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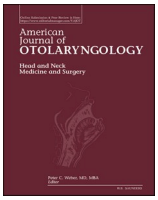

Race, not socioeconomic disparities, correlates with survival in human papillomavirus-negative oropharyngeal cancer: A retrospective study

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ABSTRACT

Purpose: Investigate the impact of black versus white race, socioeconomic status (SES), and comorbidity burden on oropharyngeal cancer (OPC) survival.
Materials and methods: This study retrospectively analyzed patients diagnosed between 1991 and 2012 at an urban tertiary care center with a high volume of head and neck cancer referrals. Data gathered included demographics, human papilloma virus (HPV) status, follow-up time, comorbidities, smoking history, and overall survival. SES was extrapolated from the 2000 and 2010 censuses. Analysis of variance, chi-square tests, multivariable Cox proportional hazards models, Cox proportional hazards regression, Kaplan Meier curves and the log-rank test were utilized.
Results: Of 208 charts reviewed, 192 patients met inclusion criteria. Black patients had significantly ($p < 0.001$) poorer survival at 1, 2, and 5 years than white patients (5-year survival: 32% vs 64%); this discrepancy persisted in only HPV-negative disease (20% vs 50%). In the HPV-negative subgroup, there was no racial difference in treatment modality received, Charlson Comorbidity Index, and proportion receiving inadequate, noncurative or no treatment. Univariate analysis identified significant differences in median household income, education level, and stage at presentation between black and white subgroups. Multivariate analysis identified white race and HPV-positive status as independent predictors of overall survival, but SES and stage at presentation were not.
Conclusion: SES did not explain the greater survival in HPV-negative white versus black patients. This indicates that race is an independent predictor of survival; future studies should examine more accurate indicators of SES and genetic differences in tumors of black and white patients.

1. Introduction

While it is well-established that tobacco and alcohol use and negative human papillomavirus (HPV−) status are correlated with poorer survival in head and neck cancer [1–3], the impact of socioeconomic status (SES) and race have yet to be extensively studied in oropharyngeal cancer (OPC). Decreased survival in OPC has been reported in locations of lower SES [4–7]. An association between higher SES and positive human papillomavirus (HPV+) status disease has also been identified [8,9]. Reduced survival has been reported in black patients, which may be due to a lower prevalence of HPV+ disease in this population [10–12]. Indeed, Jiron et al. demonstrated that once adjustment for HPV status was made, race was no longer associated with significant survival difference among patients with OPC [10]. However, the study only included 81 patients with OPC and was restricted to patients undergoing surgical treatment.

The current study aimed to determine whether race and SES may correlate with prognosis in patients with OPC.

2. Materials and methods

This retrospective cohort study was approved by our health system's institutional review board (IRB #8715). The health system's virtual data warehouse (VDW) tumor registry was queried in September 2017 to

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identify patients with oropharyngeal squamous cell tumors from June 1991 to December 2012 using the International Classification of Disease for Oncology, Third Edition, codes (C01, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, and C10.9). Patients with at least carcinoma in situ were included, and patients with non-squamous cell tumors were excluded. Chart review was performed in 2018 and 2019 to supplement and verify VDW data.

Patient-specific information included age, sex, race, vital status, date of death, date of diagnosis, and last date of contact. Disease-specific information included the HPV status and stage at presentation according to the American Joint Committee on Cancer, 7th edition (AJCC-7) criteria [13]. Of note, because the data collected was from patients diagnosed between June 1991 and December 2012, AJCC-8 staging was not used.

2.1. Socioeconomic data

As socioeconomic data at the individual level was not available within the electronic health record, census-block level data from the 2000 and 2010 US Census, depending on diagnosis date, was used as a proxy for SES of study patients. Census-block data prior to 2000 was not accessible. The census/SES data used corresponded to date of diagnosis, with those occurring prior to 2000 using the 2000 census data and those during or after 2000 using the 2010 census data. This data was obtained in April 2019 and included median household income, percentage of residents who achieved various levels of education, percentage of residents living under the 100% poverty line, and percentage of homes owned or occupied in the census-block.

2.2. Comorbidities

Comorbidities collected included myocardial infarction, congestive heart failure, peripheral vascular disease, cardiovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild chronic liver disease, diabetes mellitus, diabetes with end-organ damage, hemiplegia, moderate or severe renal disease, tumor without metastasis, moderate or severe liver disease, metastatic solid tumor, and human immunodeficiency virus/acquired immunodeficiency syndrome. The mean Charlson Comorbidity Index (CCI) for each study group was calculated [14,15].

2.3. HPV status

Testing for HPV status was done both prospectively and retrospectively within the pathology department. If a patient had OPC of unknown HPV status treated before presenting to our institution for treatment of a recurrence, the HPV status of the primary tumor was assumed to be the same as that of the recurrent tumor. Patients with unknown HPV status were excluded.

2.4. Disease status

Patients who were documented as missing any aspect of recommended treatment—such as not completing recommended full course of radiation therapy or missing dose(s) of chemotherapy—were classified as having inadequate treatment. Follow-up was measured from the date of diagnosis to last follow-up date, defined as last date of patient contact with the health system.

2.5. Statistical analysis

Univariate two-group tests were carried out using analysis of variance for continuous variables and using chi-square or Fisher's exact test as appropriate for categorical variables. Cox proportional hazards regression was used. In addition, multivariable Cox proportional hazards models were used to identify possible independent predictors of overall survival after confirming that proportional hazards assumptions were met using both the inclusion of time-dependent covariates in the model (all non-significant) and employing a proportionality test in PROC PHREG. Only patients with all pertinent variable data available were included in multivariable analysis. Kaplan Meier curves and the log-rank test evaluated survival. Statistical significance was set at $p < 0.05$. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, http://www.sas.com, RRID:SCR_008567).

3. Results

Of 208 patients initially identified for possible inclusion, 16 patients were excluded (2 patients with "other" race, 3 patients with missing race, and 11 patients with missing HPV status); this resulted in 192 patients being included in the study. Univariate hazard ratio of death for black versus white patients revealed statistically significant lower overall survival for black patients (2.32, 95% CI [1.60, 3.35]). Hazard ratios of death were then calculated for the HPV-positive (HPV+) and HPV-negative (HPV−) subgroups; this demonstrated that in the HPV+ group, there was not a statistically significant increased risk of death in black patients (1.55, 95% CI [0.80, 2.99]), and in the HPV− group, the increased risk of death in black patients persisted (2.42, 95% CI [1.49, 3.94]).

Survival probabilities at 1, 2, and 5 years were calculated for the entire cohort, the HPV+ subgroup, and the HPV− subgroup (Table 1). Significant differences are seen in survival probabilities between black and white patients in both the overall cohort and the HPV− subgroup at 1, 2, and 5 years, with black patients having poorer survival probability at each interval. In the HPV+ subgroup, there was not a significant difference in survival probability at 1, 2, and 5 years.

As survival discrepancies were identified between black and white patients in both the overall cohort and the HPV− subgroup, the average CCIs of these patient groups were examined. There was no significant difference in average CCI between whites and blacks in either the overall cohort (2.83 vs 2.56, $p = 0.612$) and the HPV− subgroup (2.46 vs 2.03, $p = 0.549$).

Univariate analysis was then performed to compare black and white patients in both the overall cohort and the HPV− subgroup (Tables 2 and 3). In the overall cohort, white patients were more likely to have HPV+ disease. Black patients were more likely to present with stage 4 disease, have shorter follow-up times, and live in census-blocks with lower levels of education, lower median household income, higher proportion of residents living under the poverty line, and lower proportion of houses occupied and owned. There was no significant difference in age at presentation, gender, or smoking history between black and white patients in the entire cohort.

In the HPV− subgroup, the differences noted in the overall cohort between black and white patients persisted, with black patients more likely to present with stage 4 disease, have shorter follow-up times, and live in census-blocks with lower levels of education, lower median household income, higher proportion of residents living under the poverty line, and lower proportion of houses occupied and owned.

Table 1
Survival probability by race at 1, 2, and 5 years (n = 192).

Group	Interval	White	Black	*p*-Value
Entire cohort	1 year	0.91	0.68	<0.001
	2 years	0.79	0.49	
	5 years	0.64	0.32	
HPV-positive	1 year	0.95	0.88	0.187
	2 years	0.85	0.79	
	5 years	0.72	0.54	
HPV-negative	1 year	0.84	0.57	<0.001
	2 years	0.68	0.32	
	5 years	0.50	0.20	

HPV, human papillomavirus.

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Table 2
Univariate comparison by race in the overall cohort (n = 192).

Covariate	Level	White, n = 124 (%)	Black, n = 68 (%)	*p*-Value
Median age at diagnosis (Q1, Q3)		59.5 (53.85, 65.27)	58.85 (53.47, 65.97)	0.742
Gender	Male	99 (79.84)	56 (82.35)	0.673
	Female	25 (20.16)	12 (17.65)	
HPV status	Negative	44 (35.48)	44 (64.71)	<0.001
	Positive	80 (64.52)	24 (35.29)	
AJCC-7 stage at diagnosis	1	10 (8.13)	8 (11.94)	<0.001
	2	13 (10.57)	2 (2.99)	
	3	39 (31.71)	7 (10.45)	
	4	61 (49.59)	50 (74.63)	
Current smoker		25 (23.36)	20 (35.71)	0.094
≥20 pack-year history		63 (59.43)	38 (67.86)	0.293
Median follow-up time in months (Q1, Q2)		64.71 (26.89, 98.07)	22.05 (7.67, 63.47)	0.002
Greatest level of education, mean % ± SD[a]	Less than high school	11.19 ± 8.3	21.17 ± 10.57	<0.001
	High school/ GED	29.66 ± 9.5	32.28 ± 7.67	0.157
	Some college	24.82 ± 6.03	25.68 ± 7.14	0.530
	Associates	8.31 ± 2.88	6.73 ± 5.72	0.083
	Bachelors	16.49 ± 8.94	8.17 ± 6.65	<0.001
	Postgraduate degree	8.81 ± 6.87	5.29 ± 5.06	0.008
	Doctorate	0.73 ± 0.82	0.67 ± 0.95	0.737
Median household income, mean $ ± SD[a]		62,862 ± 24,360	31,861 ± 16,765	<0.001
% under poverty line, mean ± SD[a]		8.29 ± 9.11	30.74 ± 16.36	<0.001
Houses occupied, mean % ± SD[a]		91.96 ± 5.18	76.59 ± 10.4	<0.001
Houses owned, % ± SD[a]		80.37 ± 15.39	53.77 ± 17.66	<0.001

Q, quartile; HPV, human papillomavirus; AJCC-7, American Joint Committee on Cancer, 7th edition; SD, standard deviation; GED, General Education Diploma.
[a] White n = 55 and Black n = 39.

Table 3
Univariate comparisons by race in HPV− subgroup (n = 88).

Covariate	Level	White, n = 44 (%)	Black, n = 44 (%)	*p*-Value
Median age at diagnosis (Q1, Q3)		61.74 (55.85, 65.27)	59.42 (53.47, 65.97)	0.866
Gender	Male	29 (65.91)	34 (77.27)	0.237
	Female	34.09 (34.09)	10 (22.73)	
AJCC-7 stage at diagnosis	1	6 (13.95)	7 (16.28)	0.041
	2	2 (4.65)	0 (0)	
	3	14 (32.56)	5 (11.63)	
	4	21 (48.84)	31 (72.09)	
Current smoker		11 (30.56)	18 (52.94)	0.057
≥20 pack-year history		28 (73.68)	29 (78.38)	0.634
Median followup time in months (Q1, Q2)		49.72 (15.87, 118.69)	14.41 (5.85, 39.98)	<0.001
Greatest level of education, mean % ± SD[a]	Less than high school	13.53 ± 10.75	25.1 ± 11.05	<0.001
	High school/ GED	29.87 ± 8.0	34.51 ± 7.34	0.045
	Some college	25.34 ± 6.58	24.49 ± 8.33	0.700
	Associates	7.7 ± 2.98	6.95 ± 7.24	0.644
	Bachelors	15.56 ± 8.24	5.4 ± 4.29	<0.001
	Graduate school	7.49 ± 5.24	3.04 ± 3.75	0.002
	Doctorate	0.51 ± 0.49	0.5 ± 1.01	0.952
Median household income, mean $ ± SD[a]		55,708 ± 17,877	24,668 ± 9755	<0.001
% under poverty line, mean ± SD[a]		10.96 ± 11.61	37.39 ± 15.14	<0.001
Houses occupied, mean % ± SD[a]		90.98 ± 6.9	72.68 ± 7.44	<0.001
Houses owned, % ± SD[a]		77.36 ± 18.17	46.42 ± 14.6	<0.001

HPV−, human papillomavirus negative; Q, quartile; AJCC-7, American Joint Committee on Cancer, 7th edition; SD, standard deviation; GED, General Education Diploma.
[a] White n = 24, Black n = 23.

Again, in the HPV− subgroup, no significant difference was seen in age at presentation, gender, or smoking history.

Multivariate survival models were created for the overall cohort and the HPV− subgroup, using race, HPV status, and the statistically significant variables identified by univariate analysis: stage at presentation, census-block level education level and median household income (Tables 4 and 5). HPV status was identified as an independent predictor of survival in the overall cohort, as expected. However, race was also identified as an independent predictor of survival—with black patients having poorer survival—in both the entire cohort and the HPV− subgroup, while stage at presentation, census-block level education level and median household income were not significant predictors in these models.

Of the 43 HPV− black patients with treatment information, 55.8% received radiotherapy ± chemotherapy, 11.6% received surgical therapy alone, 16.3% received surgical therapy with radiotherapy ± chemotherapy and 16.3% received noncurative or no treatment. Of the 42 HPV− white patients with treatment information, 52.4% received radiotherapy ± chemotherapy, 19.0% received surgical therapy alone, 16.7% received surgical therapy with radiotherapy ± chemotherapy and 11.9% received noncurative or no treatment. Fisher's exact test found no significant difference in the proportion of HPV− black and white patients receiving inadequate, noncurative or no treatment (46.5% vs 34.9%, $p = 0.3801$). There was no significant difference in the proportion of black and white patients receiving each type of treatment modality either ($p = 0.7768$).

Table 4
Multivariate survival analysis in overall cohort controlling for stage at presentation and socioeconomic status (n = 94).

Variable	Response	Adjusted HR (95% CI)	*p*-Value
Race	Black vs. White	2.58 (1.26, 5.28)	0.010
HPV status	Positive vs Negative	0.20 (0.10, 0.41)	<0.001
Median household income	Every $10,000 increase	1.13 (0.96, 1.33)	0.134
Less than high school	Every 10% increase	1.14 (0.81, 1.60)	0.445
AJCC-7 stage at presentation	2 vs 1	2.99 (0.52, 16.74)	0.292
	3 vs 1	1.57 (0.61, 4.03)	
	4 vs 1	2.30 (0.91, 5.80)	

HR, Hazard Ratio; CI, confidence interval; HPV, human papillomavirus; AJCC-7, American Joint Committee on Cancer, 7th edition.

4. Discussion

This retrospective cohort analysis found HPV+ status and white race to be independent predictors of survival in OPC—specifically in HPV− OPC—whereas gender, socioeconomic surrogates (census-block level median household income and education level), and tumor stage at presentation did not correlate with survival. CCI, representing the comorbidity burden of the patient, was not significantly different between the races in either the overall cohort or in the HPV-negative subgroup, suggesting that the survival difference cannot be attributed to

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Table 5
Multivariate survival analysis in the HPV− subgroup controlling for stage at presentation and socioeconomic status (n = 47).

Variable	Response	Adjusted HR (95% CI)	*p*-Value
Race	Black vs. White	4.97 (1.57, 15.74)	0.006
Median household income	Every $10,000 increase	1.18 (0.89, 1.57)	0.259
Less than high school	Every 10% increase	1.08 (0.72, 1.62)	0.723
AJCC-7 stage at presentation	3 vs 1	2.03 (0.70, 5.91)	0.305
	4 vs 1	2.24 (0.79, 6.30)	

HPV−, human papillomavirus negative; HR, hazard ratio; CI, confidence interval; AJCC-7, American Joint Committee on Cancer, 7th edition.

comorbidity burden. There was also no significant difference between proportion of black compared to white patients in the HPV-negative group receiving inadequate, noncurative or no treatment, suggesting that adequacy of treatment cannot account for the survival difference either. Interestingly, univariate analysis did identify a significant difference in follow-up time between black and white patients in both the overall cohort and the HPV-negative group, with black patients having shorter follow up time. This is presumably related to the lower socioeconomic status identified among black patients (suggested by residing in census-blocks with lower median household income and lower level of education observed in black patients). However, since multivariate analysis did not identify surrogates of SES as predictors of survival, one cannot conclude that this difference in follow-up time contributed to the survival difference seen, especially considering that the HPV− group did not demonstrate a significant difference in the proportion of black compared to white patients that received inadequate, noncurative or no treatment.

Race as a predictor of survival in head and neck cancer has been found in prior studies [16–24]. Previous studies have suggested that the overall survival by race was due to the lower incidence of HPV+ disease in black patients [10,11]. This is consistent with the current study, as there was no survival difference between races in the HPV+ subgroup. However, other studies demonstrated race to be an independent prognosticator. Molina et al. examined 20,915 patients with HNC, and found that race is an independent predictor of survival outcome, despite including community poverty level and treatment modality in multivariate analysis [16]. In multivariate Cox regression analysis, Zandberg et al. also demonstrated that race was a predictor of survival, with black patients having poorer survival [18]. Further, Megwalu and Ma found black patients to have worse prognosis on multivariate analysis, including treatment modality, in a study of 13,434 patients with OPC [21]. However, none of these studies included HPV status.

Prior research has also found that black patients tend to present at later stages [20], which was supported by the findings in this study. This finding could presumably be related to black patients' SES, with a higher likelihood to live in areas of lower income and education, which was also suggested on univariate analysis in this study. Therefore, this patient population may be more limited by insurance, financial, and transportation constraints than their white counterparts. However, presentation at a later stage was not identified as a predictor of poorer survival on multivariate analysis in the current study.

The findings of this study suggest that, although black patients do tend to reside in areas of lower SES and present at later stages, these factors do not appear to be associated with poorer survival in HPV− disease; however, race itself is, with black patients having a higher risk of mortality than their white counterparts. It is possible that the reason for this goes beyond SES and comorbidity. Perhaps black patients may be more susceptible to certain mutations, resulting in worse prognosis in HPV− OPC. In a previous study, black patients were found to have more mutations than non-Hispanic whites in EGFR, HRAS, KRAS, and TP53; and the presence of three or more mutations correlated with poor prognosis in patients with HNC [25].

This study was limited by a small sample size (N = 192), retrospective design, and a single institution setting. Additionally, census-block level socioeconomic data does not represent the patient's SES directly, and significant variability of SES can exist within a census-block. However, while not an ideal method to collect information about socioeconomic status, using census-block level SES proxy has been previously accepted as a meaningful solution to obtain SES data in retrospective studies. It is an imperfect tool to infer socioeconomic data, but it is the best method available in the case of this retrospective study.

Another issue encountered in this study is the lack of an agreed upon method for handling patients who did not complete their full, recommended treatment for various reasons. It is our hope to spur discussion on how these patients should be categorized in research. While it is not ideal to group all inadequately treated patients together, it was not practical to account for the wide spectrum of inadequate treatment—from a missed radiation session or chemotherapy to no treatment altogether, for example—so a hard line had to be drawn between adequate and inadequate treatment.

The AJCC-7 staging system was used for staging in this study; unfortunately, there was no practical way to convert AJCC-7 staging for each patient to AJCC-8 due to the retrospective nature of the study. This is a limitation of the study, as AJCC-7 staging is known to be a poor predictor of outcomes for HPV+ disease. In addition, disease-specific survival was not able to be examined, as cause of death of patients was largely unknown. Latency from diagnosis to initiation of treatment was also not collected; future studies would benefit from including these data in their analyses to help stratify those receiving "inadequate" treatment.

5. Conclusion

Despite the aforementioned limitations, this study contributes to understanding how race and socioeconomic factors are associated with outcomes in patients with OPC. HPV− status and black race were found to be independent predictors of poorer survival in both the overall cohort of OPC patients and patients with HPV− disease, while controlling for stage at presentation, socioeconomic status surrogates (highest education level and median household income), comorbidity burden, smoking status, age at presentation, gender, and proportion of patients who underwent inadequate treatment. Results of this study cannot rule out SES as a predictor of survival, however, they suggest that race itself is a prognosticator of survival, independent of SES. Future studies should analyze more accurate surrogates for SES and possible biological differences in tumors between races. Additionally, although SES was not identified as a predictor of survival, this study does demonstrate that black patients tend to reside in census-blocks with lower SES, which is an important consideration when providing care for these patients, as they may be limited by insurance, transportation, and financial constraints, as well as health literacy and access to medical care.

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Previously presented

The data from this manuscript was presented at the Henry Ford Health System: 16th Annual Research Symposium (2019) and the Henry Ford Medical Group Otolaryngology Resident Research Day (2019).

Ethical considerations

This retrospective, observational study did not impact patient care. IRB approval was obtained prior to study commencement.

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Declaration of competing interest

Ryan Freedman, Haley Sibley, Amy Williams, and Steven Chang have no conflicts of interest to disclose.

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