HUMAN PAPILLOMAVIRUS AND VACCINATION IN CERVICAL CANCER

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SUMMARY

Cervical cancer is not only the most frequently reported cancer among women, but also the most common female genital tract neoplasm in Taiwan. Early detection is effective, because the development, maintenance and progression of precursor lesions (cervical intraepithelial neoplasia [CIN]) evolve slowly into invasive cancer, typically over a period of more than 10 years. It is now recognized that human papillomavirus (HPV) infection is a necessary cause for over 99% of cervical cancer cases. Advances in the understanding of the causative role of HPV in the etiology of high-grade cervical lesions (CIN 2/3) and cervical cancer have led to the development, evaluation and recommendation of HPV-based technologies for cervical cancer prevention and control. The prevention of HPV infection before the onset of CIN is now possible with recently available prophylactic HPV vaccines, e.g. the quadrivalent Gardasil (Merck & Co., NJ, USA) and bivalent Cervarix (GlaxoSmithKline, London, UK). This review article provides an up-to-date summary of recent studies and available information concerning HPV and vaccination in cervical cancer. [*Taiwan J Obstet Gynecol* 2007;46(4):352–362]

Key Words: Cervarix, cervical cancer, Gardasil, human papillomavirus, HPV, vaccines, virus-like particle vaccines

Introduction

Approximately 500,000 women develop cervical cancer annually, resulting in an annual mortality of about 200,000 [1]. Cervical cancer is the second most common cancer among women worldwide, with an estimated 1.4 million cases, 493,000 new cases, and 274,000 deaths in the year 2002 [2]. In Taiwan, cervical cancer is not only the most frequently reported cancer among women, but also the most common female genital tract neoplasm [3,4], with an incidence of 17 per 100,000 women in 2002 [5]. Early detection is effective, because the development, maintenance and progression of precursor lesions (cervical intraepithelial neoplasia [CIN]) evolve slowly into invasive cancer, typically over a period of more than 10 years. Traditionally, these precursor lesions are detected with cervical cytology screening methods such as the Papanicolaou (Pap) test, which has successfully lowered the incidence and mortality of cervical cancer. However, up to 30% false-negative results [6] inherent to the Pap test have prompted many gynecologic oncologists to develop new tools for identifying precancerous cervical lesions.

It is now recognized that human papillomavirus (HPV) infection is a necessary cause for over 99% of cervical cancers [1,7,8]. Advances in the understanding of the causative role of HPV in the etiology of high-grade cervical lesions (CIN 2/3) and cervical cancer [7,9–11] have led to the development, evaluation and recommendation of HPV-based technologies for cervical cancer prevention and control. The importance of HPV is increasingly recognized by both the medical community and the public. HPV infection is among the most common sexually transmitted infections (STIs) in most populations: 15–20% in many European countries, 70% in the USA, and 95% among high-risk populations in

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Africa [12]. HPV infection is the STI with the highest incidence in the US; an estimated 20 million people are currently infected, and 6.2 million persons acquire a new infection annually [13,14]. It is estimated that 80% of sexually active women would have been exposed to HPV by the age of 50 [15]. The prevention of HPV infection before the onset of CIN is now possible with the recently available prophylactic HPV vaccines, e.g. the quadrivalent Gardasil (Merck & Co., NJ, USA) and bivalent Cervarix (GlaxoSmithKline, London, UK). This article reviews recent reports and offers up-to-date available information concerning current practices and modern trends in the prevention of cervical cancer.

HPV Viral Genetics, Molecular Biology, and the Life Cycle

HPV is recently recognized by the International Committee on Taxonomy of Viruses as member of the Papillomaviridae family. Previous classification has grouped papillomaviruses with polyomaviruses in the Papovaviridae family based on various resemblances, including similar viral capsids, lack of envelope, and their double-stranded circular DNA genome. Both families also share the same arrangement of 8–10 open reading frames within the genome, and one particularly distinctive characteristic is the arrangement of partly overlapping open reading frames on a single strand of DNA molecule. Nevertheless, differences in genome size and transcriptional strategies, as well as non-homologous proteins, have separated the polyomavirus and papillomavirus into two different families [16].

Although they are widespread among higher vertebrates, papillomaviruses have mostly been isolated from humans [17]. Other papillomaviruses are found in domestic mammals, including a number of wild and exotic mammals, reptiles, and two bird species [18–20]. Papillomaviruses exhibit strict species specificity and do not transmit from non-primates to humans [21]. Therefore, HPVs do not induce morphologic changes in animal tissues.

The viral genome is relatively small (~8,000 base pairs) [22], codes for only eight proteins and can be roughly categorized into three distinct regions: the region of late proteins (L1 and L2); the long control region without coding potential; and the region of early proteins (E1–E8) [23]. The HPV early proteins E1 and E2 produce viral proteins during viral replication and transcription; E4 seems to assist the release of virus from infected cells [24], and the late L1 and L2 are structural proteins of the individual capsomere subunits in the viral capsid. The late protein L1 (57 kDa) is the major structural and antigenic capsid protein that accounts for 80% of the viral particle, and the late L2 protein (43–53 kDa) is the minor, infectivity-enhancing capsid protein. The early proteins E6 and E7 are the most important oncogenic proteins encoded by high-risk HPV (hrHPV) types. Since the transcription of E6 and E7 genes always occurs in cervical carcinomas, this discovery marked the first clues to the link between viral genes and HPV-associated tumorigenesis [25,26]. Abundant supporting evidence from tissue cultures and animal models has demonstrated the immortalizing and oncogenic transforming potential of E6 and E7 genes that are thought to play a role in the initiation and oncogenic progression of tumors [27]. These genes are expressed after integration into the host genome during oncogenic progression. The early protein E6 is thought to speed turnover of the key tumor suppressor protein p53, while E7 has been implicated in blocking the function of retinoblastoma protein (pRB) cell replication regulatory proteins [28]; E5 has also been implicated in cellular transformation [29]. Since the *p53* and *pRB* genes are involved in the suppression of oncogenic transformation, the binding and inactivation of these cellular proteins by the E6 and E7 oncogenes are one of the mechanisms of HPV-mediated cellular transformation.

The viral life cycle is tightly linked to the differentiation program of the epithelial cell. In general, HPV infection is limited to the basal cells of a human epithelial surface and normally remains in infected basal cells; unlike some animal papillomavirus types, they do not infect or express gene products in the underlying dermis [30]. Other cells that are also infected move away from the basement membrane and differentiate into mature squamous cells as they progress towards the epithelial surface. HPV viral particles consist of the viral DNA genome surrounded by the protein capsid, which is composed of HPV L1 and L2 proteins. As a result, antibodies against L1 and L2 could possibly neutralize the virus and prevent HPV infection. Upon infection, the early viral proteins are expressed in the infected basal cells within the lower epithelial layers. As infected cells reach the surface, the L1 and L2 proteins are produced and allow shedding of mature virions as virus-laden squames. Although HPV preferentially infects squamous epithelial cells rather than columnar, cuboidal or transitional epithelial cells [31], the infection of columnar cells can render much easier formation of mucosal lesions, which form the basal layer of the stratified epithelium of the transformation zone [30]. Since they have no envelope, HPVs are relatively stable and remain infectious for months in a moist environment [21]. During infection, HPV DNA is generally

found in the cytoplasm. However, the DNA of hrHPV types integrates into the host genome of most cervical tumors. Integration commonly disrupts the HPV virus through the loss of virion production (L1 and L2 are not expressed) and accompanies the increasing expression of E6 and E7. Consequently, integration transforms the infected basal cells into a malignant phenotype, ranging from "warty" epithelium with koilocytosis to overt malignancy. In other words, the steady presence of early proteins E6 and E7 during hrHPV infection could produce a therapeutic immune response.

Cervical HPV infection is usually benign. Less than 5% of women infected with HPV develop premalignant lesions, which may progress from low-grade (CIN 1) to high-grade lesions (CIN 2/3) as well as cervical cancer, if they receive no medical intervention [32–34]. Infection alone is insufficient to cause cancer, and additional factors are required for neoplasia. Approximately 70% and 91% of new infections clear up within 1 and 2 years, respectively [35–37]. Most HPV infections are usually transient and are not associated with any sign or symptom of infection, causing no viremia or systemic manifestations. Most people never even know they have had HPV, and their immune system clears up the infection before they notice it. The nature of the immune response that controls and eliminates HPV infections is still under investigation; however, it almost certainly has a role in limiting and eradicating HPV infection. It is not known whether clearance implies that the virus is still present at levels below detection limits of existing technologies or whether it signifies an actual eradication of the preexisting viral infection.

HPV Infection, Genotypes, and Diseases

There are more than 100 different genotypes of papillomavirus [38]. The genotyping of HPV is differentiated primarily by the DNA sequences of the outer capsid protein L1 and, to a lesser extent, by those on E6 and E7. A 10% difference in DNA sequence with respect to previously established strains is sufficient to define a new HPV viral type. The HPV genotypes are numbered in sequence of their discovery. Three genera of the Papillomaviridae family are responsible for significant diseases in humans: alpha-papillomavirus (includes all genital papillomaviruses), beta-papillomavirus (papillomaviruses responsible for epidermodysplasia verruciformis), and gamma papillomaviruses (most of the viruses responsible for cutaneous lesions) [16,39]. However, the prior HPV classification as mucosal or cutaneous types based on their preferred tissues is still commonly applied clinically and will be used throughout this text. Some HPV types cause cutaneous infections (the common skin wart), whereas only about 40 types cause mucosal infections, which lead to genital tract diseases in men and women. The high-risk types of mucosal HPV, also known as "oncogenic", put women at high risk of developing cervical cancer, as opposed to other low-risk types of mucosal HPV, also known as "non-oncogenic". Based on a review of global epidemiologic studies, Munoz et al [40] have classified mucosal HPV into 18 hrHPV genotypes, 12 low-risk HPV (lrHPV), and three presenting indeterminate risk. It is now recognized that HPV-16 is the single most common hrHPV type in anogenital cancer precursor lesions, CIN as well as cervical cancers, and a subset of head and neck cancers [41–43]. The hrHPV-16 and -18 are found in 25% of all CIN 1 lesions, 70% of CIN 2/3, and anogenital cancers. HPV-16 alone accounts for more than 50–60% of cervical cancer cases in most countries, followed by HPV-18 (10–12%) and HPV-31 and -45 (4–5% each) [12,43, 44]; the remainder is caused by a variety of other types that vary globally. The other 11 less common hrHPV types (other than HPV-16, -18, -31 and -45) are HPV-33, -35, -39, -51, -52, -56, -58, -59, -68, -73 and -82; the three indeterminate (or probable) hrHPV types are HPV-26, -53 and -66.

Risk Factors for HPV Infection

Sexual transmission is the dominant mechanism for acquisition of genital HPV [35,45]. Important risk factors for HPV infection and development include number of sexual partners, immunosuppression and the risk behavior of those partners, and early onset of sexual activity. HPV is, nonetheless, common in people with few sexual partners [46]. The rates of HPV infection increase rapidly among women with only one lifetime partner (20% to 46%) to women with 10 or more partners (almost 70%) [47,48]. Immunosuppression is an important risk factor that includes those partners infected with other STIs, receipts of an organ transplant, or renal disease. Partners can be infected with other STIs that may lead to immunosuppression, such as HIV, chlamydia, and genital herpes [11,49,50]. Since HIV damages the body's immune system, HIV-infected women are at a greater risk of HPV infection, persistent HPV infection, and precancerous lesions [51–53]. An early study by Conti et al [54] reported a 42% and 8% CIN detection rate for HIV-infected and non-HIV-infected women, respectively. HPV-infected women who are seropositive for type 2 herpes simplex virus or *Chlamydia trachomatis* infection are also at greater risk for cervical cancer [8,12,50]. Most studies demonstrate

that young age (usually defined as less than 25 years) is a risk factor for infection among sexually active young women. The transmission of HPV infection during early years of sexual activity contributes to the higher rates in younger women, and the infection clears over time in most women. One study demonstrated that more than 50% of young women acquired cervical HPV infection 48 months after the first sexual intercourse [55]. The cumulative prevalence rates are as high as 82% among adolescent girls [56], but the rate is usually ~30% according to many clinic-based prevalence studies in the US [57]. Unlike most studies in the US, which revealed a decline in HPV prevalence after the age of 25 years, one prospective study reported an increase in prevalence after the age of 40 years in Guanacaste, Costa Rica [58]. Another study estimated that 70% of sexually active adults will become infected with HPV during their lifetime [59]. However, the most important risk factor for developing premalignant lesions and cervical cancer is persistent infection with hrHPV. HPV infections are frequent, but only a small percentage of HPV infections become persistent. Persistent HPV carriers are estimated to be about 3–10% of women in different populations [60]. Persistent HPV is most commonly defined as detection of the same-risk HPV types at two or more visits, 4–6 months apart [61]. Studies also revealed that persistent infection with a hrHPV is associated with a more than 10-fold risk for the development of high-grade cervical lesions (CIN 2/3) [62,63].

Additional risk factors for HPV infection that are less consistent include condom use, parity, dietary factors (nutritional deficiencies mainly related to antioxidant agents), uncircumcised male partners, and oral contraceptive use [55,64–66]. Although a January 2004 Centers for Disease Control and Prevention report stated that condom use has been associated with lower rates of HPV-associated diseases including cervical cancer, the efficacy of condoms in preventing HPV infections is still unknown [67]. One study suggested that since HPV is not transmitted through semen or bodily fluids, condoms do not protect against infection with HPV [68]. HPV infections are transmitted through skin-to-skin contact often far beyond the area covered by condoms. Another study demonstrated that non-penetrative sexual activity is associated with HPV acquisition, but much less frequently with sexual intercourse [55]. It has also been reported that, though in very rare cases, HPV may be transmitted non-sexually, possibly through contact with infected urogenital secretions from sharing towels or bathwater [69,70]. A study by Plummer et al indicated an excess risk among women smokers with HPV for promoting the progression from HPV to cervical cancer with squamous cell histologic types for current smokers, as well as ex-smokers; and these findings, however, were not true for adenocarcinomas [71]. Genetic susceptibility to HPV infection appears to be important, as reported by Magnusson et al [72,73]. These authors found that women who have a family history of cervical cancer were almost twice as likely to develop cervical cancer as women who did not have a family history of the disease.

HPV Detection Methods

Unlike many pathogens, infectious virions are produced only in the terminally differentiated cell, and this explains why no simple *in vitro* culture methods are available for identifying HPV infection. Over the years, only nude mouse [74,75] and SCID mouse [76] xenograft systems as well as raft-culture systems [77] have achieved limited propagation of infectious virus for some HPV types. Serologic testing of HPV is most commonly performed using an ELISA test for antibodies to type-specific virus-like particles (VLPs). Serologic studies of HPV are considered to be only research tools, and a consensus guideline for standard serologic method is not yet available. Unfortunately, current serologic testing of HPV antibodies has relatively low sensitivity [78], which also renders difficult the comparison of similar studies. Most persons with HPV infections or persons who develop HPV-associated cancers do not develop antibodies; in fact, only 40% of HPV-16 infections are associated with the development of HPV-16 antibodies [79,80]. The techniques for viral infection are based on the detection of HPV DNA from samples, via either signal amplification methods, such as hybrid capture, or target amplification, such as polymerase chain reaction-based assays. A paper-based HPV DNA screening test [81] is also in the development as an HPV test. Coupled with a single-step DNA extraction procedure, the paper-based test being studied in India allows for dry collection of cervical cells, along with transportation and storage at room temperature [81].

Hybrid Capture II (Digene Corporation, Gaithersburg, MD, USA) assay is the only commercially available second-generation assay that has been approved by the US Food and Drug Administration (FDA) at present for the primary screening of women aged 30 years or older and for management of atypical squamous cells of undetermined significance (ASCUS) [82]. Although both low- and high-risk HPV panels are available for Hybrid Capture II, only the high-risk panel is commonly used to detect HPV types in samples. The lack of specificity in determining the presence of a high-risk versus a low-risk HPV infection is a limitation of the Hybrid

Capture II, which has a lower analytical but not the necessarily clinical sensitivity compared with PCR [83].

Cervical Cancer Screening and HPV DNA Test

There has been a dramatic reduction in the incidence and mortality of cervical cancer among US women in the past 50 years from the second most common cancer and cause of cancer death to 11th in incidence and 13th in mortality [84]. This remarkable improvement is largely attributed to the introduction of the Pap smear evaluation, recognized as the world's most successful cervical cytology screening test for more than 40 years [85]. The Pap smear is well integrated into the health care system in many countries around the world to improve survival and reduce mortality rates in cervical cancer. Over 50 million Pap tests are performed each year in the US [86]. Even so, despite current practices of regular, high-quality gynecologic care and screening in the US, the low sensitivity of cervical cytology has rendered the screening program only about 75% effective since its introduction in 1950 [87]. The International Agency for Research on Cancer estimated the lifetime risk for developing cervical cancer among women who received regular annual cervical cytology screening to be 217 per 100,000 women (assuming a Pap test sensitivity of 70%) [88]. In the UK, Sasieni et al reported that 47% of women diagnosed with stage 1B1 invasive cervical cancer or worse before the age of 70 years had an adequate previous screening history, and some had had normal annual Pap smears [89]. Although the Pap test possesses a relatively high specificity (80–85%), it suffers from low sensitivity (50–60%) for high-grade CIN (grades 2 and 3) and is even less sensitive for lower grade lesions (CIN 1) [90]. Many rounds of screening are often required for the detection of cervical cancer and precancerous lesions [91]. The cost of multiple screenings, follow-up and treatment has turned HPV infection into one of the most costly STIs in the US [92]. The latest revised guidelines by various professional organizations, such as the American Cancer Society (ACS) and the American College of Obstetrics and Gynecology (ACOG), now recommend that cervical cancer screening should begin at 21 years of age or within 3 years of the first sexual activity [93–99]. Additionally, some organizations (ACS and ACOG) also advocate hrHPV DNA testing as well as liquid-based cytology tests as an adjunct to the Pap smear for primary cervical screening [98,99]. The US Agency of Health Care Policy and Research and the UK National Institute for Clinical Excellence have both recommended the liquid-based cytology as a cost-effective alternative to the conventional smear-based cytology [60]. The FDA has approved two liquid-based cytology methods: the Sure-Path system and the ThinPrep Pap Test. Cells scraped from the cervix are examined directly on a slide in the traditional Pap test, whereas the cells are first suspended and then applied to a glass slide in the liquid-based technique, removing much of the mucus, blood, and inflammatory cells. Although liquid-based methods are more expensive than conventional Pap tests, they possess higher sensitivity, probably due to the sample preparation method [100]. It is estimated that the ThinPrep (Cytyc Corporation, Marlborough, MA, USA) liquid-based cytology has a sensitivity of 80% for the detection of CIN [60].

The development of new technologies to identify precancerous cervical lesions with greater sensitivity and predictive value than the Pap test has been an ongoing objective for many gynecologic oncologists around the world. Research on the role of HPV DNA testing for cervical screening and management following an abnormal Pap test began in the late 1980s [101]. Molecular tests for the clinical detection of HPV have been developed for use in primary cervical screening and for women with abnormal cervical cytology [102–108]. The dependency of cervical cancer on HPV infection has highlighted the clinical benefits of HPV DNA testing as particularly significant. Several studies have reported a high sensitivity of 100% (95% confidence interval [CI], 89–100) and a negative predictive value of 100% (95% CI, 91–100) for this adjunctive approach using the Hybrid Capture II [106]. A single liquid-based Pap test is consistently reported to be 10% to 25% less sensitive than a single HPV test for the detection of CIN 3 or cancer, whereas the difference between the conventional Pap smear and HPV testing is consistently much greater (25–40%) [33,103–112]. However, the specificity of the combined tests was slightly lower than that of the Pap smear test alone. There is minimal risk of invasive cervical cancer for at least the subsequent 3 to 5 years when women have both a negative Pap and a negative HPV DNA test [99]. Sherman et al [113] demonstrated that the risk of a CIN 3 during the first 45 months of follow-up after a single negative hrHPV test at the time of enrollment was only 0.24% and was 0.87% after 10 years in the 10-year National Cancer Institute-Portland, Oregon cohort study consisting of 23,000 women who had had routine cytology screening. In contrast, the risk for CIN 2/3 remained high (4.4%) for initially HPV-positive women at 45 months and remained more than 7% at 10 years. These findings led the ACS, ACOG, and "Interim Guidance" to recommend that the subsequent combined Pap and HPV test should be done at least once in 3 years [93,97,99].

A normal Pap test result with a negative HPV test provides better prognostic assurance against the risk of future CIN 3 or high-grade disease than three subsequent negative conventional Pap tests for women aged 30 years and older and allows the safe extension of the interval from 3 to 5 years between cervical screenings [90,99]. Women younger than age 30 years have a high rate of hrHPV infection (15–46%), and most women testing positive have only transient infections [35,36, 114]. This may potentially result in the overtreatment of many women who have only transient HPV infections, thereby incurring unnecessary cost as well [115]. Only persistent hrHPV infection indicates that a patient is at risk for developing CIN 2/3 and cancer, and HPV positivity in sexually active women aged 30 years or younger is less likely to imply persistent HPV infection and high-grade lesions (CIN 2/3), unless the Pap results indicate ASCUS. HPV DNA testing is also recommended as an alternative to additional procedures (colposcopy and cytology) that often accompany an abnormal Pap result for follow-up of treated cases. Repeat HPV testing for persistent HPV infection should be performed after a year, because the usual clearance time reported for transient infection is 6–12 months [96,99]. Any woman remaining HPV positive should be referred for colposcopy, because there is a 1-in-4 risk for HPV-positive ASCUS to have CIN 2/3 during the subsequent 2-year follow-up [116], and approximately 1 in 500 women already has invasive cervical cancer [117].

Prophylactic HPV Vaccines

The discovery that HPV is etiologically linked with cervical cancer and genital warts has encouraged the development of vaccines that can potentially prevent cervical cancer. Prophylactic vaccination is given before HPV infection in order to help the immune system recognize and prevent viral entry before infection or before the disease becomes fully established in the host body. The vaccine needs to generate virus-neutralizing antibodies directed against the L1 and L2 capsid proteins that play a role in viral entry. The prophylactic vaccine approach became possible in 1991, after Zhou et al demonstrated that the HPV-16 L1 capsid proteins self-assembled into conformational VLPs that resembled native virions in a recombinant system [118]. VLP particles do not contain viral DNA and pose no infectious or oncologic risk to the individual receiving the vaccine. These particles are empty capsids that contain the major neutralizing epitopes (part of a macromolecule recognized by antibodies, B cells or T cells) of the native virion necessary for the induction of neutralizing antibodies [119,120]. The only problem that arises with this approach is that L1 VLP vaccines give type-specific protection [118,121]. Since HPV-16 and -18 account for approximately 70% of cervical cancers, vaccine development has focused on these hrHPV types. These vaccines can potentially prevent cervical cancers, cervical (CIN 1–3 and adenocarcinoma *in situ*), vaginal (VAIN 2/3) and vulvar (VIN 2/3) precancerous lesions.

The Merck vaccine (Gardasil) is a quadrivalent vaccine with HPV-6, -11, -16 and -18 VLPs and an adjuvant aluminum hydroxide that boosts immune response. Recombinant DNA technology has been used to produce L1 VLPs in recombinant yeast *Saccharomyces cerevisiae*. The results of the double-blind, randomized phase II trial of 2,392 women using the Merck vaccine demonstrated that the administration of HPV-16 L1 VLP vaccine reduced the incidence of both HPV-16 infection and HPV-16-related CIN [122]. The primary endpoint of this trial in the 2,392 young women was persistent HPV-16 infection (detection in consecutive visits) and HPV-16-related CIN. In 16- to 23-year-old women who were HPV-16-naïve at baseline, the vaccine was 100% effective; HPV-16 and CIN were detected in 41 unvaccinated (placebo) women but not in vaccinated women. The vaccine was generally well-tolerated, and there were no serious vaccine-related adverse events. Moreover, in a recent clinical trial, the Merck vaccine has demonstrated an overall 90% reduction in incident or persistent infection or genital disease associated with HPV types 6, 11, 16, and 18 [123]. Gardasil has completed phase III clinical trials and was licensed by the FDA on 8 June 2006 for use among girls and young adult females aged 9 to 26 years [124]. Gardasil is administered in a three-dose regimen as three 0.5-mL intramuscular injections (at 0, 2, and 6 months), which allows for the simultaneous injection of hepatitis B vaccine at a separate injection site, as stated in the package insert. The vaccine needs to be administered before people become sexually active, so it has been recommended for girls as young as 11 and 12 years of age over a 6-month period by the Advisory Committee on Immunization Practices, with catch-up immunization for girls and women 13 to 26 years of age and vaccination of girls at ages 9 and 10 at the provider's discretion [124]. A Stanford University study revealed that an effective vaccine could prevent 1,300 deaths if all 12-year-old girls currently living in the US received the vaccination, and that the cost of administering such a vaccine would be far less than the medical costs incurred by HPV [125]. Additional clinical trials are currently underway to establish the efficacy of the Merck quadrivalent vaccine. Other ongoing studies include

evaluating the effectiveness of Gardasil in boys and men aged 16 to 26 years, as well as in adult women aged 24 to 45 years [126]. It is important to evaluate the effect of vaccination in men, because HPV is linked to genital warts, as well as oropharyngeal, esophageal, penile and anal cancers in men; and vaccinating the men may also prevent transmission to women [127].

The other candidate vaccine (Cervarix) is a bivalent vaccine with HPV-16 and -18 VLPs, with an aluminum salt plus monophosphoryl lipid A (AS04) adjuvant to boost the immune response, currently under development by GlaxoSmithKline (GSK). The GSK vaccine is produced using baculovirus-infected insect cells. Similar to Gardasil, it is administered as three 0.5-mL intramuscular injections. However, the timing is different; it is to be given at 0, 1, and 6 months. Cervarix also appears to be up to 100% effective in preventing infections with HPV-16 and -18, as well as Pap test abnormalities and cervical dysplasia associated with these types [128]. A recent report by Harper et al [128] also suggested that Cervarix may provide cross-protection against HPV types 31 and 45. Cervarix has also completed phase III clinical trials but is currently still under review by the FDA; however, it was approved by the Australian Therapeutic Goods Administration in May 2007 for girls and women aged 10 to 45 years.

The most recent data by Harper et al [128] and Mao et al [129] suggest the extension of immunity beyond 4 years for both Gardasil and Cervarix. Goldie et al [130] reported that vaccination is expected to reduce the lifetime risk of cervical cancer by 70% to 83%, assuming that the HPV vaccine has an efficacy rate of 75% in the general population and that people maintain current Pap screening patterns. Clinical trials are still ongoing for both vaccines to determine the need for booster immunizations. Although HPV VLPs induce high titers of neutralizing antibodies even without adjuvant [131], both companies probably included aluminum-based adjuvants to reduce the dose required to induce peak antibody titers and to stabilize the vaccine during cold storage [132]. Alternate adjuvants might also be used to extend the duration of protection or reduce the number of immunizations.

Conclusion

The availability of both Merck and GSK HPV prophylactic vaccines should have an immense impact on HPV infection rates. Merck's quadrivalent vaccine for HPV not only reduces the potential mortality from HPV-induced cervical carcinoma, but it also protects the women from genital warts. However, both vaccines protect women against only two hrHPV types; they will still need screening for cervical cancer and the other hrHPV types that are responsible for the remaining 30% of HPV-induced lesions. Nevertheless, many issues remain to be addressed, including the duration of immunity, long-term safety, the optimal age for vaccination, and the optimal program of screening for cervical lesions. Cervical disease will continue to be a public health burden in developing nations. Both vaccination and screening will be difficult to accomplish in less developed countries. Women there frequently present with advanced disease at diagnosis, and treatment facilities are often limited in these developing countries. This review of the literature should provide some background for the readers on recently available HPV DNA testing and the administration of prophylactic vaccines. More importantly, it is our intention to summarize current trends in the prevention of cervical cancer. Although some clinical trials are still inconclusive, many clinical improvements have been observed in recent years. The expectation is that in a decade's time, we may observe a dramatic reduction of incidence of precursor lesions of this cancer, not only in Taiwan, but also worldwide. It is believed that investigation of an oral vaccine that could be easily delivered and administered in developing countries and a therapeutic vaccine for active treatment of cervical cancer are two ongoing objectives in the field of gynecologic oncology.

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