The Rise of HPV-Positive Oropharyngeal Cancers in the United States
Carole Fakhry, Ezza Cohen

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.

Corresponding Author: Carole Fakhry, Johns Hopkins School of Medicine, 601 N. Caroline St., 6th floor, Baltimore, MD 21287; Phone: 410-287-2024; Fax: 410-955-6526; E-mail: cfakhry@jhmi.edu
doi: 10.1158/1940-6207.CAPR-14-0425
©2014 American Association for Cancer Research.
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% 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.

Received November 19, 2014; accepted November 25, 2014; published OnlineFirst December 2, 2014.

---

**References**


5. Zandberg DP, Liu S, Goloubeva OG, Schumaker LM, Cullen KJ. Emergence of HPV16 positive oropharyngeal cancer in black patients over

---

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

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>N</th>
<th>Proportion of black patients HPV-positive</th>
<th>Detection method(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zevallos et al., 2014 (25)</td>
<td>17 of 29</td>
<td>58.6%</td>
<td>P16</td>
</tr>
<tr>
<td>Chernock et al., 2011 (26)</td>
<td>9 of 26</td>
<td>24.6%</td>
<td>P16</td>
</tr>
<tr>
<td>Weinberger et al., 2010 (27)</td>
<td>6 of 16</td>
<td>37.5%</td>
<td>P16</td>
</tr>
<tr>
<td>Isayeva et al., 2014 (28)</td>
<td>9 of 24</td>
<td>37.5%</td>
<td>RT-PCR HPV16</td>
</tr>
<tr>
<td>Settle et al., 2009 (23)</td>
<td>1 of 27</td>
<td>3.7%</td>
<td>RT-PCR HPV16</td>
</tr>
<tr>
<td>Worsham et al., 2013 (24)</td>
<td>15 of 49</td>
<td>30.6%</td>
<td>RT-PCR HPV16</td>
</tr>
<tr>
<td>Jiron et al., 2014 (29)</td>
<td>9 of 36</td>
<td>25%</td>
<td>PCR</td>
</tr>
</tbody>
</table>
The Rise of HPV-Positive Oropharyngeal Cancers in the United States

Carole Fakhry and Ezra Cohen


Updated version  Access the most recent version of this article at: doi:10.1158/1940-6207.CAPR-14-0425

Cited articles  This article cites 27 articles, 10 of which you can access for free at: http://cancerpreventionresearch.aacrjournals.org/content/8/1/9.full#ref-list-1

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.