



Published in final edited form as:

Cancer. 2017 May 01; 123(9): 1486–1487. doi:10.1002/cncr.30619.

Commentary on “The Prognostic Role of Sex, Race and Human Papillomavirus in Oropharyngeal and Non-Oropharyngeal Head and Neck Squamous Cell Cancer”

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Fakhry and colleagues present the results of an important study that examines prognostic indicators in oropharyngeal and non-oropharyngeal squamous cell carcinoma.¹ In a large head and neck cancer cohort drawn from two tertiary care cancer centers, they examine the impact of sex, race, and HPV on outcomes in oropharyngeal and non-oropharyngeal cancer. They demonstrate that sex affects prognosis differentially in oropharyngeal cancer and non-oropharyngeal cancer. Importantly, they also demonstrate that race does not impact survival in oropharyngeal cancer after adjusting for HPV status. Much of the literature on HPV-positive oropharyngeal cancer focuses on outcomes in non-Hispanic White males; the importance of this study is that it challenges us to think about this disease outside of this specific demographic.

This study is an important contribution to the extensive body of literature on racial disparities in head and neck cancer, particularly with respect to the impact of race on outcomes in HPV-positive oropharyngeal cancer. African-Americans account for less than 10% of head and neck squamous cell carcinoma patients, but contribute disproportionately to the morbidity and mortality associated with this disease process.²⁻⁴ African-American patients tend to present at higher disease stages, and previous studies have suggested that differential access to care and treatment protocols have contributed to this disparity.⁵ Reports have also demonstrated that African-American patients demonstrate worse overall head and neck cancer survival when age, disease stage, and treatment received are controlled.⁶ Previous studies suggested that racial disparities in head and neck cancer were driven largely by racial differences in HPV-positive oropharyngeal cancer, with a disproportionately high number of cases among non-Hispanic Whites compared to African-Americans.^{7,8} There is recent emerging data suggesting an increasing number of HPV-positive oropharyngeal

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Conflicts of interest: none

cancer cases among African-Americans.⁷ In the present study, a relatively large percentage of cases in both the oropharyngeal and non-oropharyngeal cancer cohorts are African-American. The finding that no difference exists in overall survival by race challenges much of the existing literature on racial disparities in head and neck cancer, and suggests that these findings may not be generalizable outside of tertiary-care cancer centers. Race represents many different exposures such as socioeconomic status, cultural background, or access to care, as well as a physical phenotype.⁹ The impact of race on head and neck cancer survival may differ based on the socioeconomic status of the population being examined. While data on socioeconomic status is not presented in this study, it is possible that the present study consists of disproportionately high income and highly educated cases, where race may simply be a measure of physical phenotype rather than represent cultural background, access to care, or socioeconomic status.

Fakhry et al. serves as a landmark study on the impact of sex on oropharyngeal and non-oropharyngeal cancer survival. The authors demonstrate that females have a survival advantage in oropharyngeal cancer after adjusting for HPV status that is not present among non-oropharyngeal cancers. The findings with respect to sex and survival in non-oropharyngeal cancer are largely in line with previous research. In a matched-paired analysis of male and female head and neck cancer patients treated at MD Anderson, Roberts and colleagues demonstrate no difference in survival by sex across all tumor sites.¹⁰ The finding that sex differentially impacts survival in oropharyngeal and non-oropharyngeal cancers is important, and may have implications for treatment decision-making and for understanding the natural history of HPV-positive and HPV-negative head and neck cancer. However, while this represents the largest cohort of females with oropharyngeal cancer, the issue of generalizability is again raised. Similar to race, sex is a non-modifiable risk factor that can represent multiple exposures within a population and thus lead to differing results by population sampled. There is the potential of effect measure modification in which women have better survival among higher socioeconomic status groups, which may be overrepresented in the patient population. Additionally, there may be effect measure modification by sex that should be explored further, including between sex and smoking or sex and HPV. There is also the possibility of confounding due to treatment, but the likelihood of disparate care by sex is considerably less likely than by race or socioeconomic status.

P16 immunohistochemistry is now a widely accepted surrogate for HPV in oropharyngeal cancer, and the results from this study further support its continued utility. As noted by the authors, previous studies have demonstrated contradictory results with respect to the prognostic significance of p16 immunohistochemistry and HPV status in non-oropharyngeal squamous cell carcinoma.¹¹⁻¹³ This is among the largest series to demonstrate that p16 does not have added prognostic significance outside of the oropharynx and should not be routinely utilized in the clinical setting.

Fakhry and colleagues are congratulated on an important contribution to the literature on prognosticators in oropharyngeal and non-oropharyngeal head and neck cancers. Importantly, this paper sets the foundation for further analyses on the impact of sex and race on HPV-positive and HPV-negative head and neck cancer. Future studies should be

conducted to replicate these results and to identify modifiable risk factors such as smoking, alcohol, socioeconomic status, and access to care that could be driving these associations.

Acknowledgments

Funding: none

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