Prospects for Cervical Cancer Prevention by Human Papillomavirus Vaccination

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Abstract

Recent clinical trials in young women have shown that subunit vaccines based on human papillomavirus (HPV) 16 and HPV18 L1 virus-like particles are ~100% effective in short-term prevention of persistent cervical infection and of cervical dysplasia by these major oncogenic types. These remarkable efficacy results, together with an excellent safety profile in thousands of vaccinated women, have led to the HPV prophylactic vaccine from one manufacturer having now been licensed for commercial use and the expectation that the vaccine from a second manufacturer will be approved in the near future. These vaccines seem to have great potential for reducing cervical cancer deaths and treatments to remove premalignant cervical lesions. However, before their public health effect can be fully estimated, several issues must be addressed. These include duration of protection, degree of cross-protection against nonvaccine types, efficacy in men, and vaccine availability to economically disadvantaged women. (Cancer Res 2006; 66(21): 10229-32)

Preclinical Development

Cervical cancer is unique in that one central overriding cause has been identified: persistent cervical infection by one of a subset of ~15 sexually transmitted human papillomaviruses (HPV; refs. 1, 2). This fact provides an exceptional opportunity for primary prevention of cervical cancer, the second most common cause of cancer deaths in women worldwide, by prophylactic vaccination to prevent cervical infection by these oncogenic HPVs. Other prophylactic viral vaccines are very effective public health interventions that overall have an excellent track record of reaching economically disadvantaged populations in addition to those in high-resource settings (3). This is a critical consideration for a new cervical cancer intervention, as 80% of cervical cancers occur in developing countries, and cases in developed countries disproportionately arise in socioeconomically disadvantaged women (4). Inadequate access to quality cervical cancer (Pap) screening programs largely accounts for this disparity.

The commercial HPV prophylactic vaccines are subunit vaccines. They are based on public sector discoveries that L1, the major papillomavirus virion protein, has the intrinsic capacity to assemble into virus-like particles (VLP) that are morphologically indistinguishable from the outer shell of authentic virions. Most importantly, they also behave like authentic virions in inducing high titers of virion-neutralizing antibodies after parenteral injection (5). All other highly successful viral vaccines are prophylactic and based on the induction of neutralizing antibodies (6), so it was reasonable to base prophylactic papillomavirus vaccines on this principle. Because only a single structural viral protein is involved in their production, the VLPs are noninfectious and nononcogenic. The HPV vaccines are conceptually similar to the hepatitis B particle vaccines, which have been shown to reduce the incidence of hepatocellular carcinoma in high-incident areas (7). A notable difference is that the hepatitis B virus (HBV) particles are composed of the viral envelope protein inserted into a lipid vesicle, whereas the HPV L1 VLPs are composed of a protein-only shell. VLP formation is important for the L1 vaccines for two reasons. First, the L1 epitopes recognized by neutralizing antibodies are conformation dependent, and therefore, denatured L1 does not induce neutralizing antibodies. The vaccines are composed of highly purified VLPs, which select for L1 in its native conformation. Second, the ordered repetitive arrangement of epitopes found on VLP surfaces is exceptionally potent at inducing antibody responses compared with structurally simple antigens (8). This property probably accounts for the >99% seroconversion that has been seen in the clinical trials described below.

Papillomavirus infections are highly species restricted, and HPVs do not productively infect or induce morphologic changes in animal tissues. Therefore, preclinical animal challenge trials were conducted using dog, rabbit, and cattle papillomaviruses in their respective hosts. In each case, parenteral VLP vaccination provided excellent protection from papilloma formation after high-dose experimental epidermal challenge (reviewed in ref. 9). Although these results were certainly encouraging, their ability to predict efficacy in human trials was limited because none of the models involved cervico-vaginal challenge or natural sexual transmission. Prophylactic vaccines against other sexually transmitted infections that cause local disease have had limited efficacy despite extensive efforts. It was therefore uncertain whether HPV VLPs would be effective at preventing sexually transmitted HPV infections in women.

Clinical Trials

Despite the uncertainties, two companies, GlaxoSmithKline (GSK) and Merck, undertook commercial development of HPV VLP vaccines. Although based on the same concept, the two vaccines have notable differences. The GSK vaccine is bivalent, containing VLPs of HPV16 and HPV18, the two types that are found in 70% of cervical cancer worldwide. It is produced in L1 recombinant baculovirus-infected insect cells and uses a proprietary adjuvant, AS04, which contains aluminum salts plus...
monophosphoryl lipid A. The Merck vaccine is tetravalent. It also contains VLPs of HPV16 and HPV18 but, in addition, has VLPs of types 6 and 11. HPV6 and HPV11 are considered nononcogenic but cause ~90% of cutaneous genital warts. Therefore, the Merck vaccine targets two distinct hyperproliferative diseases. The Merck VLPs are produced in the yeast *Saccharomyces cerevisiae* and use a simple aluminum salt adjuvant. Although HPV VLPs induce high titers of neutralizing antibodies even without adjuvant (10), the companies probably include aluminum-based adjuvants for two reasons. First, the adjuvants reduce the dose required to induce peak antibody titers, and second, they help to stabilize the vaccine during cold storage.

Five publications have reported the results of randomized, placebo-controlled, proof-of-concept phase 2b efficacy trials. Two of the studies report the initial and follow-up results of a trial using a Merck HPV16-only vaccine (11, 12), whereas the two other studies used the bivalent GSK vaccine (13, 14) and tetravalent Merck vaccine (15), respectively (Table 1). The vaccines were delivered in three 2-month injections of 20 to 40 μg per VLP type over a 6-month period. They were well tolerated, and there were no vaccine-related serious adverse events. They induced >99% seroconversion against every type in the vaccines, and peak antibody titers were at least 50-fold higher than the titers detected after natural infection. Remarkably, in fully vaccinated women, each of the vaccines induced ~100% protection from cervical dysplasia associated with the type(s) in the vaccine and similarly high levels of protection against confirmed persistent infections by the same type(s) (Table 1).

There are currently three phase 3 trials in progress: a multicenter Merck-sponsored trial of their tetravalent vaccine involving >15,000 young women, a GSK-sponsored multicentric trial of their bivalent vaccine involving a similar number of women, and a population-based trial of 7,000 young women in Costa Rica, also using the GSK vaccine and sponsored by the U.S. National Cancer Institute and the Costa Rican government.

The primary end points for these trials are persistent cervico-vaginal infection by the types targeted by the vaccines and histologically confirmed intermediate and high-grade cervical dysplasias [cervical intraepithelial neoplasia (CIN) 2/3] associated with these types. HPV DNA testing results are substantially more reproducible than pathologic diagnosis of dysplasia (16), but CIN2/3 represent the clinical end points that trigger therapeutic intervention. It would be unethical to use cervical cancer as an end point in a trial with active follow-up, as current screening and treatment protocols can prevent the vast majority of these cancers. In addition, the interval between initial infection and development of invasive cancer is usually more than a decade. Merck has presented interim analyses of their phase 3 trial to the Food and Drug Administration (FDA; ref. 17) and the Advisory Committee on Immunization Practices (ACIP) of the Center for Disease Control and Prevention (18). The results confirm the safety, consistent immunogenicity, and extremely high efficacy of their vaccine. In June 2006, Merck received an expedited FDA licensure of their vaccine for prevention of HPV6-, HPV11-, HPV16-, and/or HPV18-related cervical cancer, cervical dysplasias, vulvar or vaginal dysplasias, and genital warts in 9- to 26-year-old women (19). As stated in the package insert of the commercial product, type-specific efficacy against CIN2/3 was 100% in the combined analysis according to protocol analysis (53 and 0 cases in placebo controls and VLP vaccinees, respectively). Protection against external genital warts was 99% in the combined analysis of fully vaccinated women (91 and 1 cases in controls and vaccinees, respectively). The ACIP recently recommended that the vaccine be routinely given to all 11- and 12-year-old girls and that catch-up vaccination be undertaken in girls and women ages 13 to 26 years regardless of whether they are sexually active. GSK, which started its phase 3 trial more recently, has applied for licensure in Europe and has indicated its FDA application for licensure may be expected by the end of 2006.

### Table 1. HPV VLP prophylactic efficacy trials: protection against the HPV types in the vaccine

<table>
<thead>
<tr>
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<tr>
<td>VLP types</td>
<td>16, 18</td>
<td>16</td>
<td>6, 11, 16, 18</td>
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<tr>
<td>Adjuvant</td>
<td>AS04</td>
<td>Aluminum</td>
<td>Aluminum</td>
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<tr>
<td>Sponsor</td>
<td>GSK</td>
<td>Merck</td>
<td>Merck</td>
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<td>Trial sites</td>
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<td>US/EU/BR</td>
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<tr>
<td>Age (y)</td>
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<td>16-23</td>
<td>16-23</td>
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<tr>
<td>No. (ATP)*</td>
<td>950</td>
<td>1,500</td>
<td>470</td>
</tr>
<tr>
<td>Vaccination schedule (mo)</td>
<td>0, 1, 6</td>
<td>0, 2, 6</td>
<td>0, 2, 6</td>
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<tr>
<td>Follow-up (y)</td>
<td>3.5</td>
<td>3.5</td>
<td>2.5</td>
</tr>
<tr>
<td>No. persistent infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine/placebo</td>
<td>1/23</td>
<td>7/111</td>
<td>4/36</td>
</tr>
<tr>
<td>% Efficacy</td>
<td>96</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>No. CIN1+</td>
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<td></td>
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<tr>
<td>Vaccine/placebo</td>
<td>0/8</td>
<td>0/24</td>
<td>0/3</td>
</tr>
<tr>
<td>% Efficacy</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
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Abbreviations: US, United States; EU, European Union; BR, Brazil; CA, Canada; CIN1+, any grade of CIN; Efficacy, against the HPV type(s) in the respective vaccine.

*According to protocol (Agent Transfer Protocol) analysis for the types included in the vaccines.

1Nineteen of 111 controls and 7 of 7 vaccinees were DNA positive only at the last visit.

2Ten of 36 controls and 3 of 4 vaccinees were DNA positive only at the last visit.
Remaining Questions

Although these highly effective and apparently safe vaccines have great potential for reducing cervical cancer rates and the number of surgical treatments for premalignant cervical disease, the actual effect that they will have in practice depends on several unknowns. Although some issues are related to implementation, several questions are directly related to the performance of the vaccine. First, the duration of protection is unknown as would be expected for a vaccine in this stage of development. Most of the data from the phase 2b and phase 3 studies are for short-term follow-up, mostly an average of 1.5 years since completing vaccination (Table 1). However, Mao et al. (12) recently reported maintenance of ~100% protection against CIN for the HPV16 monovalent vaccine after 3.5 years of follow-up. Harper et al. (14) reported analogous results for the HPV16 and HPV18 bivalent vaccine. These findings are quite significant in that VLP antibody titers, which initially dropped ~10-fold in the first 1 to 2 years, had essentially reached a plateau by ~3 years at levels that were well above those induced by natural infection. If serum antibody levels are a surrogate for protection, these findings suggest that the vaccines may protect for many years. Long-term protection is highly desirable, as the need for periodic boosting would substantially increase the cost and complexity of vaccination programs. The long-term serum antibody levels induced against HPV6, HPV11, and HPV18 in the Merck vaccine do not seem to be as high as against HPV16 (15), but it is not yet known whether this apparent difference in serum antibody levels will be associated with shorter-term protection against these other types.

The second question is the degree to which the vaccines may induce cross-protection against genital infection by HPV types that are not included in the vaccines. Cross-protection would be important, as ~30% of cervical cancers and CIN3 lesions are caused by types not in the vaccines (20), and the majority of low-grade cytologic abnormalities detected in Pap screening programs are induced by types other than those in the vaccines (21). On the contrary, vaccinees receiving the HPV16 monovalent vaccine were at least as likely as placebo controls to develop CIN not associated with HPV16 (11, 12). The data suggest that the GSK bivalent vaccine is partially protective against infection by a subset of nonvaccine types (14). The cross-protection was particularly strong with HPV45, which is closely related to HPV18. It is unclear at present if this apparent discrepancy is attributable to differences in the end points examined, study design, or immunogenicity of the two vaccines. Even if substantial cross-protection is confirmed, it is quite possible that it will be less complete and of shorter duration than type-specific protection. VLP-induced cross-neutralizing titers are much lower than type-specific neutralizing titers in in vitro assays1 and might therefore wane sooner to levels not associated with protection. An alternative to cross-protection would be to add more HPV types to the vaccine. It seems likely that both companies will follow this route, and such second-generation VLP vaccines may be able to confer broader protection than the current vaccines.

The third question is whether the vaccine will be protective in men. The outstanding efficacy in women may not predict efficacy in men. Serum antibodies induced by i.m. VLP vaccination might protect women because the antibodies are extensively transudated into cervical mucus, reaching a level of ~10% serum levels after vaccination. Because most of the surfaces of the male genitalia susceptible to HPV infection are not mucosal, this mechanism would be less applicable to men. Therefore, antibody-mediated protection in men would seemingly be limited primarily to the direct exudation of serum antibodies at sites of trauma that are thought to promote infection by exposing basal epithelial cells to the virus. In this regard, it may be relevant that a herpes simplex 2 gD-based vaccine provided partial protection in women but no significant protection in men (22). On the positive side, the fact that the Merck vaccine protects women from external genital lesions (i.e., lesions of cornified skin) suggests that it might similarly protect men from infections of the external genitalia. Fortunately, VLP efficacy trials in men are under way, and the degree of protection they afford men should soon be known. Clearly, if the Merck vaccine also protects men against genital warts, it will provide added incentive for males to be vaccinated.

Implementation Issues

Genital HPV infections are rapidly acquired after initiation of sexual activity (23), and VLP vaccines are unlikely to induce regression of established lesions (9, 12). Therefore, there is general agreement that vaccination of preadolescent or early adolescent girls, as well as older girls or women who have not yet become sexually active, would be the most cost-effective use of the vaccine. However, the preadolescent and adolescent age group maybe a difficult one to target for vaccination, as there is no health care program in place for this group that matches the vaccination schedule. Vaccination of this age group will also require parental approval. Preliminary studies in the United States and elsewhere have indicated that most parents would accept vaccination of their teenage daughters (24), although it seems that a minority may not want their daughters to be vaccinated against a sexually transmitted infection even if it could protect them against a deadly cancer.

Sexually active women may also benefit from vaccination. Although the cumulative incidence of genital HPV infection can reach 80% in young women (2), many may not have been exposed to one or more of the HPV types in the vaccine. In addition, it is possible that recently acquired prevalent infection might be less likely to persist and progress if vaccination prevents successive rounds of autoinoculation. In women with prevalent or break-through infections, the vaccine-induced neutralizing antibodies might also inhibit transmission of the virus to a new partner. However, the cost-effectiveness of catch-up vaccination is likely to be inversely related to age, given the long interval between infection and cervical cancer and that older women are less likely to acquire genital HPV infection.

It is somewhat ironic that this promising primary prevention strategy targets a cancer that already has an effective secondary cancer prevention, Pap screening. In the long term, it might be possible to integrate vaccination and screening into a program that could reduce both the incidence of cervical cancer and the cost of the intervention (25) compared with screening alone. However, screening recommendations are unlikely to change in the short term, and it will be important for vaccinated women to comply with the recommendations, given that the current vaccines are not expected to protect against some infections that can lead to cervical cancer. In situations where resources are limiting, it may be prove difficult to apportion those resources...
between vaccination, which would primarily benefit the next generation of women, and screening, which can protect the current generation from cervical cancer. Screening practices could change dramatically if a second-generation vaccine is developed that targets the vast majority of HPV infections, either by incorporating additional HPV types into a bivalent vaccine or by an alternative approach, such as targeting L2, which contains cross-neutralizing epitopes (26).

It is difficult to evaluate the potential benefits of male vaccination at present, given that the efficacy in men is unknown. Direct effects on cancer incidence in men would be relatively modest. Less than 20% of HPV-associated cancers, mostly anal, penile, and oral, occur in men, although HPV16 and HPV18 also predominate in these cancers. It is also uncertain what effect male vaccination would have on herd immunity and, therefore, on infection rates in women. Transmission modeling suggests that if coverage rates were relatively high in women, the vaccination of men would add substantially to the overall cost of vaccination but have little effect on cervical cancer rates (23). As noted above, however, documentation of protection in men against genital warts associated with HPV6 and HPV11 would represent a direct benefit of the Merck vaccine that would have relevance to considerations about the use of male vaccination.

Economically disadvantaged women’s access to the vaccine will likely be the most critical implementation issue, given that most cervical cancers occur in poorer women. The current vaccines will be expensive to make, as they are highly purified products, and expensive to deliver, as they involve three injections of a vaccine that requires a cold chain. In addition, initial manufacturing capacity could well be insufficient to meet the needs of wealthy nations for steady-state age cohort vaccination and of older women for catch-up vaccination and to supply a substantial number of doses at reduced cost to less wealthy countries. It seems likely that providing large quantities of vaccine at reduced cost to less wealthy countries may be a lower priority until catch-up vaccination in wealthy countries wanes, implying that insufficient supplies of vaccine at a reasonable price could be a major impediment to implementation programs in many settings. A potential solution to this problem is vaccine production by regional manufacturers. Regional production has resulted in at least a 100-fold reduction in the cost of the HBV vaccine, which is now sold by Asian manufacturers to United Nations Children’s Fund for $0.30 per dose. However, it has taken decades to accomplish this reduction, and the HBV vaccine remains underused (7). Hopefully, public sector and industry cooperation can shorten this time line for HPV vaccines.

Acknowledgments

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We apologize to colleagues that a restriction in the number of references has limited our ability to cite their articles.

References

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