disparities in human papillomavirus types 16/18 in high-grade cervical lesions: Associations with race, ethnicity, and poverty. *Cancer*. 2013;119(16):3052-3058.
49. Vidal AC, Smith JS, Valea F, et al. HPV genotypes and cervical intraepithelial neoplasia in a multiethnic cohort in the southeastern USA. *Cancer Causes Control*. 2014;25(8):1055-1062.

**Table 1. Patient Characteristics by Race**

| | CA (N = 175) | AA (N = 48) | p-value |
|---|---|---|---|
| **p16 Positive** | **136 (77.7)** | **27 (56.3)** | **0.0030** |
| Age at diagnosis, mean (SD) | 59.2 (8.8) | 55.7 (8.2) | 0.0140≠ |
| Gender (Male) | 155 (69.5) | 39 (81.3) | 0.1825 |
| Stage | | | 0.8664 |
| Early (1 or 2) | 16 (9.1) | 4 (8.3) | |
| Stage 3 | 11 (6.3) | 3 (6.3) | |
| Stage 4 | 148 (84.6) | 41 (85.4) | |
| Tobacco Use | | | 0.0004 |
| Never | 69 (39.4) | 10 (20.8) | |
| Former | 72 (41.1) | 16 (33.3) | |
| Current | 34 (19.4) | 22 (45.8) | |
| Alcohol Use | | | <0.0001 |
| None/minimal | 126 (72.0) | 19 (39.6) | |
| Moderate | 36 (20.6) | 18 (37.5) | |
| Heavy | 13 (7.4) | 11 (22.9) | |
| Comorbidity Score, mean (SD) | 2.9 (1.7) | 2.4 (1.3) | 0.0587≠ |
| Treatment | | | |
| Surgery alone | 11 (6.3) | 0 (0.0) | 0.1265* |
| Surgery + radiation | 15 (8.6) | 2 (4.2) | 0.5380* |
| Surgery + radiation + chemotherapy | 15 (8.6) | 3 (6.3) | 0.7697* |
| Radiation alone | 5 (2.9) | 1 (2.1) | 1.0000 * |
| Radiation + chemotherapy | 126 (72.0) | 40 (83.3) | 0.1359* |
| Chemotherapy alone | 1 (0.6) | 2 (4.2) | 0.1177* |
| Employment Status | | | <0.0001 |
| Disabled or unemployed | 32 (18.3) | 29 (60.4) | |
| Employed | 101 (57.7) | 11 (22.9) | |
| Retired | 42 (24.0) | 8 (16.7) | |
| Married | 134 (76.6) | 21 (43.8) | <0.0001 |

Abbreviations:
CA – Caucasian patients
AA – African American patients
SD – standard deviation

Footnotes:
Mantel-Haenszel chi-square test utilized unless noted
*Fisher's exact utilized due to low cell counts
≠ Two-sample Student's t-test utilized

**Table 2. Patient Characteristics by p16 Status**

| | p16 Positive (163) | p16 Negative (60) | p-value |
|---|---|---|---|
| Age at diagnosis [mean (SD)] | 58.3 (8.4) | 59.0 (10.1) | 0.6157≠ |
| Gender (Male) | 141 (86.5) | 53 (88.3) | 0.7192 |
| Stage | | | 0.1056 |
| Early (1 or 2) | 12 (7.4) | 8 (13.3) | |
| Stage 3 | 9 (5.5) | 5 (8.3) | |
| Stage 4 | 142 (87.1) | 47 (78.3) | |
| Tobacco Use | | | <0.0001 |
| Never | 73 (44.8) | 6 (10.0) | |
| Former | 64 (39.3) | 24 (40.0) | |
| Current | 26 (16.0) | 30 (50.0) | |
| Alcohol Use | | | <0.0001 |
| None/minimal | 122 (74.9) | 23 (38.3) | |
| Moderate | 28 (17.2) | 26 (43.3) | |
| Heavy | 13 (8.0) | 11 (18.3) | |
| Comorbidity Score [mean (SD)] | 2.7 (1.5) | 3.2 (1.9) | 0.0734≠ |
| Treatment | | | |
| Surgery alone | 8 (4.9) | 3 (5.0) | 1.0000* |
| Surgery + radiation | 15 (9.2) | 2 (3.3) | 0.1676* |
| Surgery + radiation + chemotherapy | 13 (8.0) | 5 (8.3) | 1.0000* |
| Radiation alone | 4 (2.5) | 2 (3.3) | 0.6612* |
| Radiation + chemotherapy | 122 (74.9) | 44 (73.3) | 0.8187 |
| Chemotherapy alone | 1 (0.6) | 2 (3.3) | 0.1770* |
| Employment Status | | | 0.6623 |
| Disabled or unemployed | 40 (24.5) | 21 (35.0) | |
| Employed | 89 (54.6) | 23 (38.3) | |
| Retired | 34 (20.9) | 16 (26.7) | |
| Married | 121 (74.2) | 34 (56.7) | 0.0141* |

Abbreviations:
CA – Caucasian patients
AA – African American patients
SD – standard deviation

Footnotes:
Mantel-Haenszel chi-square test utilized unless noted
*Fisher's exact utilized due to low cell counts
≠ Two-sample Student's t-test utilized

**Table 3. Univariate Associations with p16 Positive Disease**

| | $\beta_1$ | Odds Ratio | 95% CI | p-value |
|---|---|---|---|---|
| Race (AA vs CA) | -0.9978 | 0.369 | 0.188, 0.722 | 0.0036 |
| Stage | | | | |
| Stage 3 vs Stages 1&2 | 0.1826 | 1.200 | 0.292, 4.929 | 0.8000 |
| Stage 4 vs Stages 1&2 | 0.7007 | 2.015 | 0.777, 5.228 | 0.1498 |
| Tobacco Use (Former vs Never) | | | | |
| Former vs Never | -1.5179 | 0.219 | 0.084, 0.570 | 0.0018 |
| Current vs Never | -2.6418 | 0.071 | 0.027, 0.191 | <0.001 |
| Alcohol Use | | | | |
| Moderate vs None/minimal | -1.5944 | 0.203 | 0.101, 0.407 | <0.001 |
| Heavy vs None/minimal | -1.5015 | 0.223 | 0.089, 0.558 | 0.0014 |
| Employment Status | | | | |
| Employed vs Unemployed/Disabled | 0.7088 | 2.032 | 1.009, 4.088 | 0.0470 |
| Retired vs Unemployed/Disabled | 0.1094 | 1.116 | 0.504, 2.471 | 0.7874 |
| Married | 0.7899 | 2.203 | 1.186, 4.094 | 0.0125 |

Abbreviations:
CA – Caucasian patients
AA – African American patients
CI – confidence interval

**Table 4. Multivariate Associations with p16 Positive Disease**

| | $\beta_1$ | Odds Ratio | 95% CI | p-value |
|---|---|---|---|---|
| Race (AA vs CA) | -0.4818 | 0.618 | 0.259, 1.475 | 0.2780 |
| Stage | | | | |
| Stage 3 vs Stages 1&2 | 0.0277 | 1.028 | 0.187, 5.638 | 0.9745 |
| Stage 4 vs Stages 1&2 | 0.8553 | 2.352 | 0.743, 7.450 | 0.1459 |
| Tobacco Use | | | | |
| Former vs Never | -1.4577 | 0.233 | 0.085, 0.640 | 0.0047 |
| Current vs Never | -2.2266 | 0.108 | 0.036, 0.323 | <0.001 |
| Alcohol Use | | | | |
| Moderate vs None/minimal | -1.1781 | 0.308 | 0.140, 0.678 | 0.0034 |
| Heavy vs None/minimal) | -0.8093 | 0.445 | 0.151, 1.315 | 0.1430 |
| Employment Status | | | | |
| Employed vs Unemployed/Disabled | -0.3071 | 0.736 | 0.288, 1.880 | 0.5214 |
| Retired vs Unemployed/Disabled | -0.6225 | 0.537 | 0.189, 1.521 | 0.2417 |
| Married | 0.2945 | 1.342 | 0.596, 3.022 | 0.4768 |

Abbreviations:
CA – Caucasian patients
AA – African American patients
CI – confidence interval

Footnote:
Logistic regression modeling the odds of p16 positive disease adjusted for race, tumor stage, tobacco, alcohol, employment, and marital status.

**Table 5. Crude and Adjusted Cox Proportional Hazard Models for Effect of Race and p16 Status**

| | Hazard Ratio | 95% CI | p-value |
|---|---|---|---|
| Race (AA vs CA) | 3.098 (crude) | 1.811, 5.300 | <0.0001 |
| Race (AA vs CA) | 2.643 (adjusted) | 1.534, 4.555 | 0.0005 |
| p16 Status (Positive vs Negative) | 0.303 (crude) | 0.178, 0.514 | <0.0001 |
| P16 Status (Positive vs Negative) | 0.345 (adjusted) | 0.202, 0.589 | <0.0001 |

Abbreviations:
CA – Caucasian patients
AA – African American patients
CI – confidence interval

Footnote:
Cox proportional hazards models with calendar months as time scale. Crude models are univariate with either race or p16 status, whereas adjusted model controls for both race and p16 status.

**Table 6. Cox Proportional Hazard Model for Effect of Race and p16 Status Adjusting for Covariates**

| | Hazard Ratio | 95% CI | p-value |
|---|---|---|---|
| Race (AA vs CA) | 2.102 | 1.001, 4.013 | 0.0244 |
| p16 Status (Positive vs Negative) | 0.447 | 0.244, 0.818 | 0.0091 |
| Stage | | | |
| Stage 3 vs Stages 1&2 | 0.591 | 0.112, 3.110 | 0.5345 |
| Stage 4 vs Stages 1&2 | 1.203 | 0.492, 2.943 | 0.6853 |
| Tobacco Use | | | |
| Former vs Never | 2.505 | 1.047, 5.992 | 0.0391 |
| Current vs Never | 2.017 | 0.764, 5.328 | 0.1567 |
| Alcohol Use | | | |
| Moderate vs None/minimal | 1.325 | 0.677, 2.594 | 0.4114 |
| Heavy vs None/minimal | 2.618 | 1.180, 5.811 | 0.0180 |
| Employment Status | | | |
| Employed vs Unemployed/Disabled | 0.666 | 0.308, 1.439 | 0.3010 |
| Retired vs Unemployed/Disabled | 1.251 | 0.577, 2.711 | 0.5704 |
| Marital Status (Married vs Single) | 1.063 | 0.538, 2.102 | 0.8597 |

Abbreviations:
CA – Caucasian patients
AA – African American patients
CI – confidence interval

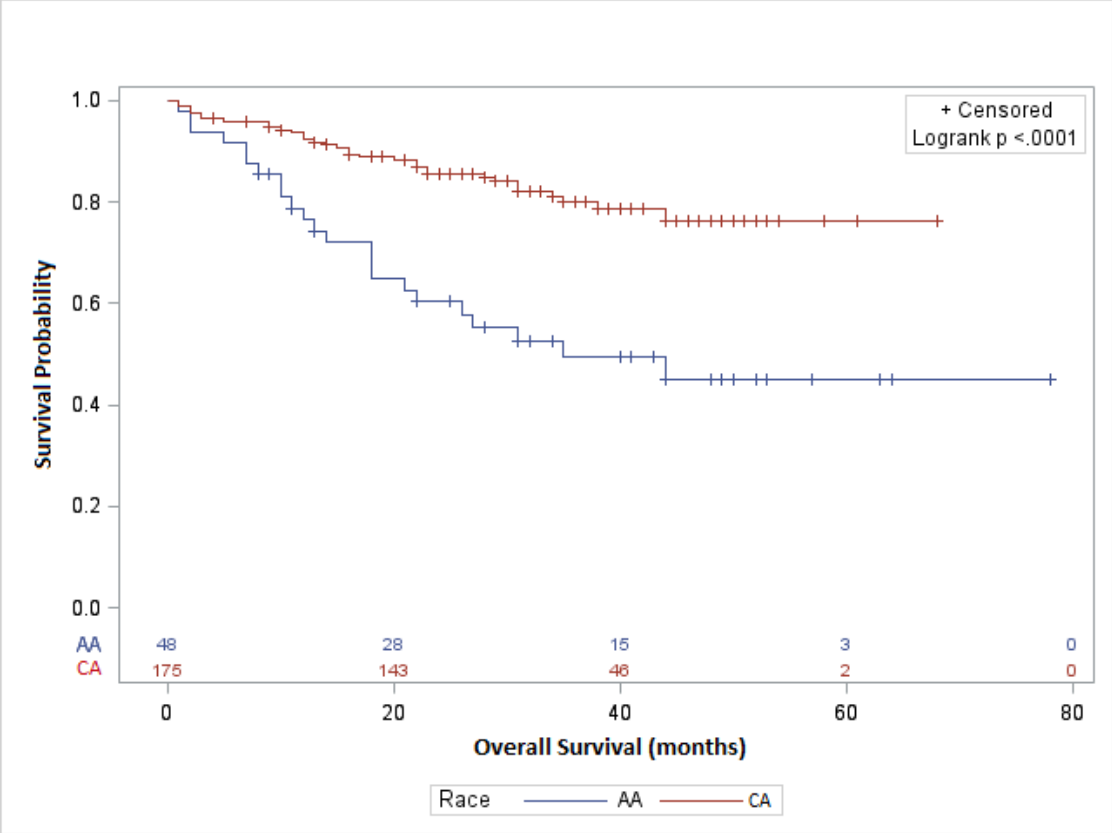
Footnote:
Multivariable Cox proportional hazards model with calendar months as time scale controlling for race, p16 status, tumor stage, tobacco, alcohol, employment and marital status.

**Table 7. Reported prevalences of p16+ OPSCC by race**

| Authors, year | AA (N) | CA (N) | p16+ AA (%) | p16+ CA (%) | p-value |
|---|---|---|---|---|---|
| Weinberger et al, 2010 | 16 | 86 | 37.5 | 60.5 | 0.12 |
| Chernock et al, 2011 | 26 | 148 | 32.6 | 83.1 | <0.001 |
| Isayeva et al, 2014 | 30 | 72 | 37.5 | 71.0 | 0.004 |
| Zevallos et al, 2014 | 32 | 126 | 53.1 | 50.8 | 0.292 |

Abbreviations:
OPSCC – oropharyngeal squamous cell carcinoma
CA – Caucasian patients
AA – African American patients

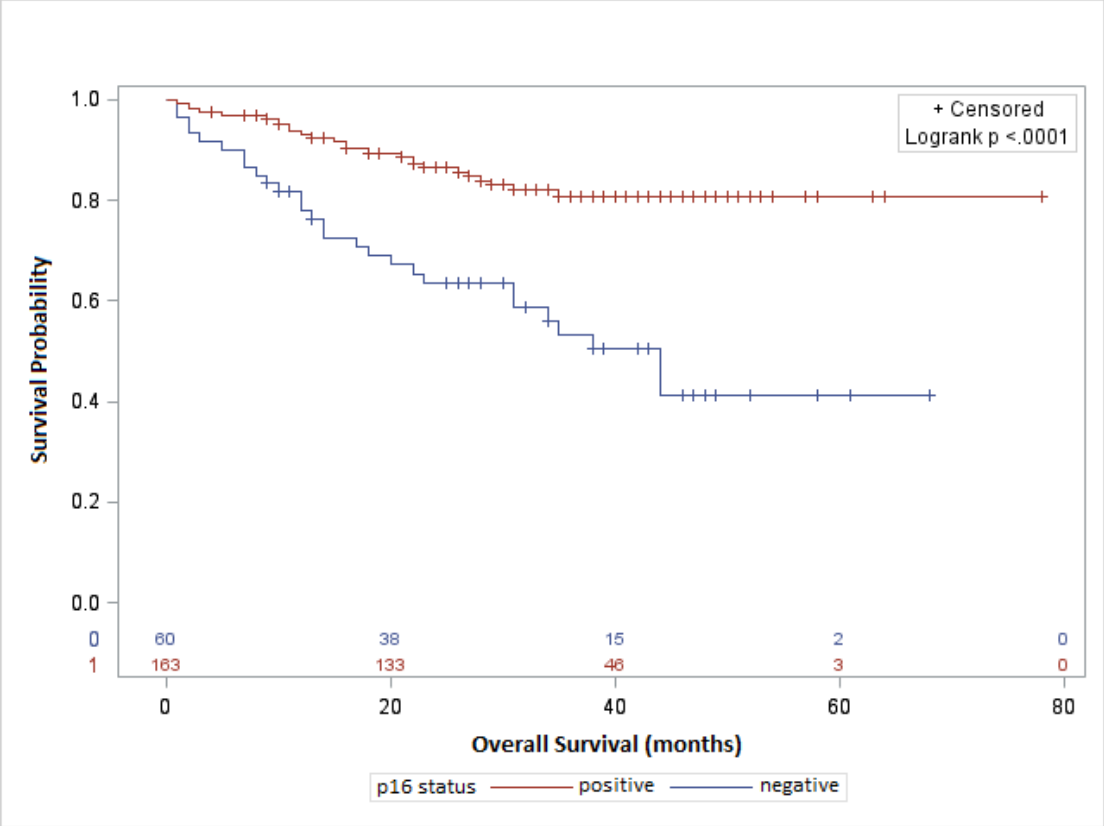
**Figure 1. Kaplan-Meier Survival Curve for Patients with OPSCC by Race**




Abbreviations:
CA – Caucasian patients
AA – African American patients

Footnote:
The number of patients at risk in each category is indicated at the base of the survival curve.

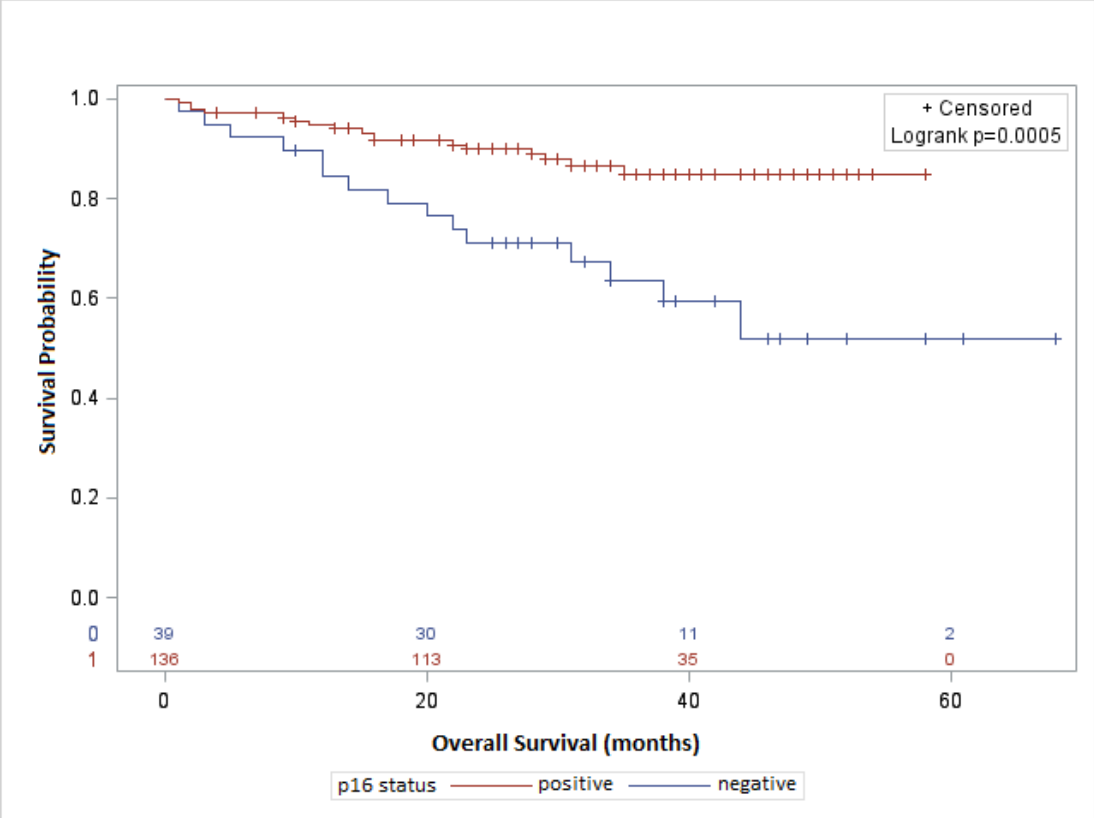
**Figure 2. Kaplan-Meier Survival Curve for Patients with OPSCC by Tumor p16 Status**




Abbreviations:
0 – p16 negative
1 – p16 positive

Footnote:
The number of patients at risk in each category is indicated at the base of the survival curve.

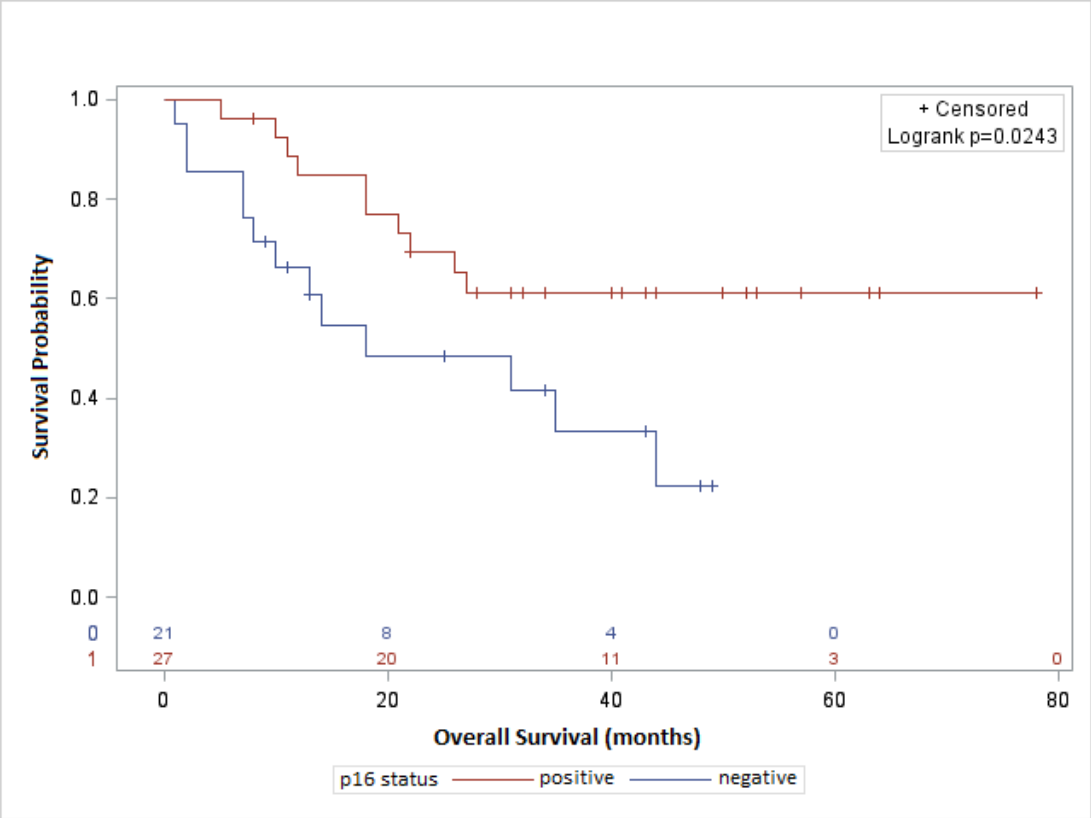
**Figure 3. Kaplan-Meier Survival Curve for Caucasian Patients with OPSCC by Tumor p16 Status**




Abbreviations:
0 – p16 negative
1 – p16 positive

Footnote:
The number of patients at risk in each category is indicated at the base of the survival curve.

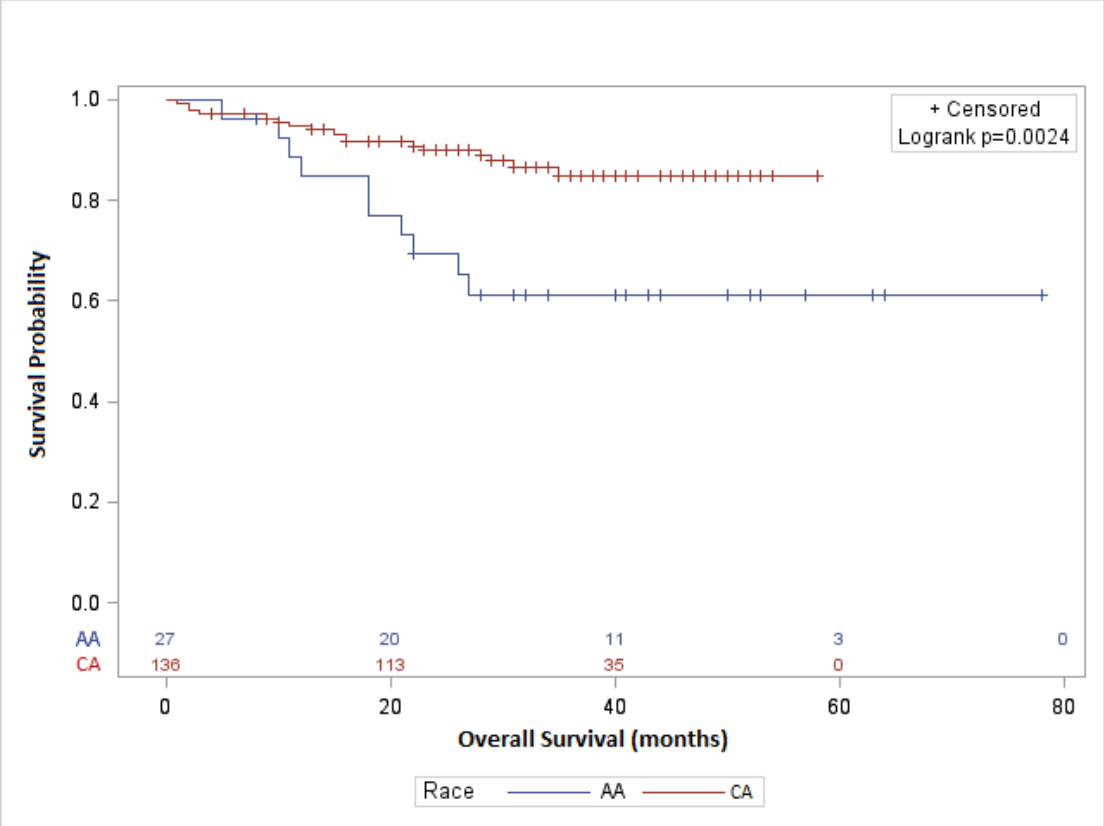
**Figure 4. Kaplan-Meier Survival Curve for African American Patients with OPSCC by Tumor p16 Status**




Abbreviations:
0 – p16 negative
1 – p16 positive

Footnote:
The number of patients at risk in each category is indicated at the base of the survival curve.

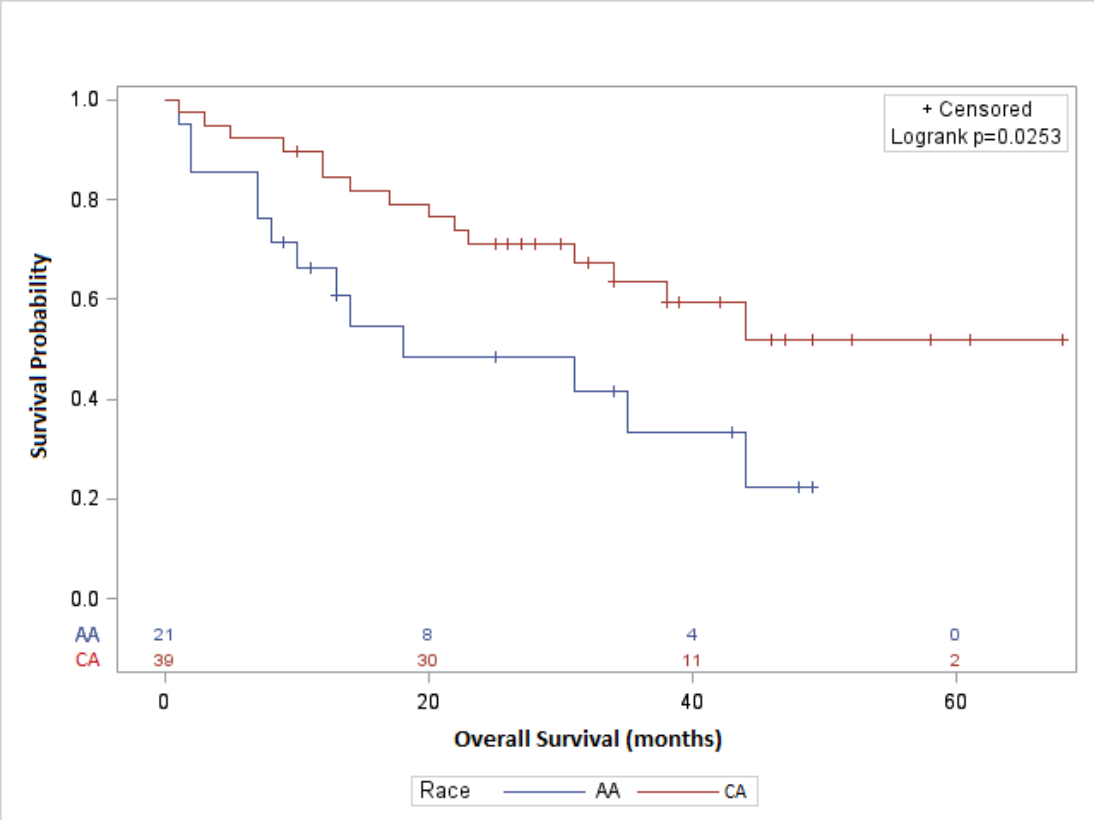
**Figure 5. Kaplan-Meier Survival Curve for Patients with p16-positive OPSCC by Race**




Abbreviations:
CA – Caucasian patients
AA – African American patients

Footnote:
The number of patients at risk in each category is indicated at the base of the survival curve.

**Figure 6. Kaplan-Meier Survival Curve for Patients with p16-negative OPSCC by Race**




Abbreviations:
CA – Caucasian patients
AA – African American patients

Footnote:
The number of patients at risk in each category is indicated at the base of the survival curve.