Review Article

Human papillomaviruses vaccine: A dermatologic perspective

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DOI: 10.4103/0378-6323.58673
PMID: 20061725

ABSTRACT

Human papillomaviruses (HPV) are responsible for both benign anogenital warts and malignant disease in humans, especially cervical cancer. Dermatologists in India recognize a great many cases of anogenital warts, and afflicted individuals may be at increased risk of coinfection with oncogenic HPV types. For this reason, dermatologists are in a position to identify potential carriers of oncogenic HPV types in the population. By targeting these individuals and their partners, as well as unaffected individuals for vaccination with the quadrivalent HPV vaccine, dermatologists have the ability to impact the morbidity and mortality of cervical cancer in India.

Key words: Human papillomavirus, vaccines, anogenital warts, cervical cancer

INTRODUCTION

Human papillomaviruses (HPV) are a family of viruses that cause infection in many species, most notably humans. Although the majority of these infections are benign, a percentage may be the instigating factor for malignancy, especially cervical and anogenital cancers. HPV is transmitted by contact, especially sexual contact, and is one of the most common sexually transmitted infections (STIs) worldwide. Anogenital warts, the most common manifestation of HPV infection, afflict almost 1% of the Indian population.[1] Globally, cervical cancer is the second most common cancer among women;[2] however, in India, it is the most common cancer in women of all ages.[3] Over 74,000 women in India die every year from cervical cancer.[3] The burden of HPV infection is unfortunately greatest in developing countries, such as India, due to lack of organized screening programs and social stigma of infection, which may prevent affected individuals from seeking medical attention. In addition, the lack of resources for large-scale immunization programs makes prevention of infection difficult.

In a dermatology practice, the majority of patients will present with HPV infections in the form of benign anogenital warts, the significance of which is not to be underestimated. The considerable morbidity of anogenital warts is often overlooked due to the stigma of the disease as an STI; however, HPV infection can have a major impact on an individual's physical and psychological health. Dermatologists also play a crucial role in the early recognition of cutaneous malignancies in which HPV is an etiologic factor. In addition, by joining in the movement for vaccination against HPV, dermatologists are in a unique position to help prevent the transmission of malignant concomitant HPV types to the partners of patients presenting for evaluation.

Background

HPV are small DNA viruses that infect a range of species, from humans to fish. There are over 100 different genotypes currently identified,[4] defined by differences in their nucleotide sequence. Many of these viruses have a predilection to cause infection in certain areas of the body; approximately 30 are known to cause disease in the genital area. HPV subtypes are classified into high-risk (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) and low-risk (HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108) for malignancy, with an additional three types identified as probable high-risk (HPV 26, 53, and 66).[5] HPV is one of the most common sexually transmitted diseases worldwide,[6] with a prevalence in sexually active adults thought to be greater than 50%. Despite the high rate of infection, 70-90% of HPV-infected individuals clear the virus naturally within 1-2 years, while only the

How to cite this article: Satyaprakash AK, Tyring SK. Human papillomaviruses vaccine: A dermatologic perspective. Indian J Dermatol Venereol Leprol 2010;76:14-9.
Received: December, 2008. **Accepted:** June, 2009. **Source of Support:** Nil. **Conflict of Interest:** None declared.

remaining percentage experience persistent infection. In the West, the greatest incidence of HPV infection is between the ages of 18-25, while in India, it is most common between the ages of 26-35, due to the later average onset of sexual activity.[4] Benign HPV infection generally manifests as a cutaneous wart on the hands, feet, or anogenital skin. Approximately 90% of benign anogenital warts are caused by HPV 6 and 11.[7] Infection with high-risk HPV genotypes contributes to malignancies of the skin, oropharynx, and anogenital area. In particular, persistent infection with high-risk HPV types has been proven as the causative agent for cervical cancer. Approximately 5-15% of women are infected with high-risk HPV types yearly,[8] and approximately 70% of cervical cancer cases globally are caused by HPV 16 and 18.[7]

Diseases caused by human papillomaviruses

HPV causes benign lesions of the anogenital area, skin, oropharynx, respiratory tract, and conjuctiva, as well as premalignant and malignant lesions in the uterine cervix, the anogenital area of both males and females, and the oropharynx. While all cases of cervical cancer can be attributed to HPV, the exact proportion of cancers in other anatomical sites attributable to HPV is more difficult to quantify due to the small size of most studies and the absence of prevalence measurements in unaffected individuals. Therefore, the fraction of cancers attributed to HPV is generally equated to the proportion in which HPV infection is detected in the affected area. Over 50% of sexually active adults worldwide, aged 15-25 years, are thought to be infected with one or more HPV types.[9] Although the majority of HPV infections seen in a dermatology practice will be benign anogenital warts, dermatologists are also in a position to recognize external genital, cutaneous, and oral malignancies and to educate their patients regarding transmission and prevention of HPV infection in their sexual partners.

BENIGN INFECTIONS

Genital warts

HPV infection has been known to cause multiple types of genital warts, and 5-25% of sexually transmitted disease (STD) clinic patients in India have been reported to have anogenital warts. Condyloma acuminata are the most conspicuous manifestation of HPV infection. Clinically, these appear soft, pink, and pedunculated, often with a cauliflower-like appearance, and are usually seen on moist, partially keratinized epithelium such as the preputial cavity, urinary meatus, labia minora, introitus, vagina, cervix, anus, and anal canal, as well as intertriginous areas. Papular warts are small, dome-shaped, and located on fully keratinized epithelium. Exophytic condyloma acuminata are nonpedunculated, firm, and papular, with a slightly rough surface; these are generally seen on dry, fully keratinized skin such as the penile shaft, outer aspect of prepuce, labia majora, and perineum. Sessile warts, small and smooth, are seen on the shaft of the penis. Flat warts, which are visualized best with acetowhitening, may exhibit a wavy-textured surface; these easily overlooked lesions may be located anywhere on the genital epithelium.[9] HPV 6 and 11 have been detected in up to 95% of condyloma acuminata, with the most common sites of infection in females being the vulva, vestibule, vagina, perineum, and perianal region; and the most common sites of infection in males being the penis, urethra, and perianal region. Areas of clinically normal skin adjacent to lesions have been shown to exhibit latent infection with detectable HPV DNA.[8] Interestingly, flat lesions on the penile surface are more likely to contain high-risk types of HPV.[10]

Other sites of benign infection

HPV 2, 4, 7, 26, 27, 28 and 29 commonly cause warts on the skin (most often on the hands, feet, knuckles, and periungual areas). Lesions of the respiratory tract, or respiratory papillomatosis, are most commonly caused by HPV 6 and HPV 11, acquired by vertical transmission in the perinatal period or by sexual transmission. One-third to one-half of children born to mothers with HPV genital infection are positive for HPV DNA by oral and respiratory swabs; however, only 1/400 children is at risk for respiratory papillomatosis. HPV can also cause papillomas in the oral cavity and in the conjunctiva.[8]

Malignant infections

Cervical cancer

An estimated 493,000 new cases of cervical cancer were recognized in 2002, along with approximately 274,000 deaths from cervical cancer in the same year. Of these cases, 80% occur in developing countries.[11] In India, the annual incidence is approximately 130,000 new cases, with 70-75,000 deaths anually; India carries greater than 25% of the global burden of cervical cancer-related deaths. HPV infection is considered a necessary condition for the development of cancer. The majority of cases are squamous cell carcinomas (SCCs), while adenocarcinomas are less common.[2] Globally, HPV 16 is most prevalent in SCCs, while HPV 18 is most prevalent in adenocarcinomas; together, HPV 16 and 18 account for 70% of cervical

cancers. In India, however, HPV 16 is the most prevalent type in both SCCs and adenocarcinomas, accounting for approximately 90% of all cervical cancers.[4,12] As cervical cancer affects women at a relatively younger age than other cancers, the years of life lost (YLL) worldwide in 2000 was estimated to be 2.7 million; cervical cancer is the largest single cause of YLL from cancer in the developing world.[2]

Other sites of malignant infection

HPV DNA (both HPV 16 and 18) has been found in 40-50% of all penile cancers, with lower incidences in populations with high rates of circumcision. HPV has been isolated by PCR from approximately 20-50% of vulvar cancers studied,[2] with incidence as high as 75-100% in the VIN-associated basaloid and warty types, and as low as 2-23% in the keratinizing, or verrucous, carcinomas.[13] Vaginal SCCs are preceded by vaginal intraepithelial neoplasia (VAIN). In PCR studies, the prevalence of HPV in these cancers is approximately 60-65%.[2] In several studies, 83-95% of anal cancers have proven positive for oncogenic HPV types.[14,15] Homosexual males have a significantly higher incidence. Infection risk is increased by preexisting HIV infection, as well as cigarette smoking, anal intercourse, and increasing number of lifetime sexual partners.[2]

HPV has been found in up to 50% of oropharyngeal and tonsillar cancers,[16] and oropharyngeal cancers have three times the likelihood of being HPV-positive than other head and neck cancers. Although HPV is an etiological factor in these cancers, the major synergistic risk factors are the use of tobacco and alcohol. Specifically in India, the use of chewing tobacco in the form of betel quid (betel leaf, slaked lime, areca nut, and tobacco), smoking bidis and cigarettes, and drinking crude, locally brewed alcohol have been linked with these cancers. Of note, women with *in situ* or invasive cervical carcinoma have a two- to four-fold increased risk of oropharyngeal cancers associated with HPV,[5] warranting close examination of the oral cavity in women known to have cervical cancer. Of specific interest to dermatologists, HPV types 5 and 7 have been linked to nonmelanoma skin cancers (NMSC) in organ transplant patients and individuals with epidermodysplasia verruciformis, as well as a percentage of NMSCs in immunocompetent individuals.[17]

Disease prevention

Prior to the development of prophylactic vaccines, prevention of HPV disease centered around transmission prevention and cervical cancer screening. Organized cytologic screening programs with pap smears have reduced the cervical cancer burden by 70-75% in developed countries during the past four decades.[18] In India, however, there is a lack or complete absence of screening in many parts, and the majority of cases are detected at late stages. Prior to the implementation of screening programs in developed nations, the incidence of cervical cancer was similar to that of developing nations today,[4] highlighting the importance of establishing organized screening programs for cervical cancer in India. With the advent of prophylactic vaccines, a method of prevention of anogenital lesions as well as cervical cancer now exists. In addition to vaccination and screening, however, widespread education regarding the relevance of HPV, route of transmission, and use of condoms to reduce transmission during sexual intercourse is necessary.

Vaccination

A prophylactic vaccine against HPV infection is currently approved for use in India. Gardasil® (Merck and Co., Inc.; Whitehouse Station, US) is a quadrivalent vaccine, effective against HPV types 6, 11, 16 and 18— the major types causing anogenital warts as well as cervical cancer. The vaccine utilizes the major capsid protein L1 of specific HPV types, which has the ability to self-assemble into virus-like particles. Infection is prevented through the induction of neutralizing antibodies against L1. Gardasil is currently dosed in a series of three intramuscular injections.

Results have been reported from large phase III clinical trials of the vaccine. The Females United to Unilaterally Reduce Endo/Ecto-Cervical Cancer (FUTURE) I study, a randomized, double-blind, placebo-controlled trial, with three years of follow-up in 5,455 healthy women aged 16-24, utilized the quadrivalent vaccine. This study showed 100% efficacy (95% CI = 94- 100) of the vaccine in preventing external anogenital lesions due to the vaccine genotypes (HPV types 6 and 11) in the protocol analysis and 73% (95% CI = 58-83) in the intention-to-treat analysis. Vaccine efficacy in preventing cervical lesions due to the covered genotypes (HPV types 16 and 18) was 100% (95% CI = 94-100) in the protocol analysis and 55% (95% CI = 40-66) in the intention-to-treat analysis. Some cross-protection against nonvaccine genotypes was also evident, as efficacy in the intention-to-treat analysis was 34% (95% CI = 15-49) in preventing external anogenital lesions and 20% (95% CI = 8-31) in preventing cervical lesions due

to any HPV genotype.[19,20] Five years after vaccination, in a Phase II study, the quadrivalent vaccine was shown to have 95.6% (95% CI = 83.3-99.5) efficacy in preventing persistent infection and 100% (95% CI = 12.4-100) in preventing disease (cervical dysplasia or genital warts associated with the vaccine types).[21] Similarly, the bivalent vaccine was shown to have 94.3% (95% CI = 53. 99.9) efficacy against persistent infection and 100% (95% CI = 42.4-100) efficacy against any type of CIN 4.5 years after vaccination.[22]

Studies are currently underway assessing the efficacy of the vaccination in males, and data will be available soon. Transmission of oncogenic HPV types throughout the population occurs via infected males. Male promiscuity has been associated with a 6.9-fold increase in cervical cancer in the female partner.[23] Some countries, such as Australia, New Zealand, and Mexico, have already approved the vaccination for use in males. If the vaccines are shown to have efficacy in males, vaccination of this population may contribute to decreasing the global burden of HPV, especially in areas where there is not high vaccine coverage in females.

Although a bivalent vaccine that protects against HPV types 16 and 18 is available, Cervarix (GlaxoSmithKline Biologicals; Rixensart, Belgium), it has not yet been approved for use in India. Both vaccines provide protection against cervical cancer, but the added protection of the quadrivalent vaccine against the HPV types that cause the majority of anogenital warts is of particular importance to dermatologists. The advantage with this formulation is while some at-risk patients, both male and female, may not recognize the importance of vaccination against an internal malignancy without external manifestations; they are more likely to embrace a vaccine that can prevent visible anogenital warts and the associated stigma. Widespread vaccination against anogenital warts carries the additional benefit of protection against cervical cancer as well as likely protection against many other HPV-associated malignancies. In addition, there is a potential for partners of vaccinated males to receive the indirect benefit of decreased transmission of concomitant high-risk HPV types. By recommending HPV vaccination to their patients, dermatologists can directly impact the morbidity and mortality of anogenital warts and cervical cancer in India, in both vaccinees and potentially, their partners.

Current American recommendations for the quadrivalent vaccination, given by the Centers for Disease Control (CDC) and American Academy of Pediatrics (AAP), are routine vaccination of girls ages 11-12 (in most cases, prior to the onset of sexual activity) and catch-up vaccination of girls ages 13-26.[2,24,25] Although women who are sexually active may have already been infected with HPV, vaccination confers protection against the remaining genotypes.[26] The vaccine can be given to patients who have abnormal or equivocal Pap smear results, who are breastfeeding, or who are immunocompromised (both acquired and iatrogenic).[25] Both HPV vaccines have shown a very high safety profile, although trials with vaccines utilizing highly immunogenic adjuvants such as AS04 reported greater reactogenicity (mainly local).[26] In translating these recommendations, it is important to note that the initiation of sexual activity and peak of HPV infection occur later in life in India than in the US. The Indian Academy of Pediatrics (IAP) currently recommends vaccination of females who can afford the vaccine prior to sexual debut. At this time, the vaccine is not covered under the Expanded Program on Immunization.[27]

Barriers to vaccination

Several barriers exist to introduction of HPV vaccines for widespread use in India and other developing nations. Historically, inhabitants of developing nations have had to wait decades before new vaccines became available through their national immunization programs.[28] Large-scale immunogenicity and efficacy trials must be conducted in these populations prior to approval for widespread use. Vaccination of adolescents, especially in three doses, is more logistically difficult than vaccination of newborns. Social attitudes toward sexual behavior in India are more conservative than those of Western nations, and thus the acceptance of a vaccine for an STI is likely lower. Lack of education relating to vaccines and the fear that the vaccine may actually cause the disease it is intended to prevent may also decrease acceptance. The vaccine is relatively expensive, and long-term efficacy has yet to be proven, both of which are barriers to appropriation of resources for its inclusion in mass vaccination programs. In addition, the HPV vaccine must compete for already scarce resources against vaccines for other diseases that cause significant morbidity and mortality in childhood. Although both the bivalent and quadrivalent vaccines protect against HPV 16, the most prevalent type in India, there is no vaccine that protects against all oncogenic HPV types. Thus, there will be a continued need for screening of vaccinated women, as there is no guarantee that they will not develop cervical cancer from another HPV types.

Solutions

A cost-effective vaccine could be produced by manufacturers in India for distribution within the nation, if permitted by the pharmaceutical companies that developed these vaccines. Most of the vaccines used in developing nations currently come from manufacturers in developing countries.[4,28,29] Childhood vaccination for HPV is an alternate strategy to adolescent immunization which would allow utilization of existing immunization programs, but studies must first be conducted regarding the safety and long-term efficacy of these vaccines when used in children.[4,28] The presentation of HPV vaccination as one that targets cervical cancer, instead of one that targets an STI, may help increase its acceptance. The utilization of agencies and individuals that are experienced in navigating cultural issues relating to sexuality will be important in educating the public, training healthcare workers to speak to their patients about these vaccines, and influencing the media and government healthcare policy-makers.[28]

Summary

HPV infection causes benign cutaneous manifestations as well as malignant lesions. The benign lesions cause considerable morbidity in the lives of the affected, while the malignant lesions cause significant morbidity as well as mortality. The global burden of HPV is significant, especially with respect to anogenital warts and cervical cancer. Developing nations shoulder the greatest burden of HPV infection, with India having the largest portion of cases. As malignant lesions are often detected at later stages in the developing world, a major goal is prevention of these diseases as well as early detection. Although effective vaccines have been developed against the most pathogenic HPV types, there are several barriers to their widespread use. There is also a lack of resources for implementation of an organized screening program for cervical cancer. In order to decrease the burden of HPV infection in India, there must be nationwide education regarding HPV, acceptance of the vaccines, and allocation of resources to screening programs and adolescent immunization against HPV. For this to occur, there is a need for vocal proponents for widespread prophylactic vaccination against HPV, as well as a need to rise above the stigma of HPV as an STI and recognize the true impact of the infection on the lives and health of those affected. As dermatologists in India recognize many cases of anogenital warts, they share the responsibility of patient education and advocating for HPV vaccination and should become the vocal proponents that are sorely needed. Early vaccination against HPV can significantly reduce the morbidity of anogenital warts as well as the morbidity and mortality of cervical cancer in India.

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Multiple Choice Questions

1. Human papillomaviruses are a type of:
   a) RNA virus b) DNA virus
   c) Protein virus d) Mitochondrial virus

2. The following HPV subtype is not a high-risk type for malignancy:
   a) 31 b) 11
   c) 16 d) 18

3. HPV subtypes 6 and 11 cause what percentage of anogenital warts?
   a) 50% b) 70%
   c) 90% d) 100%

4. HPV subtypes 16 and 18 cause what percentage of cervical cancers?
   a) 50% b) 70%
   c) 90% d) 100%

5. What is the number of deaths yearly from cervical cancer in India?
   a) 75,000 b) 130,000
   c) 274,000 d) 493,000

6. Which HPV type is not covered by the quadrivalent vaccine?
   a) 6 b) 11
   c) 16 d) 31

7. What is the risk for respiratory papillomatosis in a child born to a mother with HPV genital infection?
   a) 1/200 b) 1/300
   c) 1/400 d) 1/500

8. Which type of cancer has not been linked to HPV infection?
   a) Skin b) Penile
   c) Uterine d) Vaginal

9. What percentage of oropharyngeal and tonsillar cancers have been found to contain HPV?
   a) 30% b) 40%
   c) 50% d) 60%

10. Which population of women cannot receive the quadrivalent HPV vaccine?
    a) Breastfeeding b) Already infected with HPV
    c) Immunocompromised d) None of the above

Answers
1. b, 2. b, 3. c, 4. b, 5. a, 6. d, 7. c, 8. c, 9. c, 10. d