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Perspective

Cancer Prevention Research

The Rise of HPV-Positive Oropharyngeal Cancers in the United States

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Abstract

This perspective highlights a study that reports an increasing proportion of human papillomavirus–positive oropharyngeal cancer among blacks in recent calendar periods. The results are discussed in the context of other studies which evaluated racial differences in the distribution of human papillomavirus–positive oropharyngeal cancer and survival. *Cancer Prev Res; 8(1); 9–11. ©2014 AACR.*

See related article by Zandberg et al., p. 12

In recent decades the incidence of oropharyngeal cancers in the United States has steadily risen, whereas the incidence of other head and neck cancers has significantly decreased (1). These epidemiologic patterns are attributed to an increased prevalence of oral human papillomavirus (HPV) infection since the sexual revolution and a concomitant decrease in tobacco use. In the United States, HPV-positive oropharyngeal cancer (HPV-OPC) has significantly risen among whites, 50 to 59 year-olds, and males (2). Although less noticeable, a trend of increased HPV-OPC has also been observed among blacks. In a Surveillance Epidemiology and End Results (SEER) subanalysis restricted to blacks, a nonsignificant increase in HPV-OPC from 0% in 1984 to 1989 to approximately 25% in 1995 to 1999 ($P = 0.11$) was reported (2). HPV tumor status was determined using multiple validated methods (Inno-lipa, E6 and E7 mRNA, HPV16 rt-PCR, and *in situ* hybridization). Interestingly, in the latest report of U.S. cancer incidence, oropharyngeal cancer overall (independent of HPV tumor status) was significantly decreasing among blacks (3).

The SEER analysis of oropharyngeal cancer incidence did not provide trends among blacks after 1999, which is the time period most relevant to the current "epidemic" of HPV-OPC in the United States (1, 4). Until this can be performed at a population level, Zandberg and colleagues (5) provide single-institution estimates for changes in incidence of HPV-OPC among blacks. They reported nonsignificant increases in HPV-OPC among blacks from 1992 to 2007, from 0% to 17.7% ($n = 17$), with 25% of tumors tested in the calendar years 2000 to 2003 being HPV-positive. In the context of the SEER analysis, which showed approximately 20% of oropharyngeal cancer among blacks in 1990 to 1994 and 1995 to 1999 were HPV-positive, Zandberg and colleagues show lower prevalence in the overlapping time periods of 1992 to 1995 (0%) and 1996 to 1999 (13.3%). However, thereafter, in 2000 to 2003 and 2004 to 2007, the proportion of HPV-OPC among blacks was 25% and 18%, respectively. Therefore, the earlier estimates are lower than those seen in a sample representative of the U.S. population, which may indicate that even the later estimates from Zanberg's sample in 2004 to 2007 may similarly underestimate the proportion of HPV-OPC now present among blacks. In sum, these data reveal a rise of HPV-OPC among blacks despite an overall decreasing incidence of oropharyngeal cancer among blacks in the United States.

These trends are not surprising after consideration of the trends of cigarette use in the United States. In analogous time periods, current cigarette smoking was reported among approximately 42% of black men in the United States in 1985, 26.4% in 2000, and most recently 23.3% in 2012 (6). This notable reduction in tobacco use can be used as ecologic data to extrapolate a decreased incidence of HPV-negative oropharyngeal cancer among blacks, which has been modestly countered by a rise of HPV-OPC, resulting in the epidemiologic trends observed in oropharyngeal cancers among blacks in the United States (3). This is in contrast with the evolving epidemiology of oropharyngeal cancer among whites. Less dramatic reductions in tobacco use in similar time periods from 31.7% among white males in 1985 to 20.5% in 2012 concurrent with significant increases in HPV-OPC have resulted in a significant rise in the incidence of oropharyngeal cancer overall (2, 7). These relative trends underscore the inherent differences in HPV-OPC by race. Despite parallel trends in tobacco cessation rates, the rise of HPV-OPC has been much smaller among blacks.

Reasons for decreased incidence of HPV-OPC among blacks as compared with whites remain unknown. Oral sexual behavior is recognized to be an independent risk factor for both oral HPV infection (8) and HPV-OPC (9, 10). There are differences in sexual practices by race. Whites are significantly more likely than blacks to report earlier oral sex and greater number of lifetime sexual partners (11). Although differences in sexual behavior (and tobacco use) may in part explain the epidemiologic differences in HPV-OPC, they remain disproportionate to the racial differences in incidence of HPV-OPC. For example, white men are 147% more likely to have performed oral sex at

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Table 1. Proportion of black patients in selected case series that are HPV-positive using variable tumor detection methods

Authors, year	*N*	Proportion of black patients HPV-positive	Detection method(s)
Zevallos et al., 2014 (25)	17 of 29	58.6%	P16
Chernock et al., 2011 (26)	9 of 26	34.6%	P16
	3 of 26	11.5%	ISH
Weinberger et al., 2010 (27)	6 of 16	37.5%	P16
	6 of 16	37.5%	RT-PCR HPV16
Isayeva et al., 2014 (28)	9 of 24	37.5%	P16
	18 of 30	60%	RT-PCR HPV16/18
Settle et al., 2009 (23)	1 of 27	3.7%	RT-PCR HPV16
Worsham et al., 2013 (24)	15 of 49	30.6%	RT-PCR HPV16
Jiron et al., 2014 (29)	9 of 36	25%	PCR

the time of sexual debut, yet the incidence of oropharyngeal cancer is only 20% higher among white men as compared with black men in the United States (11). Given that the majority of individuals are exposed to HPV, improved understanding of cofactors will likely elucidate the racial and geographic differences in cancer incidence after largely similar exposures.

The report from Zandberg and colleagues is an interesting addition to the discussion of race and HPV-OPC. Consistent with the literature to date, they found a greater proportion of patients with HPV-OPC were white than black. However, their observations about race are based upon 17 black patients, 10 of whom were HPV-positive using their HPV detection methods. By contrast, prior reports investigating racial differences in HPV had equivalent or larger sample sizes (Table 1). Moreover, the proportion of blacks that were HPV-positive in the University of Maryland Greenebaum Cancer Center study population is on the higher end of the range (~60%). This may be attributable to the HPV detection methods, which included type-specific PCR, a method of high sensitivity and susceptible to misclassification and therefore can result in overestimate (2, 12). Inno-LiPA, a PCR-based method, was performed for a small subset of available tumors, which does suggest that other oncogenic types were absent from the tumors tested. Alternative robust methods for determination of HPV tumor status include *in situ* hybridization (DNA or RNA), RNA detection with PCR, or implementation of p16 immunohistochemistry, a widely acceptable surrogate for HPV tumor status (13). Of note, both p16 immunohistochemistry and *in situ* hybridization can be performed on paraffin-embedded samples and are widely available.

It is also noteworthy that 64% of all oropharyngeal cancer cases examined by Zandberg and colleagues were HPV-negative. Most contemporary case series in the United States report lower proportions of HPV-negative cases when restricted to the oropharynx (20%–40%) as an anatomic site (14–19). This reinforces the notion that there is geographic heterogeneity of HPV-OPC and that single-institution retrospective studies must be interpreted with caution. Our best estimates for HPV tumor status for oropharyngeal cancers arise from multi-institutional trials such as the cooperative group trials, which comprise of diverse patients seen by academic and community practices throughout the United States.

HPV has previously been shown to be an independent marker of prognosis both at the time of diagnosis (18) and recurrence (20–22). Zandberg and colleagues present a survival analysis that was stratified by race and HPV tumor status. Consistent with previous reports (23, 24), HPV-positive patients had improved survival as compared with HPV-negative patients after stratifying by race. However, when HPV-negative patients were stratified by race, there was a significant difference in overall survival. In the Kaplan–Meier analysis, black HPV-negative patients had significantly worse overall survival than white patients. Among patients with HPV-negative oropharyngeal cancer, whites had a striking approximately 3-fold greater median survival time when compared with blacks. Black race was independently associated with significantly worse overall survival [HR, 2.0; 95% confidence interval (CI), 1.28–3.14] when restricting to HPV-negative patients. In the largest survival analysis to date using prospective clinical data, uniformly treated patients and HPV tumor status, non-whites had an independent 2-fold increased risk for death (HR, 2.1; 95% CI, 1.4–3.3) after accounting for HPV tumor status, smoking, tumor and nodal stage, age, and treatment (19).

In a recent survival analysis focusing on racial differences, blacks had significantly worse overall survival as compared with white patients with HPV-negative oropharyngeal cancer in a univariate analysis (24). However, race was not an independent marker for prognosis in multivariate models. Similarly, in a recent study of veterans, there were no survival differences by race after adjusting for HPV tumor status as well as other important confounders (25). Nevertheless, the contribution by Zandberg and colleagues in conjunction with these reports highlights a racial difference in survival, one that may be even more profound among HPV-negative patients who already have poor prognosis.

Going forward, with the rising incidence of HPV-OPC, albeit at different rates by race, it will be important to identify reasons for such survival differences. Moreover, as clinical trial designs have accounted for HPV tumor status, this article highlights the need to design trials for the HPV-negative patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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