

HPV and the Prevention of Cervical Cancer

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Summary

Human papillomavirus (HPV) infection has many significant clinical outcomes, including the development of cervical cancer. The consequences of HPV infection are costly in terms of both direct and indirect costs. A significant advance in the prevention of cervical cancer and other adverse outcomes from HPV has occurred with the introduction of a vaccine to prevent infection with the major types of HPV.

Key Points

- HPV infection is very common and has significant consequences, including cervical cancer and genital warts.
- HPV transmission occurs through skin-to-skin contact.
- The majority of cervical cancer cases are caused by HPV infection.
- The currently available vaccine covers the four types of HPV responsible for 90 percent of genital warts and 70 percent of cervical cancer cases.

HUMAN PAPILOMAVIRUS (HPV) IS A common virus. In 2005, the Centers for Disease Control and Prevention (CDC) estimated that 20 million people in the United States had this virus.¹ The annual incidence of HPV infection is approximately 6 million cases.¹ Overall, an estimated 75 percent of sexually active men and women have HPV infection or have been exposed to HPV at some point in their lives (Exhibit 1).² Fifteen percent of

persons aged 15 to 49 are currently infected.³

There are more than 100 different types of HPV (Exhibit 2).¹ HPV can be divided into cutaneous and mucosal types. The cutaneous types cause common warts on the hands and feet. The mucosal types target warm-moist skin surfaces of the anal, genital, and oral pharynx regions. The mucosal types can be further divided into low- and high-risk groups. HPV 6 and 11 are examples of low-risk types that can lead to

Exhibit 1: HPV Infection in the United States

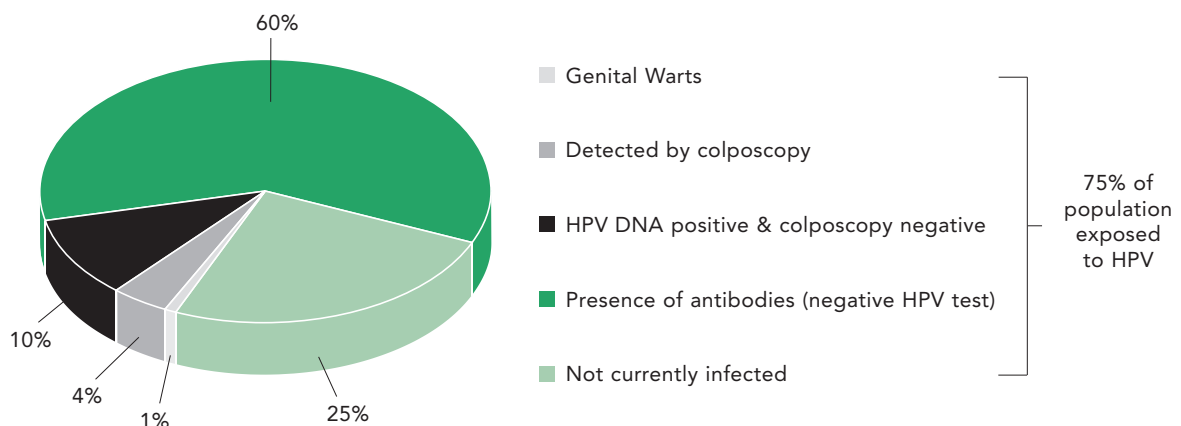
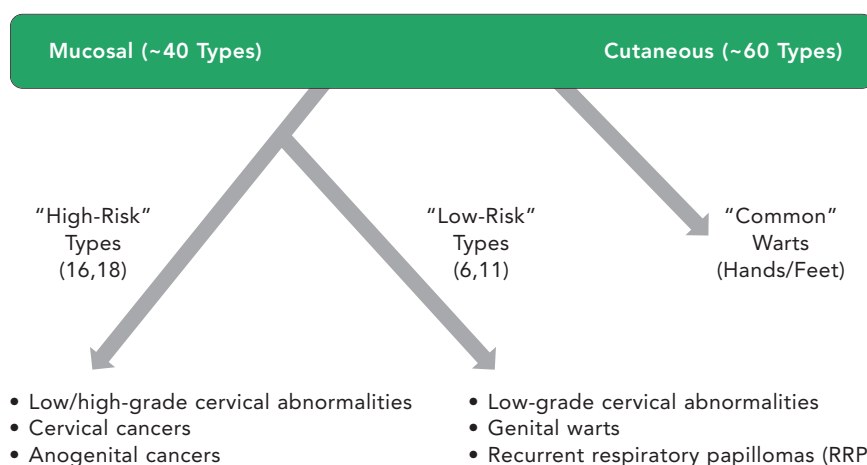


Exhibit 2: >100 Human Papillomavirus Types



mild cervical dysplasias, genital warts, and recurrent respiratory papillomatosis. HPV 6 and 11 are responsible for 90 percent of genital warts.¹ High-risk HPV refers to the potential to lead to a malignancy. The low-risk types very rarely lead to a malignancy as opposed to the high-risk types which produce both low- and high-grade cervical lesions, cervical cancers, and cancers involving the anal genital tract. HPV 16 and 18 account for about 60 percent to 70 percent of moderate and severe dysplasias, nearly all cervical cancers, and a subset of other cancers affecting the anal and genital region, both in men and in women.^{1,4} HPV 6 and 11 (low-risk types) and HPV 16 and 18 (high-risk types) account for a significant number of the consequences of HPV infection (Exhibit 3).⁴⁻¹⁰

A worldwide clinical study found virtually all (99.7 percent) cases of cervical cancer were linked to certain oncogenic types of HPV.¹¹ It is also important to note that 85 percent of anal cancer cases are caused by HPV infection. See Exhibit 4 for a summary of

Exhibit 3

HPV Types 16 and 18 are responsible for:

- ~70 percent of cervical cancers
- ~50 percent to 60 percent of high-grade cervical dysplasias (CIN 2/3)
- ~25 percent of low-grade cervical dysplasias (CIN 1)

HPV Types 6 and 11 are responsible for:

- ~90 percent of genital warts
- ~9 to 12 percent of low-grade cervical dysplasias (CIN 1)

CIN, cervical intraepithelial neoplasia; References: 4-10

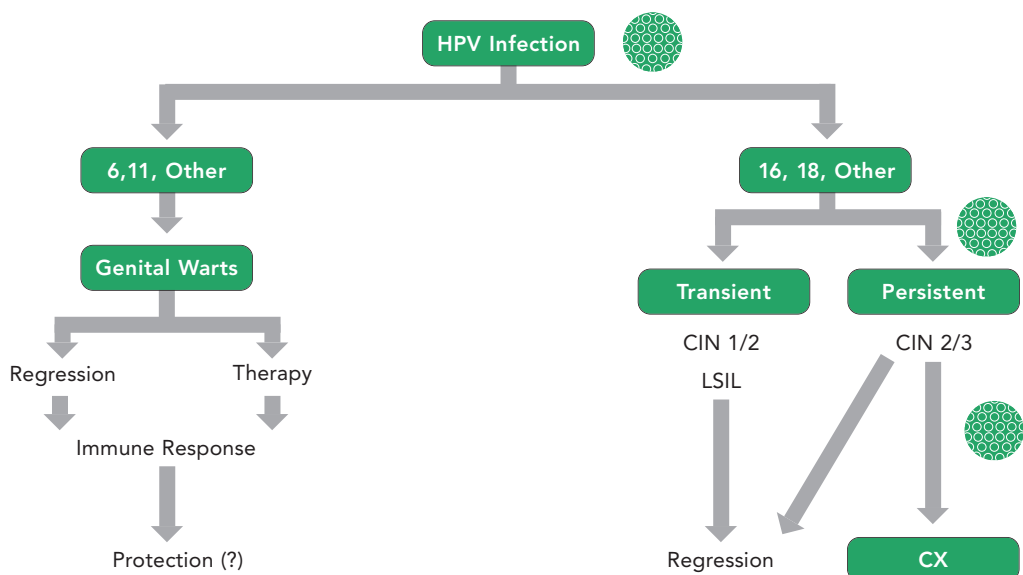
cancers attributable to high-risk HPV types.¹²⁻¹⁴

HPV is a local infection of stratified squamous epithelium. Patients can have multiple types and sites of HPV infection at the same time, including multiple high-risk types or a mix of high- and low-risk types. HPV does not cause a viremia nor does it spread throughout the body. It remains localized, which may explain why many individuals do not

Exhibit 4: Cancers Attributable to High-Risk HPV

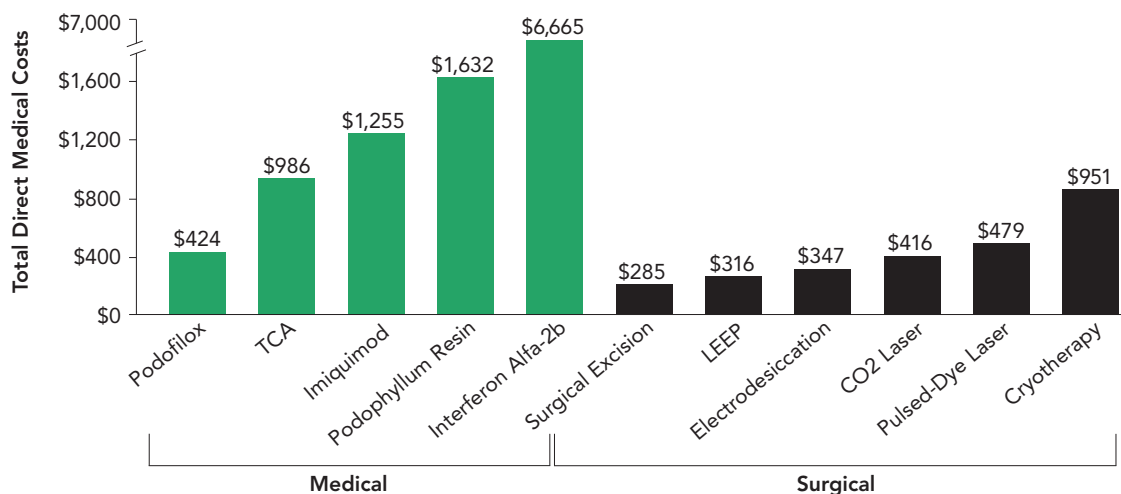
Site	Total Cancers*	HPV Attributable Fraction (%)	Estimated No. Attributable to HPV
Cervix	12,085	100	12,085
Anus	3,703	85	3,148
Vulva/vagina	4,480	50	2,240
Penis	985	40	394
Oral/pharyngeal	10,088	15	1,514

Exhibit 5: The Natural History of HPV and Cervical Cancer



LSIL= low grade squamous intraepithelial lesion; CX=cervix

Exhibit 6: Healthcare Costs Associated with Treatment of Genital Warts



Total Costs per Complete Clearance of Simple and Extensive Condylomata by Various Modalities*

*Includes costs of physician visits (initial visits and subsequent treatment visits) and costs of medications/procedures; LEEP = loop electrosurgical excision procedure; TCA= trichloroacetic acid

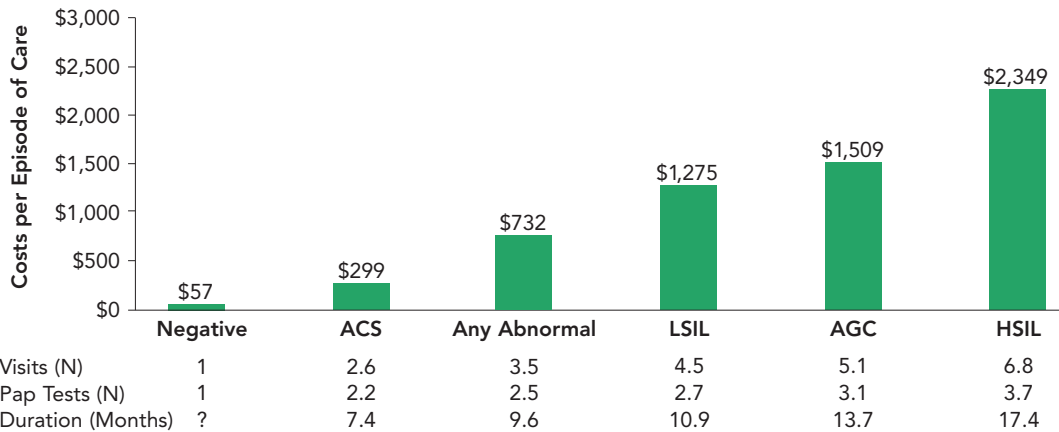
mount an appropriate immune response. Only 60 percent of women develop HPV antibodies following natural infection. Because of this lack of appropriate immune response as a marker of previous infection, prevalence of past HPV infection is estimated to be as high as 41 percent among women ages 20 to 29 years.¹⁵

HPV transmission occurs through skin-to-skin contact. Micro skin tears allow HPV to cross into the

skin through the protective epithelial surface. The most effective mode of transmission is sexual intercourse. There is a distinct relationship between an increasing number of lifetime sex partners and the likelihood of being HPV positive.¹⁶

Figure 5 illustrates the natural history of HPV infection.^{1,17} With low-risk types, regression follows a natural immune response on the part of the body. The infected person will have an itchy lump or

Exhibit 7: Healthcare Costs of Cervical HPV



*Average age adjusted to the 1998 U.S. female population; All cost estimates were converted to 2002 dollars; ASC= atypical squamous cells; AGC= atypical glandular cells; HSIL= high-grade squamous intraepithelial lesion

bump in his or her genital region, which goes away after a few weeks or months. This previously infected person is thought to be protected from further infections with that strain of HPV. With the high-risk types, transient or persistent infections can occur. The majority of transient infections will clear without therapy. Persistent infection leads to more severe precancerous changes—moderate and severe dysplasias. The majority of severe dysplasias will develop into invasive cervical cancer. Currently, there is no way to distinguish between transient and persistent infections, which leads to the need for a preventive strategy.

There are an estimated 1 million new cases of genital warts each year in the United States.¹⁸ Studies have shown that up to 30 percent of genital warts cases spontaneously regress within 4 months.¹⁹ For those patients who undergo and respond to treatment, 25 percent of cases recur within three months of clearance.¹⁹

There are an estimated 330,000 new cases of HPV-related high-grade cervical dysplasia (cervical intraepithelial neoplasia [CIN] 2/3) each year in the United States.²⁰ There are an estimated 1.4 million new cases of HPV-related low-grade cervical dysplasia (CIN 1) each year in the United States.²⁰

In the U.S., the incidence of cervical cancer is eight cases per 100,000 women.¹ This number has decreased over the years because of effective Pap smear screening programs. There are approximately

10,000 new cases and 3,900 deaths a year.²¹ Half of the new cases of cervical cancer will occur among women who have never been screened.¹ Another 10 percent of the new cases will occur among women who have not been screened in the preceding five years. There are segments of the population that continue to experience health disparities.

Figures 6 and 7 illustrate some of the significant costs of HPV infection.^{22,23} Cost of HPV includes the surgical or medical approaches dealing with warts, the surgical approaches to treating cervical dysplasias, and the costs of treating the various cancers. Among sexually transmitted diseases, the estimated direct medical costs of HPV treatment are second only to HIV among 15-to-24-year-old patients.²⁴

The introduction of a vaccine to prevent infection with the

major types of HPV has significantly improved the healthcare system's ability to fight HPV. The HPV vaccine (Gardasil[®]), which was approved in 2006, is a quadravalent vaccine. It has virus-like particles from four different HPV types – 6, 11, 16 and 18. This vaccine is FDA approved for use in girls and women nine-to-26-years old for the prevention of cervical cancer, precancerous or dysplastic lesions, and genital warts caused by the four covered human papillomavirus (HPV) types.²⁵ The vaccine is given as a three-injection series. To be effective, the vaccine must be given before any exposure to HPV. Vaccination against HPV does not substitute for rou-

Almost 100 percent
of cervical cancer
cases are caused by
HPV infection.

tine cervical cancer screening. Women who receive vaccination should continue to undergo screening per standards of care.

This is a preventive, not a therapeutic vaccine that needs to be given before exposure to the covered types of HPV. Because sexual contact is one of the prime methods of transmission, the age of vaccination needs to be before sexual contact typically occurs. Seven percent of high school students report sexual intercourse before age 13.²⁶ Some data suggest that the adolescent cervix has some unique susceptibility to HPV because of the cell types on the cervix.²⁷ Additionally, younger patients are seen on a more regular basis. Older patients are seen less frequently; thus, the opportunity to vaccinate might be missed.

Efficacy of the HPV vaccine has been assessed in four placebo-controlled, double-blind, randomized Phase II and III clinical studies. The vaccine was shown to be efficacious against HPV disease caused by each of the four vaccine HPV types. In individuals who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, and were naïve to the relevant HPV types, the efficacy against HPV-related disease was 90–100 percent, depending on the manifestation of infection.²⁵ The general population estimates of efficacy are lower than 90–100 percent because of previous exposure to vaccine-covered and not-covered types of HPV. From a cost perspective, vaccination reduced the incidence of cervical surgical procedures (e.g., loop electrosurgical excision procedure, laser conization, cold knife conization) by 16.5 percent (95 percent CI: 2.9 percent, 28.2 percent), and surgery to excise external genital lesions by 26.5 percent (95 percent CI: 3.6 percent, 44.2 percent), compared with placebo for all HPV-related diseases.²⁵

This past fall, the U.S. Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommended that girls and women aged 11 to 26 be vaccinated against HPV.²⁸ The Committee recommended the vaccine be administered to 11- and 12- year-old females and to females aged 13 to 26 who have not previously been vaccinated. They also stated that nine- and 10-year-old females may be vaccinated at the discretion of their physicians. The ACIP also recommended that females may receive the vaccine regardless of whether they have or previously had an abnormal Pap test, a positive HPV test or genital warts. The rationale for recommending that these groups be vaccinated is that even if they are infected with one or more HPV types covered by the vaccine, the vaccine will protect them against the other covered types. The ACIP voted to add the vaccine to the CDC's Vaccines for Children (VFC) program, which pro-

vides vaccines to children who are Medicaid-eligible, uninsured, underinsured, or Native American.

As a final point, because this is a preventive vaccine, the population impact must be considered. The total population impact will not be realized for several decades. The maximum impact will not be seen until the cohorts who are vaccinated today reach and move past the age of greatest risk for cervical cancer, and all the other cancers of the anal and genital region. Reductions in disease and cost-effectiveness with the vaccine have been demonstrated in mathematical models.^{29,30} Another HPV vaccine is under study. This is a bivalent vaccine, which covers HPV 16 and 18 types, and is also given as a three dose series. It may become available sometime in 2007.

Conclusion

Although much emphasis is placed on cervical cancer and cervical dysplasias when considering HPV infection, it is important to maintain a very broad perspective in terms of the overall disease burden related to HPV as well as opportunities for prevention. HPV infection can lead to a variety of conditions including genital warts, cervical abnormalities, cervical cancer, and other cancers. HPV vaccination is efficacious in preventing persistent infections and preventing clinical disease. The ACIP recommends use of the vaccine in appropriate aged girls and women. **JMCM**

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