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Prognostic factors for human papillomavirus-positive and negative oropharyngeal carcinomas

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Abstract

Objectives: Human papillomavirus (HPV)-positive and negative oropharyngeal squamous cell carcinoma (OPSCC) are distinct disease entities. Prognostic factors specific to each entity have not been adequately explored. Goals for this study were: 1) To determine whether HPV-positive and HPV-negative OPSCCs have distinct prognostic factors, and 2) To explore the prognostic significance of sex and race in OPSCC after HPV stratification

Methods: Retrospective review of 239 incident OPSCC patients from 1995 to 2012, treated at Johns Hopkins and UCSF. Women and non-White races were oversampled. All analyses were stratified by tumor HPV ISH status. The effects of sex and race on survival were considered in Kaplan Meier and unadjusted and adjusted Cox regression models.

Results: 134 (56.1%) OPSCC patients were HPV-positive. On univariate analysis, women had better overall survival than men among HPV-positive (HR=0.47 95%CI: 0.20–1.07, p=0.06) but not HPV-negative (HR=0.73, 95%CI: 0.43–1.24, p=0.24) OPSCCs. On multivariate analysis, women with HPV-positive OPSCCs remained at lower risk of death (aHR=0.34, 95%CI: 0.12–0.96, p=0.04). Survival did not vary significantly by race among HPV-positive patients. Among HPV-negative patients, Hispanic patients had significantly better survival in unadjusted (HR=0.27, 95%CI: 0.08–0.91, p=0.04) but not adjusted (aHR=0.93, 95%CI: 0.11–7.36, p=0.94) analysis.

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Conflicts of interest: None

Conclusions: Women with HPV-positive OPSCC may have improved overall survival compared to men. Sex does not play a prognostic role in HPV-negative OPSCC. There are no differences in prognosis by race among HPV-positive or HPV-negative patients.

Keywords

human papillomavirus; head and neck oncology; oropharyngeal; squamous cell carcinoma; prognostic factors

INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) incidence is increasing globally.[1,2] Between 1975 and 2012, the incidence of OPSCC increased 62.6% in the United States, most notably among White men aged 50–59.[3] This is in contrast to the incidence of oral cavity squamous cell cancer, which declined over the same period.[3] This disparity can be attributed to the rise in human papillomavirus (HPV)-positive OPSCC, which accounts for 45–90% of OPSCCs in developed countries.[4] In the United States, the incidence of HPV-positive OPSCCs has steadily increased, most prominently among middle-aged men,[5,6] whereas the incidence of HPV-negative OPSCCs has significantly declined.[6] Several case series have shown that the proportion of OPSCCs that are HPV-positive has continued to increase in recent calendar periods.[7–9]

This dramatic shift in the epidemiology of OPSCC is attributed both to a decline in tobacco use and an apparent increase in exposure to sexually transmitted oral HPV infection.[6,10] Compared to HPV-negative counterparts, HPV-positive OPSCC patients are more likely to be non-smokers, White, male, of a higher socioeconomic status, and have a history of multiple sexual partners.[11–14] HPV-positive patients also have significantly improved prognosis compared with HPV-negative patients,[13,15] with higher response rates to chemoradiation treatment[16], higher control rates with surgery and adjuvant treatment,[17] and better overall survival both at diagnosis[13,16,18] and after disease progression, relative to HPV-negative OPSCC patients.[19–21] Recent studies have also shown that extent of nodal disease differs for HPV-positive and –negative OPSCC.[22]

With the recognition that HPV-positive and HPV-negative OPSCC have different etiologies, clinical-demographic characteristics, and prognostic profiles, the two are now considered distinct entities despite arising from the same anatomic site. However, the clinical factors that influence overall survival for these separate diseases remain unknown. Most prognostic studies to date have examined OPSCCs as a single group, and included a heterogeneous sample of HPV-positive and HPV-negative OPSCCs. Evaluating the two groups together allows studies to assess the influence of HPV on survival, but not how HPV may modify other risk factors associated with prognosis.

Few studies have focused on prognostic factors for survival after stratification for HPV status in OPSCCs. Initial studies suggest that among patients with HPV-positive OPSCCs, older age, smoking, and higher AJCC 7th edition tumor stage are associated with worse locoregional control and overall survival. [23–26] Race has been observed as a prognostic factor for HPV-negative OPSCC, but not HPV-positive OPSCC.[27] Furthermore, the majority

of studies to date are comprised of mostly White men,[13] and are thus unable to examine the prognostic impact of sex and race on survival for HPV-positive and HPV-negative OPSCCs.

The goals of this study were to consider prognostic factors separately among HPV-positive and HPV-negative OPSCCs, and to explore the effects of sex and race on the overall survival of OPSCC patients within these subgroups.

METHODS

Study population

This is a retrospective analysis of 239 incident OPSCC cases between 1995–2012 at the Johns Hopkins Hospital (JHH, Baltimore, MD) and the University of California – San Francisco (UCSF, San Francisco, CA).[28,29] OPSCC was defined as histologically confirmed squamous cell carcinoma of the base of tongue, tonsils, soft palate, and oropharyngeal walls. Patients were randomly sampled from hospital cancer registries according to sex and race in order to over-sample non-White patients and women.[28] When creating a study population, we selected a random sample of men and Whites from the registry, and selected all the women and non-Whites in the registry because there were so few women and non-Whites. Therefore, a greater proportion of women (than men) and non-Whites (than Whites) available in the registry were selected. Race categories were defined as White non-Hispanic (White), Black non-Hispanic (Black), Asian non-Hispanic (Asian), and Hispanic of any race (Hispanic). Medical record review was used to ascertain clinical characteristics of interest (age at diagnosis, tobacco use, alcohol use, American Joint Committee on Cancer [AJCC] 8th edition overall stage, vital status). The study was approved by Institutional Review Boards at JHH and UCSF.

Tumor HPV status and p16 testing

Details regarding HPV tumor detection methods have previously been described.[28] Briefly, HPV detection on all tumors was performed at the Johns Hopkins Pathology Laboratory and interpreted by a single pathologist specializing in head and neck cancers (WHW). All OPSCC tumors underwent testing for p16 expression by immunohistochemistry (MTM Laboratories, Heidelberg, Germany) and HPV16 DNA by in situ hybridization (ISH) (Dako GenPoint, Carpinteria, CA). p16 expression was considered positive if a tumor showed ≥70% strong and diffuse nuclear and cytoplasmic staining.[30] Tumors that were p16 positive but HPV16 DNA ISH negative had additional testing using a RNA ISH probe targeting E6/E7 mRNA for all 18 high-risk HPV genotypes: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82 (RNAscope, Advanced Cell Diagnostics, Hayward, CA). Patients were considered HPV-positive if they were positive for *either* HPV16 DNA ISH or other high-risk HPV RNA ISH. Past studies have shown that the combination of high sensitivity p16 immunohistochemistry with direct visualization of high-risk HPV (which includes probing for transcriptionally active other high-risk HPV in the subset of p16 positive/HPV16 DNA negative patients) is a highly accurate method for determining HPV tumor status.[31–35]

Statistical analysis

Patient characteristics of OPSCCs were compared by HPV tumor status using chi-square tests for categorical variables and non-parametric equality of medians tests for continuous variables. Risk factors for overall survival among patients with HPV-positive and HPV-negative OPSCC were considered separately. The effects of race and sex were evaluated using Kaplan-Meier survival curves and compared by log-rank tests. Demographic (sex, race, age), clinical (stage, site), and behavioral (tobacco and alcohol use) risk factors for overall survival were considered in unadjusted and adjusted Cox regression models. Final models retained sex and race as key variables of interest, as well as age, stage, and tobacco use, given their established prognostic importance regardless of statistical significance. A secondary, more parsimonious, adjusted model excluding race was also generated. P-trend was calculated by modeling the hazard ratios to consider whether there was a trend of increasing hazard ratios across categories. Overall survival was defined as the time between date of diagnosis and date of death from any cause. In survival analysis, patients were censored at the time of death, loss to follow-up, or analytic censor.

RESULTS

Characteristics of the study population are summarized in Table 1. Of 239 OPSCC patients, 134 (56.1%) were HPV-positive, and 105 (43.9%) were HPV-negative. The median age for all patients was 57 years (interquartile range [IQR] 51–64). There were no differences in age ($p=0.90$) or sex ($p=0.36$) between HPV-positive and HPV-negative OPSCC. Although women were oversampled, the majority of both HPV-positive (69.4%) and HPV-negative (63.8%) patients in the study were men. When compared with HPV-positive patients, HPV-negative patients were more likely to be Black, former/current smokers, former/current drinkers, and have a higher AJCC overall stage ($p<0.001$ for each).

Given our interest in sex and race-based differences among patients with OPSCC, characteristics of the study population were also compared by sex (Supplemental Table 1) and race (Supplemental Table 2). When comparing by sex, women with OPSCC were more likely to be White ($p<0.001$), never-smokers ($p=0.06$), and never-drinkers ($p<0.001$). When comparing across races, there were several significant differences observed. Black OPSCC patients were younger, had higher overall AJCC stage, and were more likely to smoke than patients of other races (each $p\leq0.05$). A larger proportion of White patients were women than in other race groups ($p<0.001$).

The median follow-up time for the study population was 3.5 years (IQR: 1.3, 6.9). HPV-positive patients had significantly longer follow-up (4.3 years [IQR: 2.6, 7.2]) compared to HPV-negative patients (2.1 years [IQR: 0.7, 5.0], $p<0.001$), due at least in part to the fewer deaths in HPV-positive patients (Table 1). During the follow-up period, 99 (41.4%) OPSCC patients died from any cause, including 36 (17.8% of all patients) who died due to their malignancy (Table 1). HPV-positive OPSCC patients were less likely than HPV-negative OPSCC patients to die from any cause ($p<0.001$) and as a result of their primary cancer ($p=0.007$). There were 16 (6.7%) patients with persistent disease after treatment. During follow-up, 29 (12.1%) and 14 (5.9%) patients developed a recurrence and second primary, respectively. These outcomes were similar by HPV tumor status.

Factors associated with overall survival in HPV-positive OPSCC

Among HPV-positive OPSCCs, survival appeared to differ by sex (p=0.06), but not by race (p=0.18); Figures 1a–1b. 5-year overall survival was lower for men than women (74.8% vs. 87.0%, p=0.064; HR=0.47, 95%CI: 0.20–1.07), although this difference was not statistically significant. In univariate analysis, the strongest factors associated with overall survival among HPV-positive OPSCC patients (n=134) were higher tumor (p-trend=0.02), nodal (p-trend<0.001), and overall AJCC (p-trend<0.001) stage (Table 2). After adjusting for stage, age, and tobacco use, risk of death remained lower in women than men (Table 2). This reduction in death risk among women was statistically significant when models also adjusted for race (aHR=0.34 95%CI: 0.12–0.96; p=0.04), but was not significant when race was not included in the model (aHR=0.42 95%CI=0.15–1.15; p=0.09).

Of the 134 HPV-positive OPSCCs, the majority was HPV16-positive (n=114, 85.1%). To determine whether there were survival differences by HPV type, survival of HPV16-positive patients was compared with other high-risk HPV-positive OPSCC patients. Survival was similar among patients with HPV16-positive and other high-risk HPV-positive OPSCCs (78.8% vs. 77.6% at 5 years p=0.94; Figure 2). Among the 134 HPV-positive OPSCCs, the proportion caused by HPV16 was similar among men (86%) and women (83%, p=0.62), but differed by race (95% of Whites compared to 56% of Asians, 82% of Hispanics and 88% of Black patients, p=0.004).

Factors associated with overall survival in HPV-negative OPSCC

Among HPV-negative OPSCCs (n=105), there was no significant difference in overall survival between men and women (Figure 1c, p=0.24). Survival by sex was similar at 3-years (52.7% vs. 59.8%). At 5-years, overall survival appeared lower among men than women (33.9% vs. 56.1%), but there were only 27 subjects remaining in follow-up after 5 years.

Survival was similar among all races in HPV-negative OPSCCs (Figure 1d, p=0.09). Among HPV-negative OPSCCs, the 10 Hispanic patients had improved overall survival compared to non-Hispanic White patients in unadjusted (HR=0.27, 95%CI: 0.08–0.91, p=0.04 Table 3) but not adjusted (aHR=0.93, 95%CI: 0.11–7.36, p=0.94) analysis. History of tobacco use was associated with decreased overall survival, but was not statistically significant (aHR=4.81, 95%CI=0.61–38.1, p=0.14; Table 3).

Analysis according to p16 tumor status

Similar risk factor analyses were performed comparing patients by tumor p16 status instead of tumor HPV status. Risk factors for survival were similar when classifying tumors this way (Supplemental Tables 3–4). For p16-positive OPSCCs, lower AJCC overall stage (p-trend<0.001) and female sex (HR=0.49, 95%CI: 0.23–1.07, p=0.07) were associated with improved survival. Consistent with results when considering HPV status, on adjusted analysis of p16-positive OPSCCs, women had significantly improved survival regardless of whether race was included (aHR=0.32, 95%CI: 0.12–0.88, p=0.03) or excluded (aHR=0.37, 95%CI: 0.13–0.99, p=0.05) from the model. Among p16-negative OPSCCs, current tobacco

use was the primary risk factor for survival (aHR=8.70, 95%CI: 0.75–100, p=0.08). Race was not significantly associated with survival in either p16-positive or negative OPSCCs.

DISCUSSION

This is the one of the largest studies to evaluate prognostic risk factors separately in HPV-positive and HPV-negative OPSCCs. Given that HPV-positive and HPV-negative OPSCCs are distinct clinical entities with significantly different prognoses, understanding differences in prognostic factors for each disease is important. Our analysis, with a diverse sex and race distribution and including the updated AJCC staging system, suggests a better prognosis for women with HPV-positive OPSCCs. We observed that there are no survival differences by race in either HPV-positive or -negative OPSCCs, suggesting previous racial differences in OPSCC prognosis[36] may be explained by racial differences in the proportion of HPV-positive OPSCCs.[26,37]

Sex disparities are commonly seen in cancer survival in the United States. Across the majority of anatomic sites, age-adjusted mortality rates are higher for men than women.[38] We previously analyzed overall survival for OPSCC, controlling for tumor HPV status, and identified sex as a potential prognostic factor.[29] The prognostic significance of sex for HPV-positive and -negative OPSCC patients, separately, has not been previously explored. The present analysis, which stratifies by HPV status, suggests that sex *may* be a prognostic factor for HPV-positive but not HPV-negative OPSCC, although the findings will need to be reproduced. Our research is consistent with another study that also suggested men have worse overall survival than women in OPSCC, although this study did not stratify by HPV status.[27] Although the majority of HPV-positive OPSCC patients are men, most OPSCCs among women in the United States today are HPV-positive.[28] Our study is unique in having a larger proportion of females due to over-sampling women with OPSCC, allowing us to better explore the effect of sex. The reason for this observed sex disparity in HPV-positive OPSCC survival is unknown, but may involve a combination of biological and behavioral factors. Female sex hormones may affect the immune response to malignancies,[39] and women are more likely to utilize healthcare resources.[38,40] In our cohort, there was no significant sex difference in overall stage at time of diagnosis (p=0.07), suggesting a lack of lead-time bias between the two sexes in our cohort.

There are also recognized racial disparities between White and Black patients in head and neck cancer incidence and mortality.[41–43] However, recent research suggests that the proportion of HPV-positive OPSCCs is higher among White than Black patients;[44] which may explain the previously observed survival differences between Black and White patients in past analyses that did not consider HPV status.[37,45] Our results support this hypothesis, showing that race was not a prognostic factor after HPV stratification. Our findings are consistent with the Worsham et al. study that showed that among HPV-positive OPSCCs, survival was similar in Black and White patients.[27] However, in contrast to the Worsham et al. study, which showed a remaining survival difference between Black and White patients with HPV-negative OPSCCs, our results suggest that there are no racial differences in the prognosis of HPV-negative OPSCCs after controlling for differences in age, sex, tumor stage, and tobacco use.[27] Our study population, from two large metropolitan areas in distinct

parts of the United States, may be more racially and geographically diverse compared to the population in the Worsham et al. study,[27] which may contribute to differences in results.

Several studies have found smoking to be significantly associated with worse prognosis among HPV-positive OPSCC patients, [23,26,46] but this association was not detected in our HPV-positive patients. This may be due to the retrospective nature of this study, as medical records may not have fully captured tobacco exposure. Prevalence of tobacco use differed by sex (Supplemental Table 1) in this study. The inclusion of a greater proportion of women in this HPV-positive cohort may have influenced the observed effect of smoking on prognosis.[26] Among HPV-negative patients, as expected, survival appeared to be lower among smokers, although the association was not statistically significant. This may again be explained by the imprecise collection of tobacco history via medical records. Nevertheless, the magnitude of the increase in risk of death (HR ~4.8) suggests that smoking is likely a risk factor for worse survival. Previous studies have shown that smoking does indeed have an independent prognostic effect on survival, although these studies did not stratify by HPV tumor status.[47, 13]

In this study, there were no survival differences between OPSCC cases that were HPV-16 positive (i.e. caused by HPV16) and OPSCCs that were positive for other high-risk HPV types. This adds to previously conflicting reports.[48–50] While some studies suggest better overall survival for HPV-16 positive OPSCCs compared to other high-risk HPV OPSCCs,[48,49] another found that HPV-16 positive OPSCCs may be associated with more frequent metastases and worse disease-free survival.[50] Our study differs from these previous studies in our HPV detection methods, which incorporated more recently developed RNA based testing methods.[48,49] Differences in the sensitivity of these detection methods[51] may have led to misclassification and explain the different prognostic effects observed in our study compared to previous studies. However, our findings are consistent with a recent study that also used single-center tumor testing and a diversely sampled population;[52] it concluded that there were no differences in survival between HPV16 and other non-HPV16 types in OPSCCs.[52]

This is the first analysis that evaluates 8th edition AJCC stage in the context of other risk factors. Among HPV-positive OPSCCs, increasing stage was associated with worse overall survival in univariate and multivariate models. Among HPV-negative OPSCCs, stage was significant in univariate analysis but not significant in multivariate models, although hazard ratios trended in the expected direction. Other advantages of this study include a large multi-institutional study population with a higher proportion of women and non-White patients compared to previous studies[13] and centralized HPV tumor status testing. Limitations of the study include its retrospective design, with risk factors abstracted from medical records. Both study centers were tertiary care centers with a large volume of referred patients, and many patients received treatment or follow-up at other institutions. As a result, we are unable to collect complete records of patient co-morbidities and treatment regimens, both of which may influence the results. However, we believe this variety in oncologic treatment is a more accurate reflection of circumstances encountered in a real clinical setting. Unlike previous retrospective studies that focus on prognostic factors in patients receiving primary surgical or radiation therapy[53] under clinical trials, this study reflects a

patient population with a heterogeneous treatment history. Future randomized clinical trials aimed specifically at HPV-positive or HPV-negative OPSCC patients will further define differences in prognostic factors between these two groups.

CONCLUSION

Women with HPV-positive OPSCC may have significantly improved overall survival compared to men; however, this survival advantage is not observed in HPV-negative OPSCC. After accounting for other risk factors, race does not appear to play a prognostic role in either HPV-positive or HPV-negative OPSCC. These findings provide a framework to understand the effect of race and sex on overall survival for HPV-positive and negative OPSCC patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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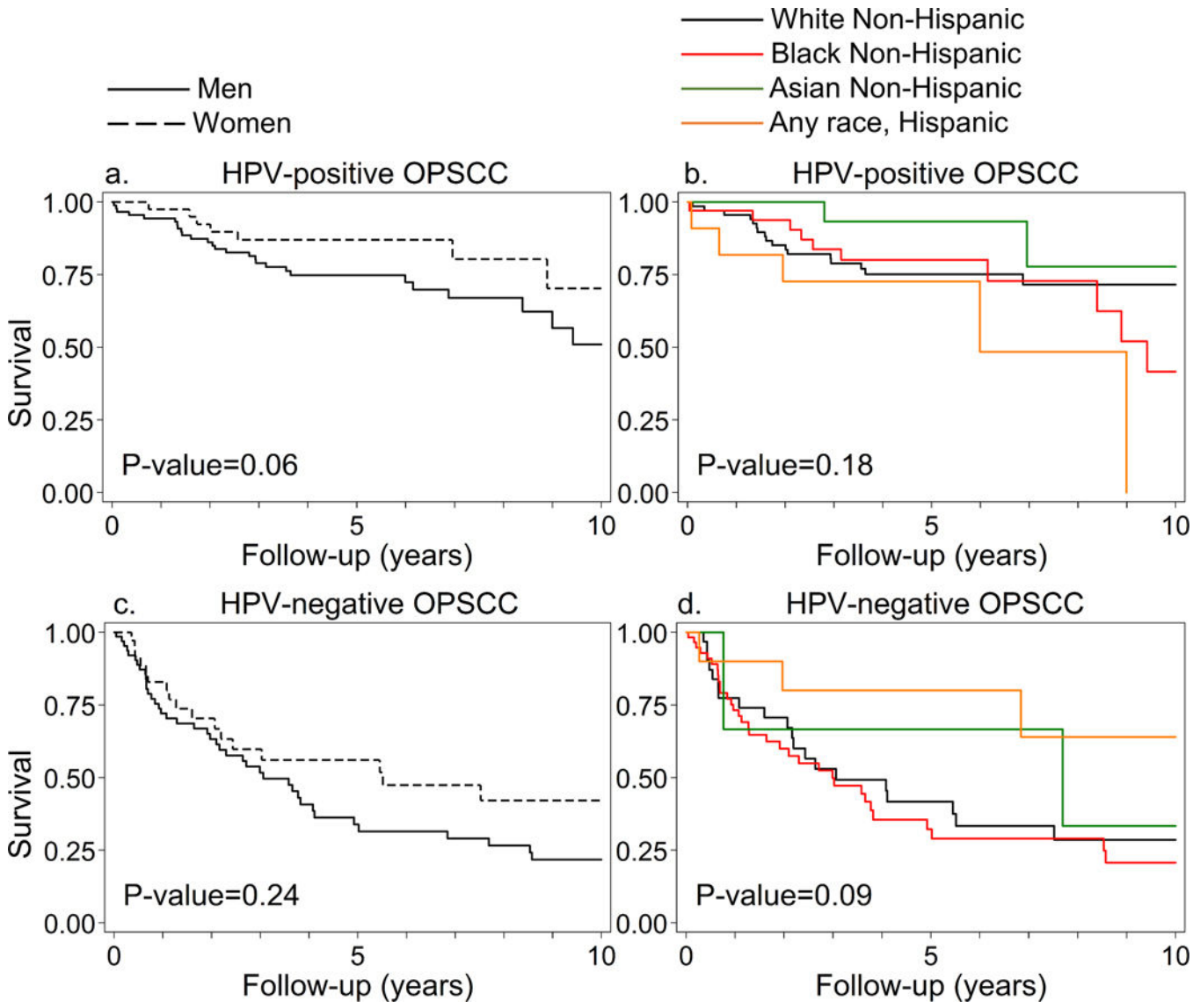

Figure 1. Survival by sex and race, ethnicity among HPV-positive and HPV-negative oropharyngeal squamous cell cancers.

Among HPV-positive OPSCCs, 1a) survival for men (n=93) and women (n=41) at 5 years was 74.8% and 87.0%, respectively. 1b) survival for White (n=71), Black (n=34), Asian (n=18), and Hispanic (n=11) patients at 5 years was 75.2%, 80.1%, 93.3%, 72.7% respectively. Among HPV-negative OPSCC, 1c) survival for men (n=67) and women (n=38) at 5 years was 33.9% and 56.1%, respectively. 1d) survival for White (n=32), Black (n=60), Asian (n=3), and Hispanic (n=10) patients at 5 years was 41.7%, 32.2%, 66.7%, 80.0% respectively.

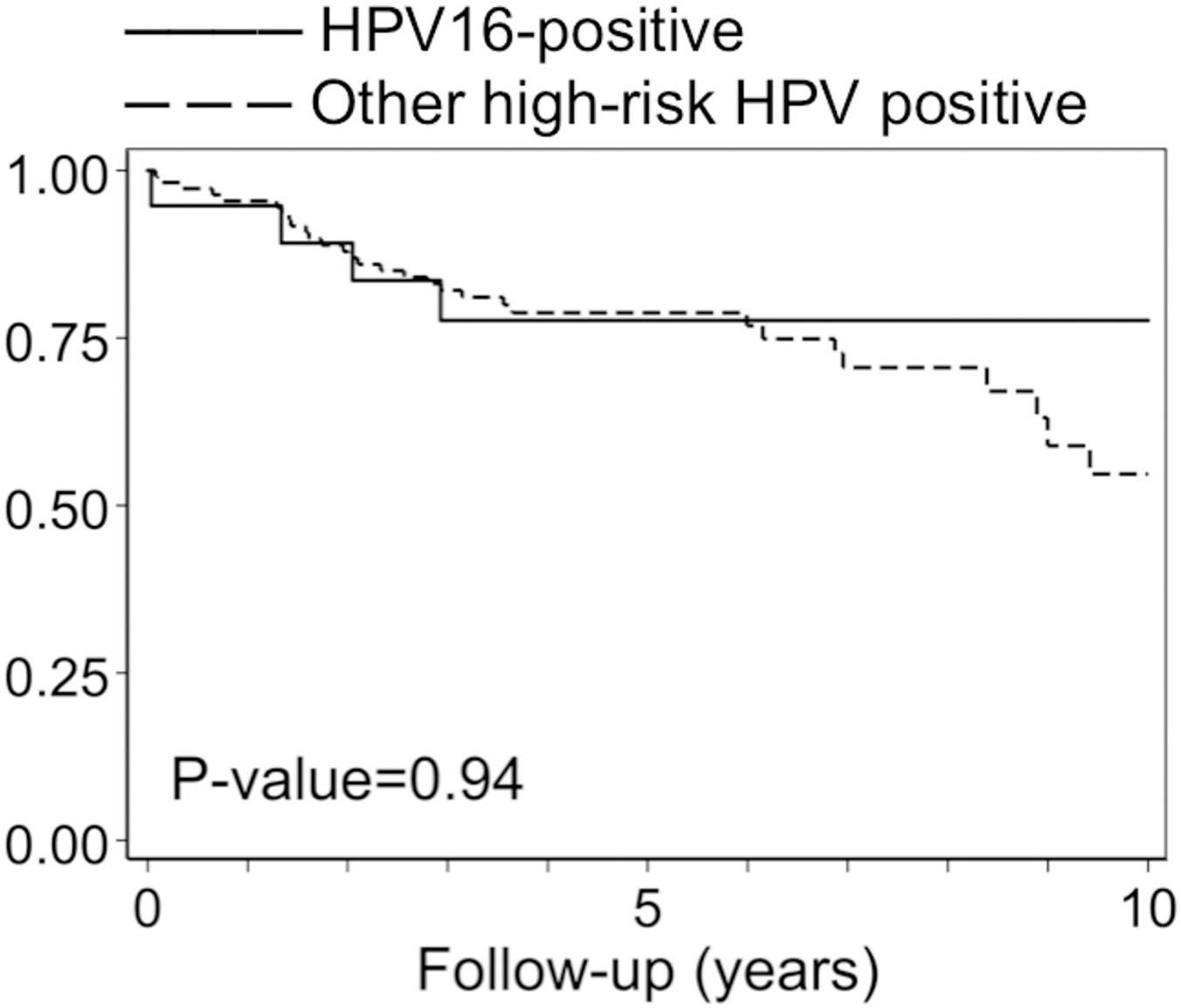

Figure 2. Survival comparing patients with HPV16-positive OPSCCs and other high-risk HPV-positive OPSCCs.

Among HPV-positive OPSCC patients, survival for HPV16-positive (n=114) and other high-risk HPV-positive patients (n=20) at 5 years was 78.8%, and 77.6% respectively.

Table 1.

Characteristics of the study population at diagnosis, overall and by human papillomavirus (HPV) tumor status

	N (%)			
	Overall (N=239)	**HPV-negative† (N=105)**	**HPV-positive† (N=134)**	**P-value**
Age, Median (Interquartile range)	57 (51–64)	57 (51–65)	57 (50–64)	0.90
Sex				0.36
Men	160 (66.9%)	67 (63.8%)	93 (69.4%)	
Women	79 (33.1%)	38 (36.2%)	41 (30.6%)	
Race and ethnicity				**<0.001**
White Non-Hispanic	103 (43.1%)	32 (30.5%)	71 (53.0%)	
Black Non-Hispanic	94 (39.3%)	60 (57.1%)	34 (25.4%)	
Asian Non-Hispanic	21 (8.8%)	3 (2.9%)	18 (13.4%)	
Any race, Hispanic	21 (8.8%)	10 (9.5%)	11 (8.2%)	
Ever tobacco use				**<0.001**
No	46 (19.2%)	5 (4.8%)	41 (30.6%)	
Yes	152 (63.6%)	79 (75.2%)	73 (54.5%)	
Unknown	41 (17.2%)	21 (20.0%)	20 (14.9%)	
Current tobacco use				**<0.001**
No	121 (50.6%)	34 (32.4%)	87 (64.9%)	
Yes	69 (28.9%)	44 (41.9%)	25 (18.7%)	
Unknown	49 (20.5%)	27 (25.7%)	22 (16.4%)	
Ever alcohol use				**<0.001**
No	44 (18.4%)	7 (6.7%)	37 (27.6%)	
Yes	44 (60.3%)	73 (69.5%)	71 (53.0%)	
Unknown	51 (21.3%)	25 (23.8%)	26 (19.4%)	
Current alcohol use				**<0.001**
No	83 (34.7%)	31 (29.5%)	52 (38.8%)	
Yes	102 (42.7%)	47 (44.8%)	55 (41.0%)	
Unknown	54 (22.6%)	27 (25.7%)	27 (20.2%)	
AJCC overall stage				**<0.001**
I	87 (36.4%)	5 (4.8%)	82 (61.2%)	
II	33 (13.8%)	10 (9.5%)	23 (17.2%)	
III	38 (15.9%)	14 (13.3%)	24 (17.9%)	
IV	73 (30.5%)	69 (65.7%)	4 (3.0%)	
Indeterminate/Unknown	8 (3.4%)	7 (6.7%)	1 (0.7%)	
Study site				0.25
JHH	145 (60.7%)	68 (64.8%)	77 (57.5%)	
UCSF	94 (39.3%)	37 (35.2%)	57 (42.5%)	
Vital Status				
Died (any cause)	99 (41.4%)	63 (60.0%)	36 (26.9%)	**<0.001**
Died (from OPSCC)‡	36 (17.5%)	22 (26.2%)	14 (11.6%)	**0.007**

	N (%)			
	Overall (N=239)	**HPV-negative† (N=105)**	**HPV-positive† (N=134)**	**P-value**
Second primary				0.84
No	186 (77.8%)	82 (78.1%)	104 (77.6%)	
Yes	14 (5.9%)	7 (6.7%)	7 (5.2%)	
Unknown	39 (16.3%)	16 (15.2%)	23 (17.2%)	
Recurred				0.15
No	162 (67.8%)	65 (61.9%)	97 (72.4%)	
Persistent disease	16 (6.7%)	8 (7.6%)	8 (6.0%)	
No treatment	15 (6.3%)	11 (10.5%)	4 (3.0%)	
Yes	29 (12.1%)	14 (13.3%)	15 (11.2%)	
Unknown	17 (7.1%)	7 (6.7%)	10 (7.5%)	

Bold indicates statistically significant

† Indicates any high-risk HPV infection as determined by in situ hybridization test as detailed in methods

‡ 34 patients with unknown cause of death were excluded

Table 2.

Clinical characteristics associated with overall survival for HPV-Positive OPSCC

Characteristics at diagnosis	Unadjusted (N=134)		Adjusted Model 1† (N=113)		Adjusted Model 2† (N=113)	
	HR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
Age (per 10 year increase)	1.28 (0.92, 1.79)	0.15	1.22 (0.76, 1.95)	0.40	1.05 (0.68, 1.62)	0.82
Tumor stage			-		-	
T1	1.00					
T2	1.81 (0.77, 4.27)	0.18				
T3	2.46 (0.73, 8.32)	0.15				
T4	**3.05 (1.14, 8.15)**	**0.03**				
	p-trend: 0.02					
Nodal stage			-		-	
N0	1.00					
N1	1.21 (0.28, 5.18)	0.80				
N2	2.09 (0.41, 10.48)	0.37				
N3	**10.79 (2.11, 55.11)**	**0.004**				
	p-trend: <0.001					
AJCC overall stage			-		-	
I	1.00					
II	2.29 (0.92, 5.71)	0.08				
III	**4.10 (1.92, 8.77)**	**<0.001**				
IV	3.81 (0.86, 16.95)	0.08				
	p-trend: <0.001					
AJCC overall stage						
I/II	1.00		1.00		1.00	
III/IV	**3.30 (1.69, 6.43)**	**<0.001**	**3.39 (1.42, 8.12)**	**0.006**	**3.16 (1.34, 7.44)**	**0.008**
Sex						
Male	1.00		1.00		1.00	
Female	0.47 (0.20, 1.07)	0.06	**0.34 (0.12, 0.96)**	**0.04**	0.42 (0.15, 1.15)	0.09
Race and ethnicity						
White Non-Hispanic	1.00		1.00		-	
Black Non-Hispanic	1.25 (0.59, 2.69)	0.56	1.09 (0.44, 2.72)	0.84		
Asian Non-Hispanic	0.57 (0.17, 1.94)	0.37	0.14 (0.02, 1.12)	0.06		
Any race, Hispanic	2.39 (0.88, 6.52)	0.09	0.83 (0.18, 3.71)	0.81		
Ever tobacco use‡						
No	1.00		1.00		1.00	
Yes	1.09 (0.49, 2.46)	0.83	0.83 (0.36, 1.91)	0.67	0.85 (0.37, 1.94)	0.70
Current tobacco use‡			-		-	
No	1.00					
Yes	1.67 (0.72, 3.88)	0.23				
Ever alcohol use§			-		-	

Characteristics at diagnosis	Unadjusted (N=134)		Adjusted Model 1† (N=113)		Adjusted Model 2† (N=113)	
	HR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
No	1.00					
Yes	0.85 (0.38, 1.93)	0.71				
Current alcohol use§			-		-	
No	1.00					
Yes	0.61 (0.26, 1.39)	0.24				

Bold indicates statistically significant

† Adjusted models were restricted to patients with known tobacco use history and AJCC overall stage (n=113 of 134).

‡ Univariate analysis was restricted to patients with known tobacco use history (n=114 of 134).

§ Univariate analysis was restricted to patients with known alcohol use history (n=107 of 134).

Table 3.

Factors associated with overall survival for HPV-negative OPSCC

Characteristics at diagnosis	Unadjusted (N=105)		Adjusted Model 1† (N=79)		Adjusted Model 2† (N=79)	
	HR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
Age (per 10 year increase)	1.19 (0.95, 1.48)	0.12	0.97 (0.73, 1.29)	0.82	1.05 (0.81, 1.37)	0.70
Tumor stage			-		-	
T1	1.00					
T2	0.70 (0.29, 1.71)	0.43				
T3	1.17 (0.57, 2.43)	0.67				
T4	1.53 (0.71, 3.32)	0.28				
	p-trend: 0.13					
Nodal stage			-		-	
N0	1.00					
N1	**2.32 (1.00, 5.41)**	**0.05**				
N2	**2.13 (1.13, 4.00)**	**0.02**				
N3	1.88 (0.67, 5.25)	0.23				
	p-trend: 0.04					
AJCC overall stage			-		-	
I	1.00					
II	0.83 (0.19, 3.51)	0.80				
III	1.57 (0.44, 5.66)	0.49				
IV	2.02 (0.62, 6.62)	0.24				
	p-trend: 0.04					
AJCC overall stage						
I/II	1.00		1.00		1.00	
III/IV	**2.15 (1.02, 4.54)**	**0.04**	1.21 (0.52, 2.79)	0.66	1.16 (0.50, 2.67)	0.73
Sex						
Male	1.00		1.00		1.00	
Female	0.73 (0.43, 1.24)	0.24	0.58 (0.31, 1.11)	0.10	0.68 (0.37, 1.25)	0.21
Race and ethnicity						
White Non-Hispanic	1.00		1.00		-	
Black Non-Hispanic	1.10 (0.65, 1.87)	0.71	0.80 (0.41, 1.57)	0.52		
Asian Non-Hispanic	0.63 (0.15, 2.70)	0.54	-			
Any race, Hispanic	**0.27 (0.08, 0.91)**	**0.04**	0.93 (0.11, 7.36)	0.94		
Ever tobacco use‡						
No	1.00		1.00		1.00	
Yes	4.10 (0.56, 29.87)	0.16	4.81 (0.61, 38.10)	0.14	3.86 (0.52, 28.9)	0.19
Current tobacco use‡			-		-	
No	1.00					
Yes	1.79 (0.95, 3.39)	0.07				
Ever alcohol use§			-		-	

Characteristics at diagnosis	Unadjusted (N=105)		Adjusted Model 1† (N=79)		Adjusted Model 2† (N=79)	
	HR (95% CI)	**p-value**	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
No	1.00					
Yes	1.69 (0.52, 5.49)	0.38				
Current alcohol use§			-		-	
No	1.00					
Yes	1.57 (0.81, 3.05)	0.18				

Bold indicates statistically significant

† Adjusted model was restricted to patients with known current tobacco use and AJCC overall stage (n=79 of 105).

‡ Univariate analysis was restricted to patients with known tobacco use history (n=84 of 105).

§ Univariate analysis was restricted to patients with known alcohol use history (n=80 of 105).