Published in final edited form as:

Head Neck. 2016 April ; 38(Suppl 1): E867–E872. doi:10.1002/hed.24117.

High Prevalence of Discordant HPV and p16 Oropharynx Squamous Cell Carcinomas in an African American Cohort

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Abstract

Background—Most studies on Human Papilloma Virus associated oropharynx squamous cell carcinoma (HPV OPSCC) have been performed in whites. Our study examined the incidence of HPV in an African American (AA) OPSCC cohort and its survival.

Methods—AA OPSCC patients in a combined tumor registry were identified. HPV16 testing was performed by PCR from DNA extracted from tumor blocks. p16 staining was performed using standard immunohistochemistry.

Results—44 patients were identified for analysis. 73% of tumors were HPV positive. Only 39% of HPV+ patients were also p16+. Survival between all three tumor types, HPV+/p16, HPV+/p16+, and HPV–/p16– patients was significantly different. ($p=0.03$). HPV/p16 status was significant on univariate and multivariate analysis.

Conclusions—HPV OPSCC is strongly present in this AA cohort. Two-thirds of HPV positive patients were p16 negative. Greater study is needed to explain the high p16 negativity amongst this HPV+ OPSCC AA cohort.

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This research was presented as an oral presentation at the International Federation of Head and Neck Oncologic Societies (IFHNOS) meeting July 2014, New York, NY.

Keywords

head and neck neoplasms; oropharynx neoplasms; human papilloma virus; healthcare disparities; African American

Introduction

Significantly different rates of overall survival and risk of mortality have been observed in head and neck squamous cell carcinoma (HNSCC) between Caucasian Americans (CA) and African Americans (AA). [1, 2] The poor survival in AA patients has been attributed to multiple factors including late stage of diagnosis, a high frequency of recurrences, and second primary tumors. [3–6] Socioeconomic status, access to care, and insurance status have additionally been shown to be significant contributors to this disparity. [7] In the last decade, a subset of HNSCC caused by the human papilloma virus (HPV), specifically in oropharynx squamous cell carcinoma (OPSCC), has been reported as a distinct molecular and epidemiological disease entity. [8] HPV associated OPSCC (HPV OPSCC) are different than traditional HNSCC patients whose cancers are caused primarily by alcohol and tobacco abuse. HPV OPSCC patients are usually younger, nonsmokers, and often have specific sexual risk factors. [9] They also have a significantly more favorable prognosis. When compared to non HPV OPSCC, the reported benefit in survival ranges from 25%–33%. [10, 11] At this time HPV OPSCC is considered a distinct disease from traditional OPSCC because of the distinct risk profile and better survival outcomes. Its increased prevalence over time has been well documented, and is projected to exceed the number of cervical cancers by 2020. [12]

To date, the majority of studies on HPV OPSCC have been reported in CA patients, with limited reports of HPV OPSCC in AA cohorts. Given the paucity of data on HPV OPSCC in blacks, we set out to examine the prevalence and outcomes of HPV OPSCC in an AA cohort. We hypothesized that given the observed racial disparity, HPV OPSCC was likely less common in AA than CA. In our analysis, we identified an unexpectedly frequent molecular subtype in this AA cohort, HPV+/p16– tumors, with demonstrated worse outcomes than HPV+/p16+ OPSCC.

Materials and Methods

Following approval by institutional IRB, a combined database of tumor registries from Temple University Hospital and Fox Chase Cancer Center from 1990–2010 were analyzed. All patients with oropharynx cancer and whose racial designation was “black” were identified. Available tumor blocks from 1997–2010 were retrieved from the archive for analysis. In some cases, no tumor block was available, or available tissue was not representative of tumor tissue. 95 cases were initially identified, 44 cases had confirmed appropriate paraffin embedded tissue for analysis with chart data. Parameters from the tumor registry were extracted for analysis. Additional data that was not available in the registry, such as smoking history including pack-year data if available, was obtained directly from the patient chart.

HPV and p16 tumor testing

For each tumor specimen, 10 unstained slides were obtained of the tumor. DNA was extracted using Archive Pure DNA Extraction Kit (5 Prime, USA). PCR was performed for the presence of HPV16 DNA using the following primers: TTT GGT CTA CAA CCT CCC CCA GGA and TTC TTT AGG TGC TGG AGG TGT ATG. PCR to Beta-globin was used as an internal control. In samples where HPV16 PCR results were equivocal or the beta-globin control was negative, additional testing using the INNO-LiPA genotyping Extra Amplification and Genotyping Extra kits (Fujireobio Europe N.V., formerly Innogenetics.) was performed. Using PCR, this kit identifies a spectrum of HPV genotypes by using a reverse hybridization line probe assay to detect 18 high risk types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82), seven low risk types (6, 11, 40, 43, 44, 54, 70), and additional types (69, 71, 74). Negative and positive controls (HPV 6) as well as an internal control (HLA-DPB1 gene) to confirm DNA quality and the absence of PCR inhibitors are included in the assay. [25–26] Inno-LiPA has been reported more sensitive than HPV16 PCR alone.[13]

Overall ten cases were further analyzed by Inno-LiPA. Three of these cases were initially HPV/p16+. In these cases, Inno-LiPA identified HPV16 DNA in all three samples, with one also containing HPV35. In five of these cases, controls for b-globin during HPV16 PCR were negative. Since Inno-LiPA is more sensitive, Inno-LiPA was applied in these cases as well. In all five cases, the control DNA was positive, with four samples detecting HPV16 DNA. One case had HPV35 alone detected. Finally, two HPV 16 PCR samples had a doublet on PCR evaluation. Inno-LiPA evaluation showed both samples to have co infection with HPV 16 and HPV35 infection.

For p16 staining, unstained tumor slides were used for direct immunohistochemical staining. After deparaffinization and rehydration, sections were subjected to heat-induced epitope retrieval by immersion in a 0.01 M citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked for 15 min in 3% hydrogen peroxide in methanol. Nonspecific protein binding was blocked with a blocking reagent (Protein Block Serum-Free, DAKO) for 30 minutes at room temperature. The slides were then incubated with p16 primary antibody (E6H4, Ventana, ready-to-use) overnight at 4°C in a humidified chamber. Immunodetection was performed with the Dako Envision⁺ system. The antigen-antibody immunoreaction was visualized using 3–3'-diaminobenzidine as the chromogen. The slides were washed, counterstained with hematoxylin, dehydrated with alcohol, cleared in xylene, and mounted. Anonymous patient samples that were shown previously to express high levels of p16 were used as positive controls. As a negative control, the primary antibody was replaced with mouse IgG. p16 staining results were initially analyzed by the Fox Chase Cancer Center Experimental Histopathology Facility, and scored as positive or negative by two experienced pathologists (JK and SP). Intermediate to strong nuclear and cytoplasmic positivity in 70–80% of tumor cells was considered p16 positive. Lack of staining, equivocal, or weak staining up to 20–30% of cells was considered negative. Any discrepancy was resolved with a third experienced pathologist.

Statistical Analysis

Statistical analysis was performed using SPSS. Univariate and multivariate hazard ratios were calculated using STATA 10.1 (CollegePark, TX). Kaplan Meier plots were used to evaluate survival and the log-rank test was performed to assess statistically significant differences in survival between the HPV+ and HPV- groups. A P-value less than 0.05 was considered statistically significant. Follow up time in months was calculated by subtracting date of initial diagnosis from date of last contact for patients who were alive, or "Date of death" for patients who were dead from all causes respectively. Kaplan-Meier Survival analyses were performed to evaluate overall survival. Both univariate and multivariate cox proportional hazard models were used to assess the relationship between known risk factors associated head and neck cancer and outcome. Variables included in both models were gender, age, HPV16/p16 status, and standard of care.

Results

Forty-four cases with clinical data and tumor blocks were available and included in this study for analysis. Demographics of these patients are summarized in Table 1. The average and median age at diagnosis was 64 years old. The majority of patients were male (68%). 73% of patients were confirmed either current or former smokers. Only one patient was a confirmed non-smoker. Most of the patients were advanced stage cancers (77%). Most tumors were moderately differentiated (59%). Most patients were treated with concomitant chemoradiotherapy (47%). Patients treated with any surgery were a minority of patients (27%).

Tumors segregated into three subtypes by HPV and p16 status. (Table 2) Thirteen (30%) of patients were HPV+/p16+, while eleven (25%) were HPV-/p16-. The majority of tumors were discordant HPV+/p16- tumors (45%). p16 negative tumors comprised the majority (61%) of all HPV+ tumors. There were no tumors that were HPV-/p16+. The prevalence of HPV+ OPSCC vs. HPV- OPSCC did not differ over time (data not shown).

The average and median follow-up time for patients still alive was 4.5 and 3.9 years respectively. Kaplan-Meier survival analysis was performed for the three tumor subtypes. (Figure 1) The 2 year and 5 year overall survival for HPV+/p16+ tumors was 75% and 64.3% respectively, while 30% and 10% for HPV-/p16- tumors. HPV+/p16- cancer 2y and 5y survival were intermediate at 50.4% and 17.3%, respectively. These three curves were statistically significantly different ($p=0.026$). However, the HPV+/p16- and HPV-/p16- survival curves were not significantly different ($p=0.48$).

On univariate and multivariate analysis, p16 positivity alone was significantly protective, but HPV status alone was not significant. As a combined variable, HPV+/p16+ was significant on univariate and multivariate analysis. (Table 3) TNM stage was not significant for survival.

Neither the year of diagnosis nor insurance type was a significant multivariate factor. (data not shown) There were no significant differences in smoking rates or age amongst the three cohorts (data not shown). Of the eleven (25%) of patients diagnosed before the age of 50, all

patients were HPV positive, but only four (44%) were also p16 positive. The single confirmed nonsmoker was an HPV+/p16+ tumor.

Discussion

The prevalence and outcomes of HPV OPSCC in AA populations has not been extensively studied. Only a few papers have been published that examine HPV OPSCC in AA cohorts. [12, 14–16] Settle et al evaluated AA OPSCC patients from the TAX324 trial. While 34% of CA patients in this study were HPV OPSCC, only one patient (4%) was HPV associated in the AA group. In their OPSCC subset analysis, they found a significant difference in overall survival of 69.4 months in CAs versus 25.2 months in AAs ($p=0.0006$). They concluded the low rate of HPV OPSCC in the AA cohort likely accounted for the observed poor outcomes [15] Chernock et al also evaluated the differences in racial HPV OPSCC rates and outcomes of CA and AA. [14] In this study of 26 AA patients only nine (34%) were p16+ OPSCC. In contrast, 83% of the 148 CA patients were p16+ ($p<0.001$). The authors noted a significant difference in both prevalence and DSS of HPV OPSCC between CA and AA cohorts ($P<0.001$). In a third study examining 49 AA patients, Worsham et al found a lower rate of HPV OPSCC in AA (29%) vs. CA (71%), with HPV negative OPSCC AA patients having the worst outcomes. p16 data was not included in this study analysis.[16] Finally, Isayeva et al evaluated HPV and p16 status in 30 AA patients. They also showed a lower rate of HPV+ and p16+ tumors in their AA cohort with also worse outcomes than CA. [12]

Because of differences in how these four studies were performed, drawing conclusions has been difficult. Each study used a different method of HPV identification, and only two of four studies report both p16 status and HPV status. All studies have small cohorts ranging in 26–49 patients. Not all studies reported smoking status. Despite this, a few common themes emerge. All studies demonstrate a lower rate of HPV OPSCC in the AA cohort compared with a CA cohort. In addition, HPV negative OPSCC AA patients consistently had the worst outcome across both race and HPV tumor types.

Our study is the largest study to examine both HPV and p16 status in an AA cohort. OPSCC tumors in our AA smoking cohort stratified into three molecular subtypes. True HPV OPSCC, defined as HPV+/p16+ tumors, had the most favorable outcome with a 5 year overall survival estimate of 64%. Non HPV associated OPSCC tumors, HPV–/p16– tumors, had the worst outcome with 10% 5 year overall survival. Most interestingly, discordant HPV +/p16– tumors were the most common tumor type in our AA cohort, and had outcomes similar to the HPV–/p16– cohort. The identification of a high number of discordant tumors with demonstrated poor outcome is a unique finding of our study.

HPV+/p16– negative tumors have been previously reported. In their study, Weinberger et al, initially separated OPSCC into three distinct classes. [17] HPV–/p16– (Class I) are classic tobacco/alcohol related tumors and have the worst prognosis. HPV+/p16+ (Class III) represent canonical HPV OPSCC tumors and have the most favorable prognosis. HPV+/p16– (Class II) discordant tumors were thought to arise in a background of patients with tobacco/alcohol use who develop p16 loss and subsequently experience a high risk HPV infection. A subsequent study also by Weinberger examining CA and AA tumors by HPV

and p16 status showed that while all three types were present in a CA cohort, only Class I (HPV-/p16-) and class II (HPV+/p16-) tumors were seen in a small AA study cohort. [18] HPV+/p16+ tumors were not observed in this group. They concluded that the absence of HPV+/p16+ tumors in their study could explain CA vs. AA OPSCC disparities.

Subsequent studies have clearly shown that that HPV+/p16+ tumors are observed in AA with associated favorable outcomes. [12, 14, 15, 19] However, these tumors make up a minority of AA cohorts, approximately 30%, in comparison to 60–70% of tumors in CA cohorts. [14] Our study shows a similar 30% rate of HPV+/p16+ tumors.

HPV+/p16- discordant tumors remain an uncommon finding among CA but are more common in AA cohorts. Both Isayeva et al and Chernock et al showed that HPV+/p16- tumors were present in their CA cohorts, but representing only 4–5% of CA OPSCC. [12, 14] By contrast, Isayeva et al noted 25% of their AA OPSCC cohort was HPV+/p16-. In our data, 45% of the total AA OPSCC cohort was discordant HPV+/p16- tumors. The reasons for a higher rate in our cohort are unclear. Isayeva et al used RNA PCR to determine HPV status, while our study used HPV16 PCR, and both are accepted as effective in identifying HPV+ tumors. Additionally, our study was mostly AA smokers; data is not available to compare our data to other studies regarding smoking status. Overall, our study suggests that discordant HPV+/p16- tumors are unusually common in AA cohorts.

The perceived low rate of discordant tumors in CA populations may be confounded by underreporting. Because some studies use p16 status alone as a surrogate for HPV OPSCC, HPV+/p16- discordant tumors may be grouped with other HPV-/p16- tumors and would not be identified. In addition, because some studies use HPV in situ hybridization as the technique for HPV identification, since in situ hybridization is known to be less accurate than other methods like PCR, the rate of HPV+/p16- tumors may be underreported. [20]

We speculate that HPV is unlikely to be a passenger virus in these p16 negative tumors. There was no difference seen in survival between HPV+/p16- and HPV-/p16- tumors ($p=0.48$). However, our study may be underpowered to identify a survival difference. We do note that all patients diagnosed under the age of 50 were HPV+, with only four of the eleven being p16+. If a passenger virus, one would expect HPV to be evenly distributed across tumors over the age spectrum. Although there was no difference in age between HPV+ vs. HPV- cohorts, it is interesting that all eleven patients under the age of 50 were HPV+. The causes of discordant tumor development is unknown. Possibilities include behavioral factors, smoking prevalence, or genetic factors that preferentially dispose AA cohorts. The pathogenesis, epidemiology, and evaluation of outcomes of these discordant tumors warrant further investigation.

There are a few limitations to our study. Due to limitations in clinical records, disease specific outcomes were unable to be obtained and only overall survival could be reported. The very low five year overall survival in both HPV+/p16- and HPV-/p16- disease may reflect other competing mortalities in our population. TNM stage was not significant for survival on multivariate analysis. This may be due to the relatively few early stage tumors and that advanced stage cancers were 80% of the evaluated cohort. Future analysis should control for

co-morbidities within the different treatment arms to ensure no bias by competing mortalities. An additional limitation is lack of a direct control group for comparison. A control CA oropharynx population with annotated HPV and p16 data would lend strong context to our findings and add to this study. The rate of discordant tumors in this population would be an excellent comparison. As mentioned previously, published CA data suggests a low discordant tumor rate. We aim to explore this possibility in future research. Finally, the 44 identified patients in this study is the second largest AA OPSCC cohort that we have identified in the literature, but is still a limited number. Future studies with a larger cohort for analysis may strengthen our conclusions and findings.

Published literature and the lay press refer to HPV associated OPSCC as a distinct clinical entity on the rise. Our study, and similar studies, suggest that not all HPV associated OPSCC is the same. The distinct incidence profile and better survival is limited to HPV associated OPSCC that is also p16+. OPSCC that has detectable HPV DNA, but is p16 negative in our study and other studies still has a poor prognosis. The definition of “HPV associated OPSCC” needs clarification and we submit that p16 positivity must also be part of the definition; the presence of HPV DNA alone through any testing method is an inadequate definition for this entity. Future clinical trials on this entity should include p16 status as an inclusion criteria. Discordant tumors, as we have identified here in a black cohort, suggest that further study is needed to understand HPV OPSCC.

Conclusions

Our study demonstrates that HPV is present in the majority of OPSCC within an AA smoking cohort. However, most of these tumors are discordant HPV+/p16– with poorer outcomes than HPV+/p16+ tumors. Although highly prevalent in this AA OPSCC cohort, its presence is rarely seen in reported CA cohorts. More study is needed to understand the pathogenesis, epidemiology and outcomes of these discordant tumors.

Acknowledgements

Dr. Jeffrey Liu is generously supported by the Eugene Myers Head and Neck Cancer Research Fund.

This study was supported in part by grant numbers CA138017 and CA006927 from the National Cancer Institute, an appropriation from the Commonwealth of Pennsylvania and the Fox Chase Cancer Center Head and Neck Keystone.

This collaboration was supported by a grant from the Department of Defense Cancer Research Program Collaborative Undergraduate Historically Black Colleges and Universities Student Summer Training Award (W81XWH-13-1-0183) (PI: VNG)

We would also like to thank the Fox Chase immunohistochemistry facility and the Temple Department of Pathology for assistance in handling tissue specimens.

Grant Support:

The Eugene Myers Head and Neck Cancer Research Fund; NCI grant numbers CA138017 and CA006927 Commonwealth of Pennsylvania and the Fox Chase Cancer Center Head and Neck Keystone; Department of Defense Cancer Research Program HBCU (W81XWH-13-1-0183) (PI: VNG).

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Figure 1.
Five Year Kaplan-Meier Survival

Table 1**Patient and Tumor Demographics**

	Category	n (%)
Age	Less than 60 years	24 (56)
	Greater than 60 years	20 (44)
	Average and Median	64 years
Gender	Male	30 (68)
	Female	14 (32)
Smoking	Current	15 (34)
	Former	17 (39)
	Non-smoker	1 (2)
	Unknown	11 (25)
Tumor Stage	Is	1 (2)
	I	4 (9)
	II	2 (5)
	III	8 (18)
	IVA	22 (50)
	IVB	4 (9)
	IVC	1 (2)
	Unknown	2 (5)
Grade	Well differentiated	4 (9)
	Moderately Differentiated	26 (59)
	Poorly differentiated	9 (21)
	Unknown	5 (11)
Treatment	Surgery alone	7 (16)
	Surgery + Radiation	4 (9)
	Surgery + Radiation+Chemotherapy	1 (2)
	Radiation alone	5 (11)
	Chemotherapy and Radiation	21 (47)
	Unknown	6 (14)

Table 2

HPV and p16 status of African American Oropharynx Tumors

	HPV+	HPV –
p16+	13 (30)	0
p16 –	20 (45)	11(25)

N= 44 patients

Percentage of total in parentheses

Table 3

Hazard Model

	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio* (95% CI)
Gender		
Male	Ref	Ref
Female	0.44 (0.18 -- 1.05)	0.43 (0.15 -- 1.24)
Age		
40–52	Ref	Ref
53–63	1.09 (0.46 -- 2.57)	0.90 (0.33 -- 2.44)
64+	1.27 (0.48 -- 3.37)	2.02 (0.67 -- 6.16)
HPV Status only		
Negative	Ref	Ref
Positive	0.69 (0.30 -- 1.6)	0.57 (0.26 -- 1.23)
p16 status		
Negative	Ref	Ref
Positive	0.35 (0.13 -- 0.92)	0.31 (0.12 -- 0.82)
HPV/p16 Status		
HPV–/p16–	Ref	Ref
HPV+/p16–	0.75 (0.32 -- 1.73)	0.60 (0.22 -- 1.64)
HPV+/p16+	0.22 (0.07 -- 0.73)	0.18 (0.05 -- 0.65)

* Adjusted for gender, age, HPV16/p16 status