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Review Article

Human papillomavirus, genital warts, and vaccines

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Human papillomavirus (HPV)–related diseases, including cancers, low-grade neoplasia, genital warts, and recurrent respiratory papillomatosis, have a substantial impact on public health. The increasing incidence of HPV infection and genital warts highlights the need for an effective strategy for the management of this disease. Immunization holds the promise of reducing the overall burden of clinical HPV-related diseases. A prophylactic quadrivalent HPV 6/11/16/18 vaccine is highly effective for reducing the risk of HPV 6–, 11–, 16–, and 18–associated cervical cancer, precancerous cervical lesions, and external genital lesions, including genital warts.

Key words: Condylomata acuminata; Human papillomavirus; Papillomavirus vaccines

Introduction

Human papillomavirus (HPV), a non-enveloped, double-stranded DNA, preferentially infects basal epithelium through microabrasions and tissue disruption [1,2]. The association of HPV infections with cervical, anal, vulvar, vaginal, and oropharyngeal cancers, recurrent respiratory papillomatosis (RRP), and genital warts (condylomata acuminata) is well established [1,2]. Transmission of anogenital HPV-associated diseases primarily occurs through any activity that involves genital skin or oral mucosa contact, including genital-to-genital, manual-to-genital, or oral-to-genital contact [1,2]. Transmission of at least some types of anogenital HPV infection is not limited to penetrative sexual intercourse. HPV can also be transmitted via non-sexual routes including mother to newborn (vertical transmission) and fomites [1-3].

Disease Burden

The annual prevalence of HPV infection is estimated at 1% of the sexually active population in the United States and the incidence is increasing throughout Europe [2,4-8]. More than 500,000 new cases of anogenital warts occur every year in the United States, and the incidence of genital warts is increasing annually [1,2,4]. The rate of new cases of genital warts increased from 117.8/100,000 population in 1998 to 205.0/100,000 population in 2001 [2]. A report in 2003 indicated that approximately 1.4 million people in the United States had genital warts [2,4]. The highest rates of genital warts were noted in individuals aged 20 to 29 years. Approximately 10% of adults will develop anogenital warts at some point in their lives [1,2,5].

In the United Kingdom, diagnoses of genital warts increased by approximately 25% between 1996 and 2005 [9]. In 2005, new diagnoses of genital warts were made at genitourinary medical clinics for approximately 40,000 men and 32,000 women [1,2,9]. The highest rates were concentrated in men aged 20 to 24 years (750/100,000 population), and in women aged 16 to 19 years (700/100,000 population) and 20 to 24 years (650/100,000 population) [Fig. 1]. Young people aged 16 to 24 years accounted for 50% of cases of genital warts in 2007 [1,2,9].

In Spain, the overall annual incidence of genital warts was estimated at 160.4/100,000 population [6]. Overall, the prevalence was calculated to be 182.1/100,000 population, corresponding to 56,446 cases annually in the 14- to 64-year-old population.

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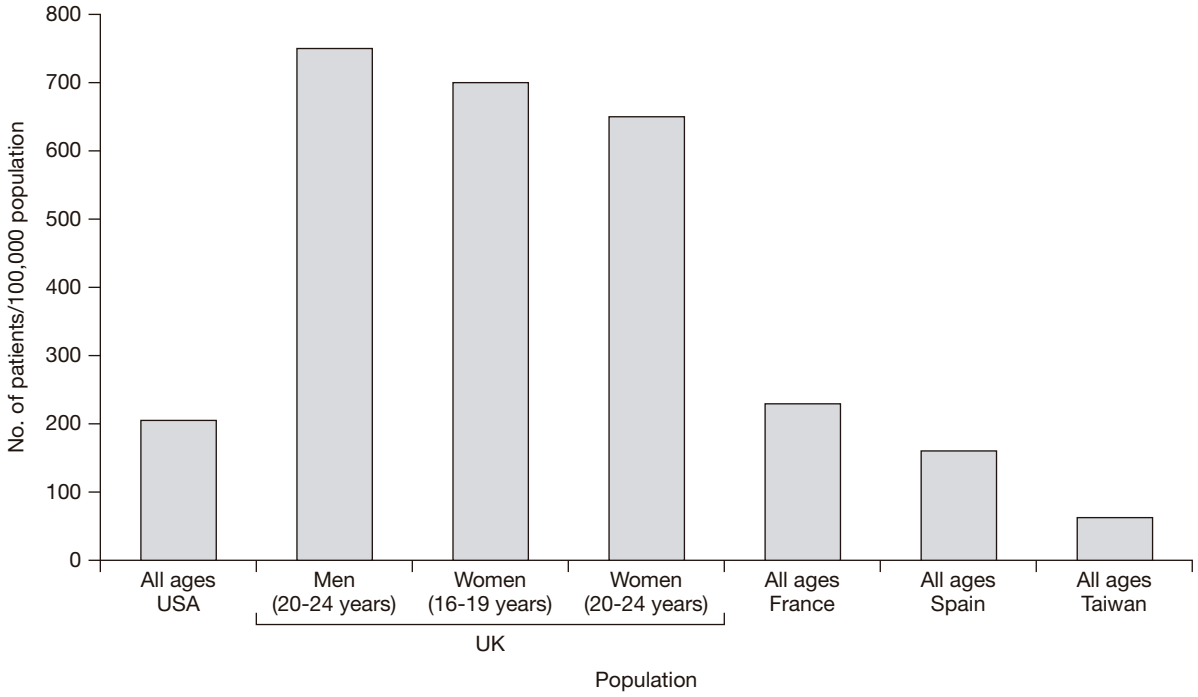

Fig. 1. Incidence of genital warts in selected countries.

In France, the overall incidence was estimated to be 228.9/100,000 population in women aged 15 to 65 years, corresponding to 47,755 cases managed by gynecologists annually [10].

In Taiwan, the overall incidence of genital warts is unknown [11-15]. Data from the National Health Insurance Research Database showed that the number of all-age patients who had visited urology and obstetrics/gynecology departments with the diagnosis of genital warts was 13,287 in 2002 and 14,261 in 2003. It is estimated that the incidence of genital warts in Taiwan was 57.8/100,000 population in 2002 and 62.0/100,000 population in 2003. Approximately 70% of these patients were women, with a mean age of 33 years (range, 1 to 94 years). More than 65% of patients were aged 20 to 39 years during 2002 and 2003 (Fig. 2).

Importantly, all of the incidence data from individual countries are likely to underestimate the real occurrence of genital warts, because this disease is likely to be underreported [1,2].

Human Papillomavirus Types

More than 100 different HPV types have been identified based on DNA homology, and approximately 40 of them are known to infect the anogenital tract [1]. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are classified as high-risk types. Among them, HPV 16 and 18 are the most common causes of infections and cervical cancers throughout the world. Low-risk HPVs include types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108 [1,2]. Infection with low-risk types (particularly types 6 and 11) can result in genital warts [1,2,4,6]. In general, more than 90% of genital warts and RRP are due to HPV types 6 and 11 [1,2]. However, HPV types 16 and 18 are frequently (60-70%) associated with cervical dysplasia and cervical and colorectal or anorectal cancer. Twenty five percent of low-grade cervical lesions and 50% of high-grade cervical lesions are associated with infection by HPV types 16 and 18 [1,2,4,16].

In Taiwan, the 5 most common HPV types by decreasing frequency for cervical cancer are HPV 16, 18, 58, 33, 52 and, for women with normal cytology, are HPV 16, 52, 58, 18 and 51 [14]. The prevalences of HPV in women with abnormal Papanicolaou smear test results, including atypical squamous cells of unknown significance (ASCUS)/atypical glandular cells of unknown significance (AGUS)–negative histology, ASCUS/AGUS, low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions, and invasive cancer are 33.8%, 38.3%, 74.9%, 84.3%, and 100%, respectively, with an overall positive rate of 68.8% [14]. The most common HPV types are HPV 16 (18.5%), 52 (16.5%), 58 (13.2%), 33, 51, 53, 18, 39, 59, 66, MM8, and 31 [13-15].

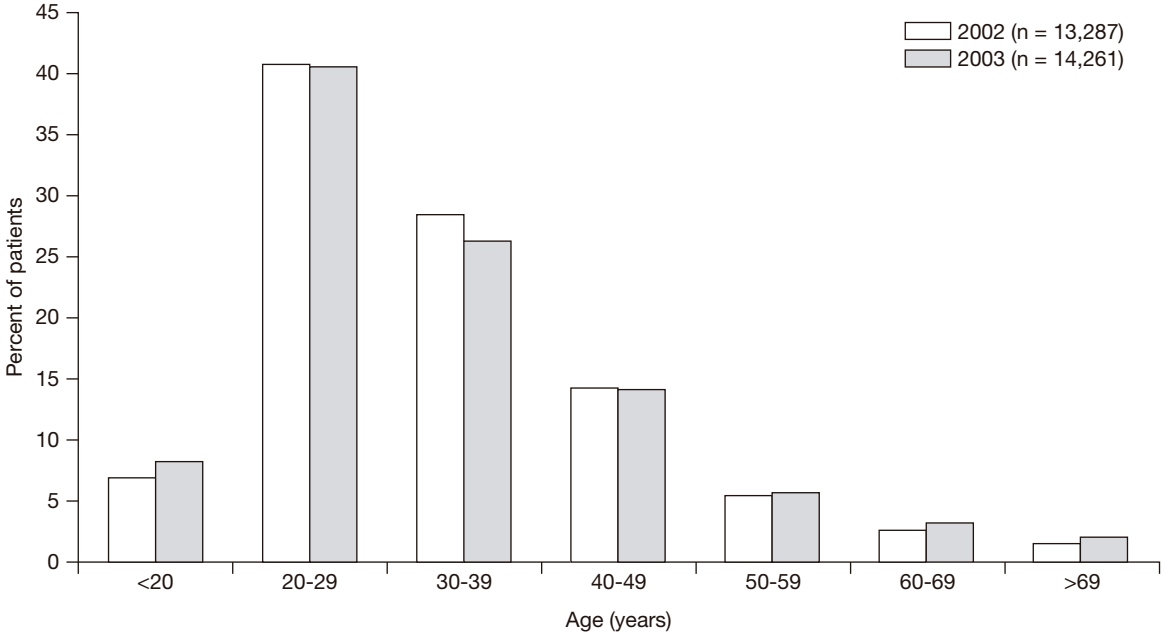

Fig. 2. Age distribution of patients who visited urology and obstetrics/gynecology departments with the diagnosis of genital warts in 2002 and 2003 in Taiwan. Data obtained from the National Health Insurance Research Database, Taiwan.

A study of HPV in 15 genital condyloma biopsy specimens by Southern blot hybridization, reported in 1994, found that 12 (80%) of the 15 condyloma specimens contained HPV 6 or 11 sequences [12].

Treatment and Prevention

Although genital warts are not life threatening compared with cervical cancer, they are common and can have a negative psychological impact [1,2]. The main causes of concern among men and women with genital warts include transmission, recurrence, local pain, cervical or penile cancer, and treatment efficacy [1,2,17,18]. Treatment for genital warts can also require multiple clinic visits for patients, which are associated with increased cost [5,11,19]. This cost was highest in young adults (US$1717/1000 person-years for women aged 15 to 24 years, US$1114/1000 person-years for women aged 25 to 34 years, and US$1692/1000 person-years for men aged 25 to 34 years) [5].

HPV cannot be eradicated therapeutically, so the primary treatment aim is removal of symptomatic warts [17,18]. These therapies include surgical excision, loop electrosurgical excision, laser treatment, and treatment with trichloroacetic acid, imiquimod, and podophyllin [1,17,18]. However, such treatments are often long and painful, with a high number of recurrent and resistant cases. Anogenital warts often recur within the first 6 months after initial diagnosis and therefore require repeated treatment sessions. In rare instances, anogenital warts become locally invasive and require extensive surgery for removal [1,2,17,18].

Total abstinence from all genital contact is the most effective method for preventing HPV infection [1,2,20]. Lifetime mutual monogamy is also an effective HPV prevention strategy. However, a monogamous individual is at risk from a non-monogamous partner. In a study of monogamous women, the risk of acquiring HPV was 46% at 3 years after first intercourse [1,2]. Condom use, which is essential for the prevention of other sexually transmitted diseases, reduces, but does not eliminate, the risk of HPV infection [1,2,5,20].

For natural cervical HPV infection, the immune response is slow and weak, occurring 6 to 12 months after viral acquisition and not occurring for all infected women [1,2,21]. In a study of the relationship between HPV DNA in the genital mucosa and serum antibodies to HPV 16, 18, and 6 performed among 588 women, approximately 40% of women did not develop a measurable response [21]. Furthermore, antibodies against one HPV type may not protect against subsequent reinfection with the same or another closely related type, and antibody responses vary with HPV type [21].

Prophylactic Human Papillomavirus Vaccines

Vaccination is currently regarded as one of the most effective strategies for controlling HPV-related diseases

[22]. A prophylactic quadrivalent HPV vaccine (HPV 6/11/16/18 vaccine [Gardasil®; Merck & Co., Inc., Whitehouse Station, NJ, USA]) contains virus-like particle (VLP) viral capsid proteins L1 of HPV types 6, 11, 16, and 18, which are synthesized in *Saccharomyces cerevisiae* and adsorbed on amorphous aluminum hydroxyphosphate sulfate adjuvant [23,24]. This HPV 6/11/16/18 recombinant vaccine was first licensed in the United States in June 2006, and subsequently in the European Union in September 2006. The vaccine has been shown to be up to 100% effective in preventing cervical cancer, precancerous cervical lesions, and external genital lesions, including genital warts. The presumed prophylactic efficacy of the vaccine against HPV 6/11/16/18–related genital warts was 98.9%, according to the United States Food and Drug Administration (FDA) in 2008 [23,24].

Another HPV vaccine (HPV16/18 vaccine [Cervarix®; GlaxoSmithKline Biologicals, Rixensart, Belgium]), a mixture of VLPs derived from the L1 capsid proteins of HPV types 16 and 18, is formulated with the AS04 adjuvant system [25-29]. This HPV16/18 vaccine was licensed in Taiwan in March 2008 for women aged 10 to 25 years for the prevention of cervical cancer by protecting against incident and persistent infections, cervical intraepithelial neoplasia (CIN), and precancerous lesions causally related to HPV types 16 and 18. The indication is based on demonstration of efficacy in women aged 15 to 25 years following vaccination with HPV 16/18 and on the immunogenicity of the vaccine in girls and women aged 10 to 25 years. However, this vaccine doesn't provide any protection against genital warts, which are mainly caused by HPV 6/11 [25-29].

In Taiwan, the quadrivalent, HPV 6/11/16/18 recombinant vaccine has recently received regulatory approval (in October 2006) for the prevention of cervical carcinoma, high-grade cervical dysplasia (CIN 2/3), low-grade cervical dysplasia (CIN 1), high-grade vulvar and vaginal dysplasia, and external genital warts for females aged 9 to 26 years [11].

The United States FDA has not approved the use of the HPV 6/11/16/18 recombinant vaccine for boys or men [1,2]. There are currently no published data demonstrating that the vaccine can protect men from getting genital warts or developing HPV-related cancers (such as penile cancer) [1,2]. A randomized, double-blind, placebo-controlled, phase III study of the efficacy of HPV 6/11/16/18 recombinant vaccine for preventing HPV-related external genital disease (genital warts, penile/perineal/perianal intraepithelial neoplasia or cancer) in men aged 16 to 26 years (men having sex with men [MSM] and heterosexual men) with 0 to 5 lifetime partners has been ongoing globally since 2003 (since 2005 in Taiwan) [1,2]. All participants were given vaccine or placebo at enrollment, month 2, and month 6, and underwent detailed anogenital examinations and sampling from the penis, scrotum, and anal (MSM cohort only) and perianal regions at enrollment, month 7, and every 6 months thereafter. The endpoints of this trial include HPV 6/11/16/18 infection and the incidence of HPV 6/11/16/18–related external genital lesions at 36 months. Preliminary data from this trial of 4065 participants at a mean duration of 29 months follow-up revealed that the reduction rate (compared with the placebo group) for all external genital lesions, genital warts, and penile/perineal/perianal intraepithelial neoplasia was 90.4% (case no. of vaccine group/case no. of placebo group, 3/31; $p < 0.001$), 89.4% (3/29; $p < 0.001$), and 100% (0/3), respectively.

A recent cost-effectiveness study using a transmission dynamic model to estimate the long-term epidemiologic and economic consequences of quadrivalent HPV vaccination was reported in 2008 [11]. Two vaccination strategies were evaluated, including vaccination of 12-year-old girls and vaccination of 12-year-old girls with a temporary 5-year catch-up vaccination for girls and women aged 12 to 24 years [11]. This study revealed that both vaccination strategies would reduce the overall incidence of HPV 16/18–related cervical cancer by 91% during year 100 following vaccine introduction. Thus, both vaccination strategies would reduce the incidence of CIN 2/3, CIN 1, and genital warts by approximately 90%, 86%, and 94%, respectively, at this time point [1,2,11]. The catch-up strategy is both more effective and efficient than the strategy that vaccinates 12-year-old girls only, with an incremental cost-effectiveness ratio of NT$410,477 or US$12,439/quality-adjusted life-year gained [11]. These researchers concluded that vaccination of women may not only substantially reduce genital warts, CIN, and cervical cancer, but also improve quality of life, survival, and cost-effectiveness [11].

In Spain, the mean management cost was €833 and €1056/patient from the Third Party Payer (TTP) and societal perspective, respectively [7]. The overall annual cost was estimated at €47 million and €59.6 million from the TPP and societal perspective, respectively [7]. In France, the annual direct cost of genital warts management was estimated at €23.1 million, of

which €16.4 million was funded by the French health care system [10].

Some controversy about the vaccine does exist. There is little information available on the duration of HPV vaccine–induced immunity [1-3]. There are no published data demonstrating that HPV vaccination in men can prevent transmission of HPV virus to women. For already-exposed women (women receiving HPV vaccine who have evidence of past or current HPV infection with HPV vaccine types), current vaccine trial data have demonstrated equivalent safety but no equivalent efficacy. HPV testing before initiating vaccination is not recommended because there are no good measures of past exposure and current clinically available testing reflects only recent viral shedding [2,3].

Conclusions

The increasing incidence of HPV infection and genital warts highlights the need for an effective strategy for the management of this disease. Even though many different treatment modalities exist, none of these have been proven to 'cure' the disease. Increasing public knowledge about prevention and transmission of HPV and genital warts is essential in the fight against these conditions. Immunization with HPV 6/11/16/18 recombinant vaccine holds promise for reducing the overall burden of clinical HPV-related diseases. Studies are ongoing to evaluate vaccine efficacy in girls and women aged 9 to 45 years and boys and women aged 9 to 26 years. A 10-year planned long-term efficacy and safety analysis, as well as pilot programs to evaluate vaccine impact on oropharyngeal HPV infection, particularly among human immunodeficiency virus-infected men, are also underway.

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