The Beginning of the End: Vaccine Prevention of HPV-Driven Cancers

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In this issue of the Journal, Saraiya and coauthors present an important analysis of human papillomavirus (HPV) detection in tumors retrieved from select US sites prior to HPV vaccine implementation (2006) (1). Not only are these data necessary to evaluate future vaccine effectiveness in reducing cancers caused by HPV infection, but they will also aid in the growing assessment of the worldwide burden of tumors attributable to HPV infection. These data raise the question: How many cases of cancer can be prevented by HPV vaccination in the United States?

Twenty years ago, in 1995, the World Health Organization recognized for the first time that HPV 16 is the cause of cervical cancer. In 2005, 10 years after this report, there was sufficient accumulated evidence to state that HPV 16 is also the cause of multiple cancers in men and women, and that HPV 16 is only one of 13–15 HPV types deemed “high-risk” types that cause cervical cancer (2,3). Growing evidence that HPV causes cancers, combined with the technology to develop efficacious vaccines against DNA viruses (4), simultaneously led to vaccine development. This was followed by demonstration of vaccine efficacy in women and men (5–8) and, ultimately, licensure of multiple vaccines that protect against HPV infection acquisition and prevention of the lesions these viruses cause (9–11). The recent licensure in the United States of Gardasil 9 presents an opportunity to further expand vaccine protection to prevent 90% of all cervical cancers worldwide (12,13).

While there has been tremendous progress in the prevention of cervical cancer through screening of adult women in high-resource countries and, recently, prevention of cervical precancer with vaccination (14), less progress has been made in the prevention of HPV-related cancers in men, cancers for which screening interventions are not routinely available. Despite clear evidence that HPV causes cancer at the oropharynx, that HPV-related oropharyngeal cancers (OPC) disproportionately affect men, and that OPC incidence is increasing in the United States, there have been no trials conducted to assess the efficacy of HPV vaccines to prevent these cancers. There is preliminary evidence of prophylactic HPV vaccine efficacy against prevalent oral HPV16/18 infections in women (15); however, it remains unknown what proportion of HPV-related OPC can be prevented with broad dissemination of HPV vaccines to males. Moreover, it remains unclear what proportion of OPC that have HPV DNA present are truly attributable to HPV.

Using HPV DNA-based detection to ascribe causality to tumors at different anatomic sites requires caution. There is strong evidence that HPV infection causes all cervical cancers and that DNA detection correlates well with markers of viral activity; thus, the use of DNA detection alone may be well justified at the cervix. However, for noncervical sites, particularly in the head and neck, HPV DNA-based detection methods overestimate the HPV attributable proportion. Identification of viral DNA in the tumor can occur if there is simply a transitory infection (not causal), as well as in cases where HPV is causally involved in the development of the tumor. As an example, a recent meta-analysis of the attributable fraction of HPV in head and neck squamous cell carcinomas showed that HPV DNA was detected in 46% of OPC, 22% of laryngeal cancers, and 24% of oral cavity cancers. When E6/E7 mRNA and p16INK4a status were assessed in these same tumors, the proportion caused by HPV infection was similar for OPC (40%) but overestimated for laryngeal (9%) and oral cavity cancer (16%). Thus, in the current analysis (1), in which 70% of OPC, 21% of laryngeal cancers, and 32% of oral cavity cancers were HPV DNA-positive, it is possible that the HPV attributable fractions for oral cavity and laryngeal cancers were overestimated by two- to three-fold, respectively. Given the documented increases in the proportion of OPC tumors attributable to HPV over the past several decades, the absolute number of cases due to HPV should not be viewed as static; future estimates of the HPV-related OPC burden may be affected by changes in the underlying causes of these cancers, including smoking...
prevalence and HPV, especially as vaccination dissemination increases. Similar data on the importance of using measures of viral activity to determine HPV causality for noncervical anogenital tumors (penile, vulvar, vaginal, anal) are currently unavailable but will be critical in determining whether HPV DNA detection is sufficient to determine causality (as at the cervix) or whether markers of viral activity should also be utilized (as at the larynx and oral cavity).

Most cancer registries do not have access to molecular data to classify HPV infection status and therefore rely on anatomic site and histology to estimate HPV-related cancer incidence and case counts. In a best-case scenario, such as reported by Saraiya et al., registries have access to discarded samples that enable molecular analysis of tumors. For the purposes of monitoring HPV vaccine impact, these data allow surveillance of HPV-related tumor burden reduction in the post-HPV vaccination era. However, studies aiming to determine the true attributable proportion of HPV in cancers outside the cervix should assess causality with laboratory measures that capture viral activity.

The proportion of HPV-driven cancers that can be prevented with HPV vaccination differs by world region. The United States, like other high-resource countries with organized cervical cancer screening programs, has a low invasive cervical cancer rate but higher rates of noncervical cancers, particularly OPC in men. In contrast, in countries that have not yet benefited from cervical cancer screening programs or tobacco control policies, cervical cancer incidence is higher and HPV-related OPC incidence lower. In the last decade, OPC incidence increased in many economically developed countries as smoking prevalence decreased (16,17). Data reported in this issue indicate that approximately 60% to 70% of OPCs are caused by HPV infection in the United States (1), contrasting with data reported from less economically developed regions where less than 10% of tumors are HPV-positive (18–20). In a comprehensive review of the global burden of infection-associated cancers, de Martel et al. estimated that HPV infection accounts for 38% to 56% of OPC in Australia, Japan, North America, and Northern and Western Europe, compared with only 13% to 17% of OPC in other parts of the world (21). The proportion of OPC attributed to HPV may be even lower in certain African countries (19).

Regardless of how precisely we define the total number of cases due to HPV, vaccination against HPV has the potential to prevent multiple cancers in men and women, cancers for which we have no evidence-based prevention modalities, except in the case of cervical cancer. The data presented by Saraiya and coauthors estimate the number of cancers in the United States we can expect to prevent in the era of HPV vaccination. However, until we reach the national goal of 80% of men and women fully vaccinated against HPV (22), the prevention of multiple cancers with a relatively simple intervention will remain a dream. Providers are the key to implementing the national vaccine recommendations, ensuring this dream becomes a reality. Strong messages from providers to vaccinate age-eligible men and women can move the United States from among the lowest rates of HPV vaccination to the highest, with reductions in the national cancer burden to follow sooner rather than later.

**Note**

The authors have no conflicts of interest to declare.

**References**