

# Continuing Education for Pharmacists

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## Cervical Cancer: Prevention by Immunization Against Human Papillomavirus Infections

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**Goals.** The goals of this lesson are to discuss the association between human papillomavirus infection and cervical cancer, and describe the new vaccine to prevent HPV infection.

**Objectives.** At the conclusion of this lesson, successful participants should be able to:

1. summarize key points relative to the human papillomavirus (HPV);
2. identify the pathological response to infection by HPV;
3. describe the new vaccine for prevention of HPV infections in terms of its physiological and clinical characteristics; and
4. select from a list important points to convey to patients relative to the new vaccine.



Gossel



Wuest

### Introduction

About 1400 women worldwide are diagnosed with cervical cancer every day, resulting in more than 500,000 new cases and 276,000 deaths annually. More than 10,000 new cases of cervical cancer will be diagnosed and 4000 deaths recorded in the U.S. in 2006. Human papillomaviruses (HPVs) are the primary cause of cervical cancer. In fact, of the 10 million cases of all types of cancer that develop annually throughout the world, more than 15 percent are estimated to be attributed to infectious agents. Infection by HPVs accounts for approximately 30 percent of virus-induced cancers.

### Etiology and Pathogenesis

**HPV Infection.** HPV infection is believed to be the most common sexually transmitted infection in the U.S. and worldwide. The HPVs include a group of approximately 120 small DNA viruses, of which about 40 can infect the epithelial lining of the genital tract. Of the approximate 40 types, HPV 16 and HPV 18 are considered high-risk oncogenic types, and account for development of about 70 percent of all cervical cancer cases. In addition to cervical cancer caused by HPV types 16 and 18, infection with low-risk HPV types such as 6 and 11 can result in anogenital warts

(condyloma acuminata), which are outgrowths of the cervicovaginal or vulvar tissues and external genitalia. They rarely cause cancer. The HPVs also cause other, less common, types of cancer (Table 1). Among them are vulvar and vaginal cancer in women and penile cancer in men.

Epidemiological evidence linking cervical cancer with HPVs was confirmed in the 1980s when HPV DNA was identified in virtually all cervical cancer cells and precursors. It is now accepted that HPV infection is necessary for development of virtually all cervical squamous cell carcinomas and adenocarcinomas. HPV infection is usually transmitted during sexual intercourse. The risk of infection within five to seven years of the first sexual contact is 50 percent, with a 70 percent lifetime risk. One study of more than 600 female university students revealed that 24 months after sexual activity, the incidence of HPV infection was 40 percent. Most HPV infections are transient (i.e., benign), however, and only 3 to 10 percent of women will become persistent HPV carriers and constitute the high-risk group who will contract cervical cancer.

Condoms offer limited protection against HPV transmission. Perinatal infection may occur via maternal transmission, through amniotic fluid during gestation or delivery, or direct exposure to HPV lesions of the cervix or genitalia during birth, thus resulting in laryngeal papillomatosis. This rare, but debilitating, disease results in papillomas (benign tumors derived from epithelium) that obstruct the airway. Postnatal transmission by non-

**Table 1**  
**Cancer types attributed to HPV Infection**

Cancer Type	Association With Certain HPV Types (%)
Cervical*	≥95
Vaginal*	50
Vulvar*	>50
Penile	50
Anal	>70
Oropharyngeal	20
Nonmelanoma skin/cutaneous	90†

\*Includes cancer and intraepithelial neoplasias

†Immunocompromised patients

Adapted from Pichichero ME. *Clin Pediatr* 2006;45:393.

sexual activities has also been documented.

**Risk Factors.** Young age (20 to 24 years for females; 25 to 29 years for males) is the most significant risk factor for development of HPV infection. Most risk factors (Table 2) are linked to sexual behavior, including the total number of sexual contacts. Women who are HPV-positive for type 2 herpes simplex virus (HSV-2) or *Chlamydia trachomatis* antibodies are at moderately increased risk. Males who are not circumcised are at increased risk of acquiring HPV infection or transmitting it to a sexual partner of either gender. Having sexual intercourse at an early age is a risk factor for females, as well as having intercourse with sexually promiscuous male partner(s). HPV-positive women who report seven or more full-term pregnancies have a four-fold increased risk of cervical cancer as compared to similar HPV-positive women who are nulliparous (have never given birth). Smoking is associated with a two-fold statistically significant increased risk of cervical cancer. Among HPV-positive women, any use of oral contraceptives is associated with an increased risk of cervical cancer.

**Cervical Cancer.** In women worldwide, cervical cancer is second to breast cancer as the most common cancer, and generally the most common cause of death from cancer. It is the eleventh most common cancer among women in the United

States. In developing countries, cervical cancer is the most frequent cancer in women, with more than 80 percent of new cases appearing in these locales.

#### **Prognosis of Human Papillomavirus Infection**

Seventy to 90 percent of HPV infections are transient in women at high risk for HPV infection. The median duration of new HPV infection shown in a longitudinal study of female university students was eight months. Infection is considered persistent when the same HPV type can be detected two or more times in the same woman within several months to a year. Factors correlated with persistent HPV infection include older age, high risk types of HPV (i.e., HPV 16 and/or 18), infection with multiple types of HPV, and immune suppression. Consecutive premalignant stages (i.e., cervical intraepithelial neoplasias [CIN]) are involved in progression from persistent infection with HPV to cervical cancer, usually over a period of 12 to 15 years.

**Cervical Screening.** Cancer of the cervix is unique among malignant diseases. It has a well-characterized and long-lasting pre-invasive phase which invariably precedes clinical cancer. Cervical cancer prevention, therefore, focuses on routine screening with the Papanicolaou test (Pap smear) followed by early intervention. The Papanicolaou test aids detection of early

dysplastic (abnormal tissue growth) and neoplastic cellular changes, thereby reducing cancer-associated mortality by more than two thirds. Countries with organized cervical cancer screening programs report a marked reduction (in compliant individuals) of nearly 75 percent in the incidence of invasive cancer.

Cervical screening imposes technical limitations and results are sometimes difficult to interpret. Moreover, screening and treatment are not equally accessible to all groups of women; more than half of all cervical cancer cases in the United States occur in women who have never or rarely been screened. Although the Papanicolaou test is significant from its historical perspective, its impact on the incidence of cervical cancer, and its position as the most widely used cancer screening test in the world, must be realistically considered. Recent publications suggest that the sensitivity of the Pap smear is only 50 to 60 percent.

Cost-effective public health strategies designed to reduce the risk of cervical cancer in vulnerable groups are a high priority. From a national policy perspective, among the most pressing concerns are the escalating costs associated with current screening practices. For example, more than \$6 billion is spent each year in the United States on the evaluation and management of low-grade lesions, the majority of which would regress naturally without intervention. At present, these lesions cannot be identified as such. The need for a vaccine to prevent HPV infection, and thus cervical and other less common cancers, is therefore apparent.

#### **Quadrivalent HPV (Types 6, 11, 16, 18) Recombinant Vaccine**

A non-infectious recombinant, quadrivalent vaccine (Gardasil/Merck & Co., Inc.) has been approved for use in the United States. It is prepared from the highly purified virus-like particles (VLPs) of the major capsid protein of HPV

Types 6, 11, 16, and 18. Vaccine proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae*, and assembled into VLPs. VLPs are morphologically and antigenically similar to natural virions and, consequently, induce a potent neutralizing immune response following vaccination. They do not contain the viral genome and, therefore, cannot spread infection.

Efficacy was assessed in an early clinical trial involving 552 young women (age 16 to 23 years) who received the vaccine or placebo. The primary end point was the combined incidence of infection with one or more of the oncogenic (cancer causing) HPV types, or cervical or external genital disease (i.e., persistent HPV infection, HPV detection at the last recorded visit, CIN, cervical cancer, or external genital lesions caused by one of the HPV types in the vaccine). Vaccine efficacy was 100 percent for prevention of clinical disease associated with the HPV types. Overall, the combined incidence of persistent infection or disease with HPV types 6, 11, 16, or 18 declined by 90 percent in women who received the vaccine compared with those given placebo. The study was not powered to assess vaccine efficacy for specific disease end points. Only six women (all in the placebo group) developed genital warts or type-specific CIN during follow-up. The vaccine proved to be highly immunogenic, with all patients showing evidence of HPV 6-, 11-, 16- and 18-specific antibodies following vaccination. There were no serious vaccine-related adverse events.

A more recent study enrolled 12,167 women aged 16 to 26 years at 90 centers in 13 countries. The study was double-blinded; women were randomized to receive three doses of the quadrivalent vaccine or placebo over six months. Recipients of a full course of vaccine who were free of infection with HPV types 16 and 18 at month 7, were 100% infection free at 17 months. In the 5301 vaccinated women, there were

no observed cases of high grade precancers or non-invasive cancer (CIN 2 or 3 or adenocarcinoma) related to HPV 16 or 18. There were 21 cases in the women who received placebo.

**Mechanism of Action.** HPV is specific for humans, but animal studies with papillomaviruses suggest that the efficacy of the VLP vaccines is attained through development of immune responses. Gardasil prevents HPV 6-, 11-, 16-, and 18-related cervical cancer, cervical dysplasias, vulvar or vaginal dysplasias, or genital warts from occurring.

**Adverse Effects.** In pre-marketing clinical trials, vaccine-related adverse experiences included pain, swelling, redness, itching, and fever.

Gardasil may be given concomitantly with hepatitis B vaccine (recombinant) but at a separate injection site. Co-administration with other vaccines has not been studied.

Subjects in premarketing clinical trials who used hormonal contraceptives did not experience an altered response to the vaccine. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and high doses of corticosteroids, may interfere with the immune response to vaccines.

Hypersensitivity to the active substances or to any excipients in the vaccine is a contraindication to its use. Individuals who develop symptoms suggestive of hypersensitivity after receiving a dose of Gardasil should not receive further doses.

**Indications and Uses.**

Gardasil is indicated for prevention of the following diseases caused by HPV types 6, 11, 16, and 18 in girls and women nine to 26 years of age:

- Cervical cancer
- Genital warts (condyloma acuminata) and the following precancerous or dysplastic lesions:
  - Cervical adenocarcinoma

*in situ*

**Table 2  
Risk Factors for Human  
Papillomavirus Infection**

**Females**

- Young age (peak age group, 20 to 24 years)
- Lifetime number of sexual partners
- First sexual intercourse at early age
- Male partner's overall sexual behavior
- Smoking
- Oral contraceptive use
- Previous pregnancies
- Uncircumcised male partners

**Males**

- Young age (peak age group, 25 to 29 years)
- Lifetime number of sexual partners
- Lack of circumcision

Adapted from: Pichichero ME.  
*Clin Pediatr* 2006;45:393.

- Cervical intraepithelial neoplasias grade 2 and grade 3
- Vulvar intraepithelial neoplasias grade 2 and grade 3
- Vaginal intraepithelial neoplasias grade 2 and grade 3
- Cervical intraepithelial neoplasias grade 1

The vaccine does not protect against infection by HPV types not contained in the vaccine or diseases that are not caused by HPV. Individuals with impaired immune responsiveness, whether due to use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization. Safety and efficacy have not been assessed in girls younger than nine years or women older than 26 years.

As is true with other intramuscular injections, Gardasil should not be given to individuals with bleeding disorders, including hemophilia or thrombocytopenia, or to individuals using anticoagulant therapy, unless the potential benefits from the vaccine clearly outweigh the risk of administration. If the decision is made to administer Gardasil to such persons, it should be given cau-

tiously with measures to avoid the risk of hematomas.

**Dosage, Administration, and Availability.** Gardasil is given intramuscularly as three separate doses: first dose at a chosen date, second dose two months after the first dose, and third dose six months after the first dose. Injections should be administered in the deltoid region of the upper arm or in the higher anterolateral area of the thigh. The vaccine should not be injected via any other site.

Gardasil is available in prefilled syringes and vials for single use. The vaccine should be stored under refrigeration, brought to room temperature, and shaken well before use. No dilution or reconstitution of contents is necessary.

**Patient Information.** Information to convey to the patient, parent, or guardian includes the following points:

- Vaccination does not substitute for routine cervical cancer screening. Women who receive Gardasil should continue to undergo cervical cancer screening.
- Be sure to read the information that is provided with each vaccination.
- Report any adverse reaction to the vaccination to your physician.
- Do not receive the vaccine if pregnant.
- This vaccine is maximally effective following three injections spread over six months. Be sure to complete the immunization series, unless contraindicated.

### **Anticipated Impact of HPV Vaccination in the United States**

It is difficult at present to predict the impact of the new vaccine on HPV infection and cervical and other cancers caused by HPV. However, it is possible to arrive at some estimates. The greatest short-term impact in developed nations such as the United States will be a reduction in the overall number of CIN 2 or 3 cases to about one-third to one-half as many such lesions in vaccinated women compared with

non-vaccinated women, given that, as noted earlier, HPV 16 and HPV 18 together account for approximately 70 percent of such lesions. This level of protection can translate to a substantial reduction in morbidity and treatment together with a reduction in related costs. The eventual reduction in the incidence of cervical cancer and its consequences can be anticipated to be at least as great. If the vaccine were widely administered to populations that historically are less likely to be screened regularly, it could prevent most serious infections that currently are not detected. The impact on subclinical and low-grade dysplasias would be expected to be more modest, since only a minority of these infections are attributable to HPV types 6, 11, 16, or 18. Although these anticipated reductions in CIN 2 or 3 and invasive cervical cancer are impressive, it must be recalled that there would still be many serious HPV infections against which the vaccine will not protect. Therefore, it will still be necessary for vaccinated women to follow the most current cervical cancer screening guidelines.

Another HPV vaccine for use in women is also in development, but was not yet available at the time this lesson was prepared. GlaxoSmithKline is testing a bivalent vaccine against HPV types 16 and 18 that is also administered in three doses (at birth, one month, and six months).

### **Vaccine Use in Males**

Although the immune response of men to the approved vaccine seems to be similar to that of women, it is not known whether the vaccine will confer protection in men or reduce their ability to transmit HPV to others. Gardasil is not approved for use in men.

While many vaccines have comparable efficacy in males and females, a subunit vaccine for herpes simplex virus (HSV-2), another sexually transmitted viral infection, was shown to be effective

in women but not in men. This raises the possibility that an analogous difference might be noted with the HPV vaccine. HSV-2 infection is more likely to be mucosal in women and cutaneous in men; therefore, the difference in protection from the HSV vaccine might be attributable to higher antibody titers in mucosa than in skin. At the same time, the high level of protection afforded by the new vaccine against cutaneous genital warts in women would also be expected to apply to men, since these warts appear on keratinized skin in both genders. Future efficacy trials of the HPV vaccine in men will most likely address this issue.

### **Overview and Conclusion**

The thought that cervical cancer and other cancer types caused by HPV can be safely and effectively prevented by a vaccine is both exciting and challenging. Candidates for the new quadrivalent HPV vaccine now have a means of protection against HPV infection caused by four common HPV types. HPV vaccination will most likely result in health gains that will justify the cost.