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Review Article

Human Papillomavirus Vaccine: Its Application and Perspective

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Abstract

Two prophylactic vaccines against HPV16 and 18 infections are commercially available. Published clinical trials with these HPV vaccines report their use in protection against cervical CIN2+ if girls are vaccinated before their sexual debut. Even though HPV 16 and 18 cause approximately 70% of cervical cancer and an almost 100% of effectiveness would be expected against these cancers, other types may frequently cause cervical cancers in aged women > 50 years. Serious adverse events of the vaccine are a matter of public concern in Japan despite a low incidence rate. After the current vaccines have been implemented world-wide, cervical cancer screening must be undertaken with special attention to changing HPV types and age distribution of patients with cervical cancer.

INTRODUCTION

Cervical cancer is an important global public health problem, because it is a common cause of death among women and is attributable to Human Papillomavirus (HPV) infection [1]. Worldwide HPV prevalence in women with normal cytology is approximately 10% at any given point in time indicating that HPV is one of the most common sexually transmitted infections. Most HPV infections are harmless and clear spontaneously. However, persistent infection with high-risk HPV, particularly type 16 can cause cancer of the cervix, vulva, vagina, anus, penis, and oropharynx.HPV 16 has been detected in approximately 24% of women with HPV infection; HPV 18 has been detected in approximately 9% [2]. HPV 16 and 18 account for approximately 70% of all cervical cancer.

Two prophylactic vaccines against HPV16 and 18 infections have been recently become commercially available. One is a bivalent vaccine (Cervarix™, GlaxoSmithKline Biologicals, Rixensart, Belgium) and the other is a quadrivalent vaccine (Gardasil®, Merck & Co., Inc., Whitehouse Station, NJ USA).

This article reviews the results of published clinical trials using these HPV vaccines and considers the perspective of cervical cancer screening in the future if these two vaccines are theoretically used world-wide.

HPV infection and pathogenesis of cervical lesion

Harald zur Hausen and his colleagues who proposed the link between cervical cancer and HPV gave a firm molecular basis through discovery and molecular cloning of HPV16 and 18. They identified that these were carcinogenic, high-risk HPV for the majority of cervical cancers, and observed that the HPV E6 and E7 genes were preferentially retained and expressed in cervical cancer cell lines. Thereafter, several epidemiologic studies validated that HPV infection is the primary cause of approximately 100% of cervical cancers [3].

HPV infection is the most common infection worldwide, and most sexually active individuals of both sexes acquire it at some point during their life [4]. More than 100 types of HPV have been identified, and over 40 mucosal HPV types infect the lower female genital tract. Low-risk types 6 and 11 cause 10% of low-grade lesions and 90% of condylomatous genital warts. Another 15 high-risk HPV types can cause cervical cancer and are known as cancer-associated HPV types [5]. HPV 16 and 18 are among the carcinogenic HPV types, causing approximately 70% of all cervical cancers worldwide, and they are targeted by the current versions of the HPV vaccine [6]. Persistent infections with these carcinogenic HPV types are essential to cause cervical cancer [7-9], and they can cause several other cancers, such as cancer of the anus, vagina, vulva, penis, and oropharynx [9-11].

Prospective studies have shown that HPV infection includes a mixture of incident and persistent infections that have accumulated over time [12,13]. More than 90% new HPV infections at any age regress in 6–18 months [14], and longer persistent infection is a prerequisite for progression to Cervical Intraepithelial Neoplasia (CIN) [15]. HPV infections detected in women aged > 30 years persist longer compared with those in younger women because these infections are more likely to be persistent [16,17].

The life cycle of HPV is integrally linked to epithelial differentiation. Initial infection of the basal cell occurs because of microscopic breaks in the epithelium [18,19]. The infecting HPV

virions appear to attach to the basal stem cell through tissue-specific heparan sulfate proteoglycans [20-22]. The HPV genome encodes DNA sequences for six Early (E) proteins associated with viral gene regulation and cell transformation, two Late (L) proteins, which form the shell of the virus, and a region of regulatory DNA sequences known as the long control region or upstream regulatory region [23,24].The two most important HPV proteins in the pathogenesis of malignancy are E6 and E7. Both E6 and E7 proteins act in a cooperative manner to immortalize epithelial cells [25]. For some high-risk HPV infections, E6 and E7 are effective at breaking negative regulators of the cell cycle. At the molecular level, E6 and E7 proteins start oncogenesis through well-characterized interactions with products of tumor suppressor genes: TP53 for E6 and Retinoblastoma (Rb) for E7. E6 targets TP53 for degradation through the ubiquitin pathway, preventing apoptosis and enabling potentially transformed cells to replicate [26]. E7 contributes to oncogenesis through its interaction with the Rb family members RB1, RBL1, and RBL2. High-risk E5 works with E6 and E7 to drive cellular proliferation, and it may be a weak cofactor in the development of malignancy [27].

HPV vaccines

At present, two vaccines have been developed against HPV infection. One is a bivalent vaccine (Cervarix™) and the other is a quadrivalent vaccine (Gardasil®). Cervarix™ was designed to prevent HPV 16 and 18 infection. Gardasil® targets the same two types, and it is also intended to prevent infection by HPV 6 and 11, which cause 75%-90% of external genital warts. These vaccines contain HPV L1 self-assembling virus-like particles (VLPs), which induce strong neutralizing antibody responses against HPV infection [28]. The HPV L1 VLPs do not contain the HPV viral genome or any other genetic material; therefore, they are considered non-infectious and non-carcinogenic. Preclinical research demonstrated that L1 is highly immunogenic with and without an adjuvant [29,30].

In natural genital HPV infections, lesions are cleared because of a successful cell-mediated immune response directed against HPV E proteins. The humoral response in natural HPV infection mostly targets the conformational epitopes in the variable regions of the major viral coat protein L1 [31]. However, the humoral response to natural infection is slow and weak [32,33]. Seroconversion, defined as the appearance of anti-HPV antibodies, appears to occur 6–18 months after the infection. HPV L1-specific antibodies have been considered to be markers of past or current infection because they are more frequently detected in subjects with persistent infections and precancerous lesions. In contrary, HPV antigens, such as E1, E2, and E6, do not appear to evoke measurable antibody responses in natural infections [34].

In contrast to natural infections, HPV vaccination induces high antibody titers against HPV L1, conferring protection against new infections and disease amongst virtually all women naive to those HPV types [35,36]. Both vaccines were shown to be highly immunogenic in clinical trials, resulting in essentially 100% seroconversion. Following vaccination, geometric mean antibody titers for the vaccine types peaked at month 7, with titers 10-100-fold higher compared with those induced by natural infection [35,37]. Titers for both vaccines generally peaked one month after the third dose, declined over the next year, and remained relatively stable for the duration of follow-up (an additional 4.0 and 4.5 years for Cervarix™ and Gardasil®, respectively) [38,39].

Efficacy of vaccines

As shown in several global randomized clinical trials, the two vaccines confer almost 100% protection against infection and diseases related to the HPV types mentioned above [36,38-44]. The vaccines showed high efficacy against CIN2+ associated with HPV16 and 18 as well as some non-vaccine oncogenic HPV types. They also showed substantial overall effects in cohorts that are relevant to universal mass vaccination and catch-up programs. Data from the end-of-study analysis of PATRICIA using the bivalent vaccine [45] showed a cross-protective efficacy of the HPV 16 and 18 vaccine against four oncogenic non-vaccine HPV types, HPV 33, 31, 45, and 51. This cross protective efficacy is associated with cross-protective immune responses in HPV types that are phylogenetically related to HPV 16 and 18, respectively [46]. The quadrivalent vaccine is expected to prevent a large proportion of anogenital warts and recurrent respiratory papillomatoses in both men and women. In addition, these vaccines could provide protection to prevent HPV-related cancers at several other sites in which HPV 16 accounts for an overwhelming majority of HPV-associated cancers. These include cancers of the vulva and vagina in women, penile cancers in men, and cancers of the anal canal and oropharyngeal / tonsillar region in both men and women. The UK Health Protection Agency analyzed the effect and cost effectiveness of the two HPV vaccines and concluded that the quadrivalent vaccine may have an advantage over the bivalent vaccine in reducing healthcare costs and quality adjusted life-year lost while the bivalent vaccine may have an advantage in preventing death due to cancer [47]. These results imply that we should consider the differential benefits of the two available HPV vaccines in terms of their efficacy against non-vaccine HPV types, duration of protection, and preventative diseases.

Who to vaccinate

Clinical trial data of vaccine efficacy in males and females suggest that immunization with HPV vaccine is most effective among individuals who have not been infected with HPV (e.g., patients who are “HPV-naïve”). Thus, the optimal time for HPV immunization is before the individual’s sexual debut.

Various HPV vaccination programs are coming into force, although the primary goals of HPV vaccination programs have been the prevention of cervical cancer among women and girls. Nevertheless, recent clinical trial data has shown the efficacy of vaccination in men [48] and the potential for herd immunity; thus, vaccination of adolescent boys is being recommended in some developed regions. Australia provides an example of a successful publicly funded mass vaccination program, which began in April 2007 using the quadrivalent vaccine. New cases of genital warts have not only fallen by 73% in vaccine-aged young women but also by 44% in young men who were not part of the free vaccination program. These findings strongly suggest that mass vaccination of girls provides substantial herd immunity [49]. The quadrivalent HPV vaccine demonstrated high efficacy, immunogenicity, and acceptable safety in women aged 24-

45 years, regardless of previous exposure to HPV vaccine type [50,51]. In the UK, the uptake of vaccination in a school-based program for girls aged 12–13 years was 83%. In the catch-up campaign for older teenagers, which relied largely on general practices, only 41% of eligible individuals received three doses (https://www.gov.uk/government/organisations/department-of-health). A history of an abnormal Papanicolaou test, genital warts, or HPV infection is not a contraindication to HPV immunization [52]. However, immunization is less beneficial for females who have already been infected with one or more of the HPV vaccine types.

To accommodate a wider range of on-request vaccinations, the USA and other countries have included a catch-up age range for vaccination, which overlaps with the typical age of onset of sexual activity. Because the effectiveness of the vaccine as prophylaxis is higher for a fully vaccinated woman who has not had any sexual activity compared with a woman vaccinated after the onset of sexual activity, the catch-up vaccination policy has implications for health economics. Prophylactic HPV vaccination has been estimated to be cost effective, with the up-front expenditure for vaccination offset by the costs averted through disease prevention [53]. This assumption depends on the age at vaccination, screening intervals, female only or male and female programs, and the cost of the vaccine. The data obtained suggest that the cost of cervical cancer screening could be substantially reduced by ensuring high coverage HPV vaccination with its consequent drop in high-grade cytology and colposcopy referrals. The association between HPV infection and several other anogenital diseases, including anal, vaginal, and vulval cancers, as well as oropharyngeal cancers [54], suggests that prophylactic HPV vaccination may also protect against some of these cancers. Despite proven efficacy against HPV-associated anal disease [48], cost effectiveness models in regions of the world that offer vaccination to both girls and boys have shown that providing vaccination to both sexes is considerably less cost effective compared with vaccination of girls only, unless vaccine costs can be substantially decreased or a high coverage in adolescent girls cannot be achieved [55].

In contrast, mathematical modelers have compared the effect and cost effectiveness of bivalent and quadrivalent HPV vaccination, concluding that the quadrivalent vaccine may have an advantage over the bivalent vaccine in reducing healthcare costs and quality adjusted life-year lost primarily because the bivalent vaccine does not protect against anogenital warts [47]. Arguments for male vaccination do not solely relate to the cost but also to the additional health benefits of moving from a sex-specific strategy to a vaccination policy seeking to prevent disease in both sexes, with the potential for herd immunity. Haupt et al reported the effect of a HPV vaccine on the development of CIN grade 2-3 or adenocarcinoma in situ (CIN2-3/AIS) in women with ongoing HPV16 or 18 infections for pre-vaccination [56]. The results revealed no difference between vaccine and placebo groups in the incidence of HPV16/18-related CIN2-3/AIS. In other words, these data suggest HPV vaccination neither reduces nor enhances progression to HPV16/18-related high-grade cervical lesions. These vaccines have little, if any, prophylactic effectiveness in people that have been previously exposed to the virus types contained in the vaccine because they were not designed as therapeutic vaccines [44,57]. In women who were DNA positive for one vaccine HPV type, the vaccine was efficacious against the other vaccine type. The vaccine did not affect the outcome of HPV 16 and 18 infections present at the time of vaccination [58].

In FUTURE I and FUTURE II trials, retrospective analysis was performed to determine the effect of HPV quadrivalent vaccine on the risk of developing subsequent disease after an excisional procedure for cervical intraepithelial neoplasia or diagnosis of genital warts, vulvar intraepithelial neoplasia, or vaginal intraepithelial neoplasia. Vaccination was associated with a significant reduction in the risk of any subsequent high-grade disease of the cervix by 64.9% [59]. However, HPV vaccination does not reduce progression to cervical pre-cancers in women with ongoing infections at the time of vaccination [56,60,61], and no studies have considered the effect of HPV vaccination in preventing subsequent disease after treatment for such pre-cancers thus far. In other words, vaccination does not reduce the progression to disease in women who are infected with HPV at the time of vaccination; however, vaccination offered substantial benefit to women who were treated for disease in the context of these studies and were at risk for developing subsequent disease [59].

Safety of HPV vaccine

VLPs are noninfectious protein subunit vaccines and may, therefore, be expected to have safety profiles similar to other protein subunit vaccines, such as tetanus or hepatitis B virus vaccine. The most common vaccine-related adverse eventsincluded local transient mild to moderate pain and erythema at the site of injection. These reactions were significantly elevated compared with controls. For instance, local pain reported in VLP vaccines and controls was 90.5% and 78.0% in the PATRICIA study, and 85.3% and 75.4% in the FUTURE I trials, respectively [36,42]. Other adverse events were allergic reaction; dermatologic/mucosa (25%), rash (22%), and local/injection site reaction (20%). Furthermore, of 133 (0.019%) adverse events among 691994 quadrant HPV vaccine doses distributed in a school-based program in Ontario, Canada reported in 2014, 10 (7.5%) were serious events, including 2 anaphylaxis, 2 seizures, 1 thrombocytopenia, and 1 death. This report stressed on the significance of continued assessment of adverse event survaillance data [62]. For instance, in 2013, Japan television aired a shocking movie about a school girl who suffered a serious neurological event following the vaccination. Although the relation between the event and vaccination remains unclear, the event was reported so critically that the vaccination program has been under re-evaluation with no progression until February 2014.

Post-vaccine cervical cancer screening

The HPV vaccine is almost 100% effective in preventing HPV 16 and 18 infections. However, it cannot perfectly prevent other high-risk HPV infections. In Japan and some other countries, HPV 52 and 58 are also frequently detected in addition to HPV 16 (Table 1). Moreover, in Japan, HPV 52 and 58 detection rates are higher compared with HPV 16 detection rates observed in individuals > 50 years of age (Figure 1; [63]). In some cases vaccinated people can still get an HPV infection, and there is still

Table 1: High Risk Type HPV in HPV Positive Cervical Samples in Japan.

	HPV Types							
Classification	16	52	58	51	31	56	39	18
ASCUS+ (n=868)	236 (27.2%)	232 (26.7%)	198 (22.8%)	83 (9.6%)	74 (8.5%)	63 (7.3%)	61 (7.0%)	60 (6.9%)
HSIL/SCC/ADC* (n=486)	174 (35.8%)	138 (28.4%)	119 (24.5%)	42 (8.6%)	48 (9.9%)	18 (3.7%)	27 (5.6%)	35 (7.2%)

Abbreviation: ASCUS+: Atypical Squamous Cells of Undetermined Significance or more; HSIL: High Grade Squamous Intraepithelial Lesion; SCC: Squamous Cell Carcinoma; ADC: Adenocarcinoma

Number and percentages in the parenthesis were obtained from the final data of CCLBC study [62], in which 11,039 cervical samples were enrolled and 868 (66.7%) in 1302 ASCUS+ were HPV positive. HPV typing was performed by multiplex PCR method [64].

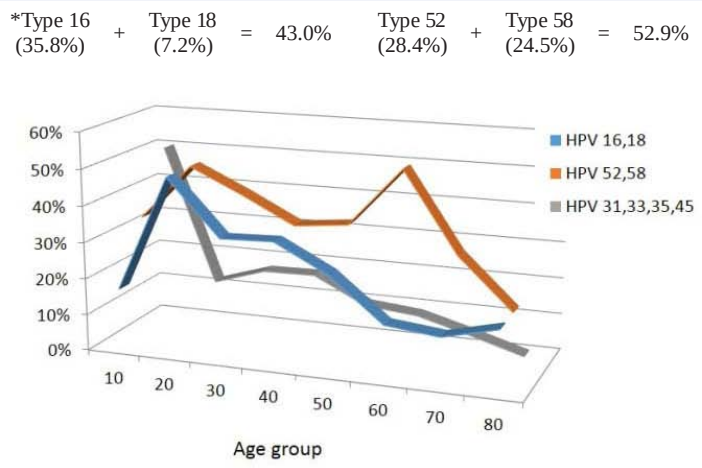

Figure 1 Age-specific detection rates of high-risk HPV in HSIL+ cytological findings indicating the highest incidence of HPV 52 and 58 in patients who were in their 60s. They were obtained from the final data of CCLBC study [63].

a possibility of developing cervical cancer and cervical lesions caused by pre-vaccine infection of HPV. Therefore, all women including those vaccinated for HPV should be routinely checked for cervical cancer starting at age 21 years or within 3 years of first sexual contact even after the HPV vaccination. There is a debate concerning the efficacy of a "pap smear" versus an HPV test. The effectiveness of these tests depend on how developed the system for cervical cancer screening is in a specific community or nation. The "pap smear" would be more beneficial in countries with sufficient well-trained cytotechnologists, cytopathologists, and well-organized autoanalyzers of cervical cancer. However, in other countries with less developed screening systems, HPV tests would be more beneficial. Novel techniques or markers to predict disease progression of cervical pre-cancer lesions need to be explored.

CONCLUSION

HPV vaccines that are available today protect against precancerous lesions associated with HPV 16 and 18. The quadrivalent vaccine also targets HPV 6 and 11. We should consider the differential benefit of the two available HPV vaccines. Most importantly, we should promote broad vaccination and cancer screening to avoid cervical cancer burden and severe adverse events.

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