Human papillomavirus-independent cervical cancer: what are the implications?

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We would like to congratulate Dr Fernandes and colleagues on their excellent and thorough review of human papillomavirus (HPV)-independent cervical cancer.[1] While the majority of cervical cancers have been shown to be caused by HPV, several studies have reported HPV-independent disease. It is thought that these tumors are more often associated with lymph node involvement in early stages, more distant metastases, and worse prognosis. Despite these potential differences in oncologic outcomes, there are no specific recommended treatment strategies based on HPV status. The authors review the molecular profile of HPV-independent tumors including the absence of p16 and presence of mutations in genes including *p53, PTEN, KRAS,* and ARID1A, thus providing targets for future research into new therapies. Similarly, they suggest that given the lower expression of inflammatory-associated genes in HPV-independent cervical cancer, the response rate to checkpoint inhibitors such as PD-L1 inhibitors may be dampened. They ultimately conclude that future research should focus on ongoing reporting of clinical outcomes and treatment responses, as well as the consideration of new biomarkers for prognostication.

The review suggests different scenarios in which a tumor can be associated with HPV-negative status and has in-depth explanation for each of their postulated five scenarios. Interestingly, they report that in cases of re-testing suspected HPV-independent tumors, between 48% and 57% of those cervical cancer samples remain truly negative with deep sequencing. This suggests that 43%–52% of these tumors are in fact HPV-associated, emphasizing the uncertainty of the true proportion of cervical cancers that are HPV-independent. The authors also present an excellent explanation of the "hit and run viral theory", which hypothesizes that these tumors are HPV-associated, but there is an absence of the HPV viral genome as the expression of viral proteins is no longer required for tumor maintenance once sufficient cellular alteration has occurred. With respect to oncologic outcomes, the authors present a review of the literature suggesting HPV-independent tumors are associated with worse prognosis, but do note that no prospective evidence evaluating these outcomes currently exists.

Ultimately, while HPV-independent tumors certainly represent an area requiring further research, the overall rarity of these tumors does limit the clinical generalizability of the findings from this review. However, as advances in treatment paradigms and public health efforts encouraging HPV vaccination and screening with HPV testing become more prevalent, we may begin to see a shift in the relative proportion of HPV-independent cervical cancer compared with HPV-dependent cervical cancer. As such, it is important to continue to deepen our understanding of the molecular profile and behavior of these tumors.

In their comprehensive review, Fernandes *et al* highlight the many unanswered questions that remain in the study of HPV-independent cervical cancer. While this topic certainly represents an interesting area for further research, the presence of these less common tumors should not cause us to lose sight of our current efforts to increase HPV vaccination and improve access to cervical cancer screening, particularly in resource-constrained areas both in the US and abroad.

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REFERENCE

1 Fernandes A, Viveros-Carreño D, Hoegl J, *et al*. Human papillomavirus-independent cervical cancer. *Int J Gynecol Cancer* 2021;8. doi:10.1136/ijgc-2021-003014. [Epub ahead of print: 01 Nov 2021].

Correction: *Human papillomavirus-independent cervical cancer: what are the implications?*

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