Human papillomavirus prophylactic vaccine in preventing cervical cancer

RADU VASILCANU, DAIANA VASILCANU, PADRAIG D’ARCY

Department of Oncology and Pathology, Cancer Centrum Karolinska

ABSTRACT Human papillomavirus (HPV) infection has been implicated as a causative agent in 99% of cervical cancers, the second most common cancer in women worldwide. In light of this numerous attempts have been made to eliminate HP infection. Clinical trials for HPV L-1 virus-like particle prophylactic vaccines have shown 100% effectiveness in short-term prevention of HPV infection and of cervical dysplasia. These vaccines have excellent safety profile and enormous potential for reducing mortality caused by cervical cancer. However, many questions and challenges lay ahead: such as, persistence of immunity, optimal age for vaccination and affordability. This review deals with these questions and highlights future directions.

KEY WORDS HPV virus, cervical cancer, morbidity, vaccine

Rezumat

Infectia cu HPV a fost implicata in 99% din cancerii cervicale, a doua cauzata la femei. S-au facut numeroase cercetari pentru eliminarea infectiei cu HPV. Studiile clinice pentru vaccinurile profilactice cu particule HPV L1 virus-like au aratat eficienta de 100% in prevenirea infectiei cu HPV si a displaziei cervicale de 100%. Aceste vaccinuri au un profil de siguranta excelent si un potencial enorm de reducere a mortalitatii cauzate de cancerul cervical. Totusi, multe intrebari si provocari vor mai urma cum ar fi: persistenta imunitatii, varsta optima de vaccinare si abordabilitatea. Acest articol se ocupa de aceste intrebari si pune in evidenta viitoarele direccii.

Cuvinte cheie HPV virus, cancer cervical, mortalitate, vaccin
Cervical infections by approximately 15 carcinogenic HPV types represent the main cause of cervical cancer (11). Most HPV infections are typically transient and become undetectable within a year or two, sometimes causing mild cytopathologic changes, including atypical squamous cells (ASC), low-grade squamous intraepithelial lesions (LSIL), and cervical intraepithelial neoplasia Grade 1 (CIN1) (18). However, some infections persist, and women with persistent carcinogenic HPV infections are at the risk of developing precancerous lesions and subsequently cancer (19, 20). HPV16 is unique in that it is the most prevalent type in cervical intraepithelial neoplasia Grade 3 or CIN3+ (21). However, not all persistent infections progress to precancerous (high-grade) lesions, and not all high-grade lesions develop into cancer. Approximately 75% of low-grade lesions in adults and 90% of low-grade lesions in adolescents resolve without treatment (22). The longer an HPV infection persists, the less likely a patient is to clear the infection (21).

The development of invasive cancer from HPV acquisition to HPV persistence and to development of cancer precursors and invasion takes 20 years on average, with the longest amount of time from high-grade lesions to invasive cancer, although there are cases that develop more rapidly (23). The relatively slow development of cancer from the time of initial infection has contributed to the success of cytology-based programs.

The sexual transmission of HPV is most important factor in considerations for vaccination strategies, including the optimal age of vaccination. HPV is the most common sexually transmitted infection, although there is significant regional variability in the prevalence of HPV even in regions of close proximity and common ancestry (24), which may be due to differences in sexual and cultural norms. An estimated 20 million people in the United States are currently infected as detected by HPV DNA assays (25). Almost half of the infections are in those aged 15 to 25 years. Point prevalence estimates for young women range from 27% to 46% (26). At least half of all sexually active men and women acquire HPV at some point in their lifetime, and modeling studies suggest that up to 80% of sexually active women will have become infected by age 50 (27). Approximately 1.4 million people in the United States currently have genital warts (28). Over 500,000 new cases of anogenital warts are diagnosed annually in the United States, and about 90% are caused by HPV types 6 or 11(29). Anogenital warts are benign tumors that often recur and therefore require frequent treatments (30).

**HPV L-1 virus-like particle prophylactic vaccines**

Possibilities to develop prophylactic vaccines for HPV came with the discovery that viral capsid proteins (L1 and L2) can assemble into virus-like particles (VLPs) following expression in microbial organisms. VLPs resemble native HPV particles and provide epitopes that elicit HPV-neutralizing antibodies in humans. HPV VLPs elicit vigorous antibody responses specific to the genotype of origin and this response could be effective across subtypes with certain vaccine preparations. The resulting VLPs are morphologically identical with native virions, but are not infectious since they lack the viral genome. The binding of an antibody to intact papillomaviruses is thought to block the interaction with cell surface receptor on the cervical epithelium thus facilitating degradation of the virion particles by macrophages (31).

### References

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<td>Exclusion criteria</td>
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*References*
The bivalent vaccine (Cervarix)

Cervarix is a bivalent HPV 16 and 18 VLP prophylactic vaccine containing a unique adjuvant consisting of aluminum and a proprietary lipid agent. Clinical trials have involved more than 27,000 women and girls aged 11 to 55 years. The Cervarix vaccine consists of VLPs composed of L1 capsid protein produced in a baculovirus system. These are not live viruses since there is no viral DNA core. Cervarix includes an adjuvant known as ASO4 (aluminum hydroxide and deacylated monophosphoryl lipid A) which boosts antibody production to higher levels than those seen in natural infection. Antibody levels show progressive elevation through the series of three vaccinations in clinical trials.

Initial results from a randomized clinical trial with Cervarix were reported in 2004 (32) with further follow-up reported in 2006 (33). In this trial, women aged 15 to 25 years were randomly assigned to receive either the bivalent vaccine or to receive a placebo that contained the vaccine adjuvant alone. Subjects were screened for evidence of current or past HPV infection using a serologic test. Women were allowed to enter the trial only if the serologic test was negative for 14 different oncogenic HPV types and they had normal cervical cytology. The vaccine was administered at study entry and 1 and 6 months later. Women were then retested every 6 months using cytology and HPV DNA testing. In this clinical trial, the primary outcome used to determine vaccine effectiveness was the presence or absence of type-specific HPV infection. The 2004 published study results include reported rates of detectable HPV 16 or 18 DNA through 27 months of follow-up for 560 women in the vaccine group and 553 women in the control group. This study demonstrated a statistically significant reduction in detectable HPV 16 or 18 in the vaccine group. In the active vaccine group, the rate of HPV 16 or 18 infections, measured by cervical swab PCR analysis, was 7 in 560 subjects compared with 42 of 553 subjects in the placebo-treated group. During 27 months of follow-up, 1 of 560 women in the vaccine group developed persistent cervical infection with HPV 16 compared to 20 of 553 women in the control group. These data translate to 95.1% vaccine efficacy for prevention of persistent cervical HPV infection (32).

In a combined analysis of the initial efficacy and extended follow-up studies, vaccine efficacy of 100% was demonstrated for CIN lesions associated with the vaccine specific HPV types as well as a decrease in incident infection with HPV 45 and 31 (33).

Antibody levels were measured throughout the follow-up period. These levels, expressed as geometric mean titers, were 100 times higher than antibody levels with natural HPV 16 infection and 80 times higher than natural HPV 18 infection. Levels remained detectable throughout the follow-up period and at 18 months were still 10 to 16 times higher than antibody levels following naturally acquired HPV 16 or 18 infections (32). Beyond 18 months, the antibody levels reached a stable plateau during more than 4 years of follow-up.

Subjects in both arms of the clinical trial reported soreness at the injection site with swelling and redness also common. Injection site symptoms were reported in 94% of vaccine subjects compared with 88% of control subjects. One or more flu-like symptoms, including fatigue, gastrointestinal tract upset, low-grade fever, and headache, was reported in roughly 86% of subjects in both the vaccine and placebo groups. No subject required hospitalization for adverse effects because serious adverse events were rare, and 93% of subjects were compliant with all three doses (32).

The qadrivalent vaccine (Gardasil)

Gardasil is a quadrivalent prophylactic VLP vaccine, effective against HPV types 16, 18, 6, and 11 having aluminum incorporated as a vaccine adjuvant. Completed and ongoing clinical trials have involved more than 25,000 women and girls between the ages of 9 and 26 years and an...
ongoing trial includes 500 boys aged 9 to 15 years.

The L1 proteins are expressed in yeast (Saccharomyces cerevisiae), generating noninfectious VLPs that resemble the HPV capsids of HPV types 16, 18, 6, and 11. The VLPs are then purified and adsorbed into an amorphous aluminum hydroxyphosphate sulfate adjuvant with no preservatives. The quadrivalent vaccine then has 20 \( \mu g \) each of HPV 6 and HPV 18, and 40 \( \mu g \) each of HPV 11 and HPV 16. In clinical trials, the vaccine has been given as a series of 0.5-mL intramuscular injections at 0, 2, and 6 months.

The objectives for the clinical trial of the quadrivalent vaccine were to define the magnitude of prophylactic efficacy with respect to the incidence of diseases related to HPV types 6, 11, 16, and 18. The secondary objective was to assess the impact of Gardasil on the overall burden of clinical HPV disease in women and then to review disease outcomes in HPV-infected women. Immunologic objectives were established to determine the immune correlates of efficacy and to aid in defining the duration of immune response. Safety objectives were established to describe vaccine safety in all relevant populations and pregnancy outcomes in subjects who received Gardasil.

The completed clinical trials have shown that the prophylactic administration of Gardasil is effective in the prevention of cervical and genital disease caused by HPV types 6, 11, 16, and 18 and in reducing the overall burden of HPV disease.

With 30 months of follow-up, the incidence of persistent infection with HPV types 6, 11, 16, or 18 was decreased by 89% in women who received at least 1 dose compared with the incidence in those who received placebo. Biopsy-proven disease, including CIN, vulvar intraepithelial neoplasm, vaginal intraepithelial neoplasm, genital warts, and invasive cancer was reduced by 100% for type-specific HPVs; however, the numbers were small, with 6 diagnoses among 275 controls and no diagnoses among vaccine recipients (34). To date, no information has been published regarding the occurrence of incident or persistent infection or CIN for non–vaccine-specific HPV types for the quadrivalent vaccine. The protection was seen at least 3.5 years after completion of the vaccine series for HPV 16 and 2.5 years after dose 3 for HPV types 6, 11, and 18. Clinical trials are ongoing to define the duration of efficacy. Gardasil is well tolerated in subjects 9 to 26 years old; however, when compared with placebo, it is associated with increased injection site–related adverse events such as pain and erythema and a higher incidence of low-grade fevers. The most common systemic adverse event was headache.

Pregnancy outcomes for women who received Gardasil were comparable to those who received placebo.

The quadrivalent HPV vaccine Gardasil is approved by the US Food and Drug Administration for use in women and girls aged 9 to 26 years. In June 2006, the federal Advisory Committee on Immunization Practices (ACIP) issued the following recommendations:

1. The ACIP recommends routine vaccination of females 11 to 12 years of age with three doses of quadrivalent HPV vaccine.

2. The vaccination series can be started as young as 9 years of age.

The ACIP certified the goal of immunization before the onset of sexual activity but allowed for extended application to capture young women not previously vaccinated. Therefore, vaccination is also recommended for females 13 to 26 years of age who have not been previously vaccinated.

Unanswered questions

Bivalent and quadrivalent HPV L1 vaccination appear to be efficient and will be helpful in reducing the burden of cervical cancer. However, many questions remain unanswered.

One major question is the duration of immunity induced by HPV vaccination. This is important because the critical window for protection begins at the start of sexual activity and extends for several decades. The trial of the bivalent vaccine showed a decline in HPV 16 and HPV 18 titers from peak responses 1 month after the third vaccination to a stable level beginning at month 18 (33). Overall, an important elevation in titer values occurred between the vaccine and placebo groups for both HPV 16 and HPV 18 at the end of the extended follow-up period (4.5 years). Gardasil also showed antibody levels clearly elevated over both the placebo group and natural infection, and at month 36, the levels remained elevated at or above the titers recorded for women who had immune response to natural HPV infection (34).

It is still not clear if HPV L1 vaccines offer cross-protection. Extended follow-up of the bivalent HPV vaccine demonstrates some cross-protection with the HPV 16 and 18–related HPV types 31 and 45, respectively (33).

Age of vaccination is also essential as patients must be vaccinated before the age at which exposure is likely to occur. The lower age limit is bound by the age of study participants, the...
youngest being aged 9 years. As the vaccine is prophylactic, it is essential to consider risk of prior infection, which is best estimated by prior sexual activity.

Another issue is the desirability for vaccination of males. HPV is a sexually transmitted disease and present in both men and women. Clinical implications are in women and the VLP clinical trials have primarily involved women, but both men and women should share responsibility. Vaccination may be recommended in the future for the purpose of preventing anogenital warts in males and, indirectly, infection and anogenital neoplasia and warts in female and male partners. Prevention of HPV infection could have an important impact on a subset of anal, penile, oral, and head and neck cancers and in juvenile respiratory papillomatosis in their children.

Considering global perspective, the development of HPV immunization seems to be crucial for low-resource nations where the use of Pap tests and HPV screening is not available. The population most in need of the protection from HPV vaccines is living in the countries with the poor developed health care systems. The encouraging thing is that the two oncogenic virus types represented in these first vaccines reflect the two predominant HPV types in cervical cancers worldwide. The hope is a large-scale implementation of an effective HPV vaccine, offering an unprecedented opportunity to prevent millions of deaths and dramatically reduce the world's cancer burden.

Conclusions

The high vaccine efficacy observed in actual studies suggests that women receiving prophylactic HPV vaccine will experience a reduction in the morbidity and mortality associated with HPV-related anogenital diseases. The vaccination should be achieved for those groups of women for whom access to cervical cancer screening services is difficult and the protective effect of vaccination that is successfully provided women who are unlikely to undergo regular Pap screening will be of greater magnitude than that provided to women who will undergo regular screening regardless. It remains critical that women undergo regular screening regardless of whether they have been vaccinated.

HPV infection is the origin of 5, 2% of all cancers worldwide and the new VLP vaccines provide the opportunity to reduce cancer rates in a couple of decades.

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