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Why is it appropriate to recommend human papillomavirus vaccination as cervical cancer prevention?

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Two common concerns that are raised with regard to human papillomavirus (HPV) vaccination are that: (1) because the vaccine clinical trial endpoints were high-grade cervical lesions and not cancer, the vaccine has never been shown to prevent cancer, and (2) Papanicolaou (Pap) smear screening/cervical cytology is sufficient to prevent cervical cancer. These 2 concerns, when taken in tandem, do not account for the underlying biology of HPV infection and natural history to carcinogenesis and the mechanisms of cancer prevention offered through these interventions. Because Pap smear screening is designed to identify and facilitate treatment of cervical abnormalities prior to development of invasive cancer, it is important to realize that these same abnormalities (cervical intraepithelial neoplasia [CIN] 2/3) are the endpoints used in the HPV vaccine clinical trials. Therefore, to argue that vaccine-induced prevention of CIN 2/3 does not prevent cancer is akin to arguing that Pap smear testing does not prevent cancer. In this Viewpoint, we describe these biological mechanisms to facilitate an evidence-based discussion with HPV vaccine-hesitant parents and young adults, to address these misconceptions that may be negatively affecting HPV vaccination uptake.

In 2006, the US Food and Drug Administration approved the quadrivalent HPV vaccine for licensure,¹ followed by a recommendation by the Centers for Disease Control and Prevention for routine HPV vaccination of girls aged 11–12 years.² Despite being recommended for routine adolescent vaccination shortly after 2 other adolescent vaccines (tetanus, diphtheria, and acellular pertussis vaccine; quadrivalent meningococcal conjugate vaccines), HPV vaccine uptake substantially lags behind that of the other 2 vaccines.³ Multiple efforts have been made to understand and mitigate barriers to HPV vaccination,^{4–6} but it is unclear what effect these efforts will have in improving the stagnated HPV vaccination rates.

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One factor that may contribute to suboptimal HPV vaccination rates is dissemination of misinformation about the safety and effectiveness of HPV vaccines.^{7,8} Many studies have been conducted to address concerns about the safety of HPV vaccine^{9–11} and the perceived potential to lead to sexual disinhibition.^{12–14}

Large HPV vaccine safety studies by Arnheim-Dahlstrom et al⁹ (N = 696,420 HPV vaccine doses), Gee et al¹⁰ (N = 600,558 HPV vaccine doses), and Klein et al¹¹ (N = 346,972 HPV vaccine doses) assessed a large number of outcomes, including acute (eg, anaphylaxis, syncope) and chronic (eg, Guillain-Barre syndrome, autoimmune disorders) conditions. Arnheim-Dahlstrom et al⁹ and Gee et al¹⁰ did not identify any adverse outcomes with statistically significant elevated risks that met criteria for potential causal relationships. The only conditions with statistically significant elevated risks that were found to be likely associated with HPV vaccination after detailed medical record review were skin infections in the 2 weeks after vaccination and syncope on the day of vaccination.¹¹ Concerns about potential increases in sexual activity after HPV vaccination had previously been addressed largely through survey-based methods.^{15–22} From 2012 through 2015, there were 3 studies^{12–14} evaluating this topic using clinical outcomes from medical record databases; in all 3 publications, there were no significantly elevated risks of clinical outcomes related to sexual activity after HPV vaccination identified.^{12–14}

Even in light of the HPV vaccine safety findings discussed above, HPV vaccine safety remains a concern in the United States,^{7,23} and internationally—particularly following recent changes in the Japanese HPV vaccine program.^{24,25} However, concerns raised by activists opposing HPV vaccination—that the HPV vaccine does not prevent cancer^{26–31} and that the HPV vaccine is unnecessary because we have an effective screening tool (ie, Pap test) to prevent cervical cancer^{27,32,33}—have not been discussed as frequently.

The widespread dissemination of these concerns may contribute to the difficulty in appropriate messaging to communicate about the necessity and effectiveness of HPV vaccination, leading to knowledge gaps on the part of both parents and health care providers.⁴ The impetus for this article was preliminary evaluations of open-ended responses from a survey of Brazilian primary care providers conducted by 2 authors of this perspective (D.F-D. and R.A.B.). These responses indicate hesitance around HPV vaccination because of perceptions that the vaccine has not been proven to prevent cancer (unpublished data).

We posit that the continued use of these arguments against HPV vaccination shows a lack of understanding of the biological underpinnings of both Pap smear screening and HPV vaccination. To argue that HPV vaccination has not been shown to prevent cancer because the clinical trial endpoints were high-grade cervical lesions (CIN 2/3 and adenocarcinoma in situ)² is to also argue that the detection and treatment of high-grade cervical lesions through Pap smear screening does not prevent cancer but only addresses a precancerous lesion, given that the purpose of Pap smear screening is to identify these lesions that are not cancerous. By preventing the development of these high-grade lesions, cancer has been prevented as the natural history of cervical cancer progresses from HPV-infected cells through neoplastic lesions to carcinoma (Figure).

With increased use of the Pap test in the United States, the incidence of invasive cervical cancer decreased approximately 4-fold from 1950 through 2007.³⁴ This substantial reduction in invasive cervical cancer is evidence of the effectiveness of detection and treatment of precancerous cervical lesions, and is often used as supporting evidence to argue that Pap smear screening is sufficient for cervical cancer prevention. However, these dramatic reductions in invasive cervical cancer have not eliminated cervical cancer from the United States. As of 2012, there were nearly 13,000 new cervical cancer cases in the United States (crude incidence rate 8.1 cases/100,000 women; age-adjusted incidence rate 6.6 cases/100,000 women).³⁵ This is related to incomplete coverage with Pap smear screening; in 2013, it was estimated that >19% of US women aged 21–65 years did not have a history of a recent Pap smear.³⁶ Notably, utilization of Pap smear testing is lowest for individuals with incomes <200% of the federal poverty level³⁷ and cervical cancer incidence and mortality rates are highest among racial and ethnic minorities.³⁸ However, uptake of at least 1 dose of HPV vaccine has typically been higher among individuals living below poverty compared to those above poverty and among racial and ethnic minorities relative to non-Hispanic whites.^{3,39–41} Within each racial and ethnic group, HPV vaccine initiation is higher among individuals living below the poverty level.⁴² Deemphasizing the role of HPV vaccine in cervical cancer prevention in women at highest risk for developing cervical cancer may allow racial, ethnic, and socioeconomic disparities in cervical cancer incidence to continue unchecked.

As indicated above, it has been argued that HPV vaccination only prevents HPV infection and precancerous cervical lesions, which often spontaneously resolve.^{27,29,30} While this is borne out from natural history studies of HPV infection,^{43–45} >26% of young women monitored for >38 months on average during a large longitudinal study who acquired an incident infection with HPV type 16 or 18 developed biopsy-confirmed CIN 2/3 within 36 months.³⁴ Regression from CIN 2 and CIN 3 to lower-grade lesions is estimated to occur in 43% and 32% of cases, respectively, with approximately 5% of CIN 2 and 12% of CIN 3 progressing to invasive cervical cancer.³⁶ Given that CIN 2/3 development is a necessary step in the biological progression to invasive cervical cancer absent any preventive measures (Figure), and modeling of the burden of high-grade cervical lesions in the United States estimates approximately 550 cases of CIN 2/3 per 100,000 women aged 20–29 years,⁴⁶ it is clear that there is a substantial burden of HPV-related disease in the United States that can be prevented through HPV vaccination.

Targeting this progression from HPV infection to invasive cervical cancer through the use of both HPV vaccination and Pap smear screening allows for a double-barreled approach (ie, incorporating both primary and secondary prevention) to targeting the same biological process—development and persistence of CIN 2/3 that would progress to invasive cancer without either of these interventions. In sum, the biological mechanisms by which HPV vaccination and Pap smear screening prevent cervical cancer act on the same exact portion of the pathway—preventing CIN 2/3 progression to invasive cancer. We believe that health care providers who are faced with these concerns that HPV vaccine has not been shown to prevent cancer will be able to use the arguments presented here to address these concerns during HPV vaccination counseling, in an effort to increase acceptance and uptake of HPV vaccination in the United States.

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FIGURE. Biological processes in cervical cancer prevention by Pap smear and HPV vaccination
A, Natural history of cervical cancer development, from human papillomavirus (HPV) exposure and infection through precancerous cervical intra-epithelial neoplasia (CIN) to development of invasive cervical cancer. **B**, Mechanism of prevention of cervical cancer through Papanicolaou (Pap) smear screening by detection and treatment of existing CIN, preventing progression to invasive cervical cancer. **C**, Mechanism of prevention of cervical cancer through HPV vaccination, by prevention of HPV infection, which results in prevention of CIN. CIN prevented by HPV vaccination is identical to CIN detected and treated through Pap smear screening. Biologically, both are identical in their mechanism to prevent cervical cancer through prevention of long-term CIN establishment.

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