Advances in protection against oncogenic human papillomaviruses: The 9-valent vaccine

Can the HPV vaccine help prevent oropharyngeal cancer—a disease that is predicted to become more common than cervical cancer in 5 years?

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When Dr. Harald zur Hausen received the 2008 Nobel Prize in Physiology or Medicine for his discovery of the link between human papillomavirus (HPV) infections and genital cancers, he completed a 40-year odyssey to prove that viruses caused human cancer. Initially, zur Hausen, working in the University of Pennsylvania laboratory of the noted virologists Drs. Werner and Gertrude Henle, discovered that the Epstein-Barr virus was involved in the development of Burkitt lymphoma.[1] On return to his native Germany, he sought a link between HPV and genital tumors.[2]

First he isolated HPV 6 and HPV 11 directly from genital warts.[3] Then zur Hausen utilized the nucleic acid sequences from HPV6 and the technique of low stringency hybridization to discover HPV 16 and HPV 18 in cervical cancer specimens.[4,5] Oncogenic HPV DNA contains 2 genes that produce the oncoproteins E6 and E7. E6 increases the degradation of p53 and E7 inactivates the retino-blastoma protein.[6] The double-hit inactivation of 2 tumor suppressor genes, p53 and retinoblastoma protein, increases the mitotic activity of the infected cells, eventually leading to cancer.

zur Hausen tried to persuade companies to develop anti-HPV vaccines but was rebuffed for years. Today, building on his research, we have HPV vaccines that are 2-valent (against HPV types 16 and 18), 4-valent (against HPV types 6, 11, 16, and 18), and 9-valent (against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58). zur Hausen richly deserved the Nobel Prize for his life-saving discoveries.

Cervical, vulvar, and vaginal cancers

HPV types 16 and 18 cause about 70% of cervical cancers. HPV types 31, 33, 45, 52, and 58 cause about 20% of cervical cancers.[7] The 2-, 4-, and 9-valent HPV vaccines have been demonstrated to prevent premalignant cervical disease, including cervical intraepithelial neoplasia (CIN) 2 and CIN 3 and adenocarcinoma in situ.[8–11] The development of a 9-valent HPV vaccine is an important advance because it provides more complete immunization against cancer causing viruses.

Approximately 70% of vaginal cancers are caused by HPV infections.[12] Among squamous cell vulvar cancers, HPV is detected in approximately 70% of cancers with warty or basaloid histology and 12% of cancers with keratinizing histology.[13] In vulvar cancer, HPV 16, 33, and 18 are the most common types detected, representing 73%, 7%, and 5% of cases, respectively. The HPV 4- and 9-valent vaccines have been reported to reduce precancerous lesions of the vagina and vulva.[9,11] In most trials, vaccinations that occur before exposure to HPV through sexual encounters appear to provide greater protection than vaccinations that occur after HPV infection.

Anal cancer

Approximately 90% of anal cancers are caused by HPV infection, and HPV types 16 and 18 are detected in 81% and 4% of anal cancers, respectively.[14] Among men who have sex with men, the HPV 4-valent vaccine reduced the rate of anal intraepithelial neoplasia, a precursor to anal cancer, by 50%.[15] Women receiving the HPV 2-valent vaccine had an 84% reduction in the detection of anal cancer involving HPV types 16 and 18.[16]

Penile cancer

Approximately 48% of penile cancers harbor oncogenic HPV types.[17] Among penile cancers the prevalence of HPV varies from 22% in verrucous cancer to 66% in basaloid and warty cancer. The most prevalent HPV types were 16, 6, and 18, which were observed in 31%, 7%, and 7% of the cancers, respectively.[17] Penile cancer is not common and there are no studies directly demonstrating that HPV vaccination prevents penile cancer.

Oropharyngeal cancer

The rate of oropharyngeal cancer caused by HPV is rising rapidly and increasing more rapidly among men than among women.[18] Remarkably, **HPV-induced oropharyngeal cancer is projected to become more common than cervical cancer in 2020.[18]**

In one report, 72% of oropharyngeal cancers harbored HPV 16, and antibodies against the HPV 16 oncoproteins E6 and E7 were detected in the blood of 64% of the cancer cases.[19] In a case control study, having 6 or more lifetime oral-sex partners was associated with a 3.4-fold (95% confidence interval, 1.5 to 6.5) increased risk of developing oropharyngeal cancer.[19]

According to a population survey, 10% of men and 3.6% of women harbor HPV viruses in their oropharynx.[20] In this study approximately 50% of the HPV viruses detected were high-risk types, with the following rank-order prevalence from highest to lowest: 16, 66, 51, 39, 56, 52, 59, 18, 53, 45, 35, 33, and 31.[20] Theoretically, the 9-valent vaccine, with protection against HPV types 16, 18, 31, 33, 45, and 52, may be an optimal choice to prevent HPV-induced oropharyngeal cancer because of its broad coverage.

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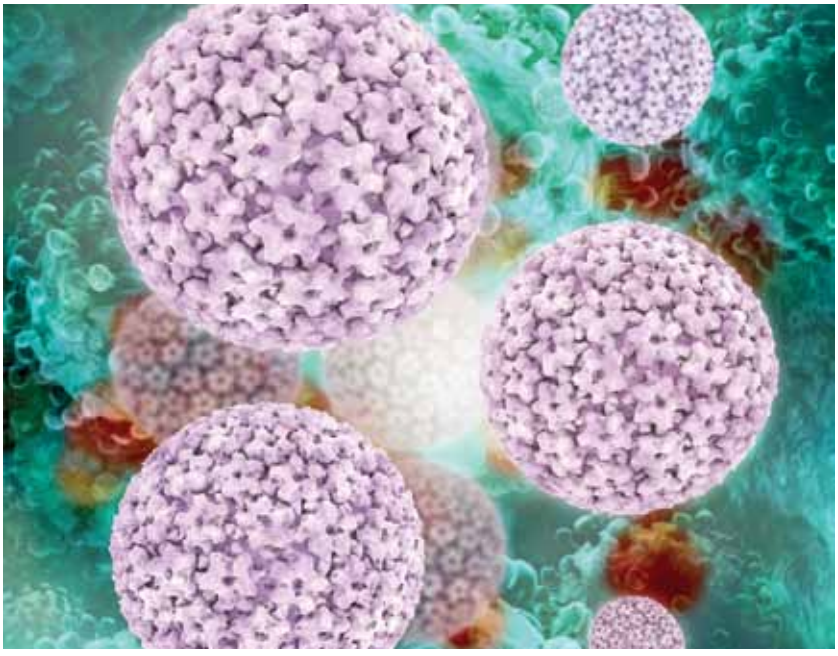

No study has yet proven that HPV vaccination reduces the risk of developing oropharyngeal cancer, but one study demonstrated that vaccination of girls against HPV types 16 and 18 reduced oral carriage of HPV 16 and HPV 18 by 93%.[21] Vaccinating boys against HPV has been reported to be cost effective because it could reduce the high health care expenditures associated with treating oropharyngeal cancer.[22]

Will you be an immunization champion?

Although HPV vaccination reduces the disease burden of cervical, vulvar, vaginal, and anal neoplasia, the CDC reported that, as of 2013, only 38% of girls and 14% of boys in the United States had received 3 doses of HPV vaccine.[23] The realization that oropharyngeal cancer caused by HPV is rapidly increasing may provide another catalyst to redouble our efforts to increase the vaccination rates for both boys and girls.

zur Hausen and many other experts have passionately advocated for vaccinating all boys and girls in order to maximize the beneficial effects of HPV vaccination.[24] Every clinician can become an immunization champion by advocating that all boys and girls be vaccinated against HPV.

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