



Human Papillomavirus: A Catalyst to a Killer

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ABSTRACT

Genital human papillomavirus (HPV) is the most prevalent and widespread sexually transmitted disease and is responsible for almost all cases of cervical cancer worldwide. However, HPV has received little public health attention, is not a reportable STD, and often is absent from the repertoire of STDs. In addition, there is pervasive misinformation about HPV among health care providers, professionals, patients and the public. This paper provides a comprehensive literature review of HPV by 1) addressing important epidemiological issues such as HPV prevalence, contraction, symptoms, transmission, detection, prevention, screening and treatment, 2) addressing specific gaps in the literature and 3) addressing future steps that can be taken among public health agencies, health care professionals, health educators and the general public to ensure HPV prevention, detection and treatment.

INTRODUCTION

Genital human papillomavirus (HPV) is the most prevalent and widespread sexually transmitted disease (STD),¹ causing nearly all cases of cervical cancer worldwide,² and is of public health concern. However, HPV has received little public health attention, is not a reportable STD, and often is absent from the repertoire of STDs. In addition, there is pervasive misinformation about HPV among health care providers, professionals, patients and the public.³ This paper will provide a comprehensive literature review of HPV by addressing important epidemiological issues, specific gaps in the literature and future steps for public health agencies, health care professionals, health educators and the general public.

Human Papillomavirus

HPV is a DNA tumor virus that stems from the papovavirus family.⁴ There are over 100 different types of HPV.⁵ In humans, only 40 types are sexually transmitted and affect the genital area, and the remainder affect the skin, hands and feet.⁶ Genital HPV can present itself as genital warts and as cervical dysplasia. Most genital HPV infections subside on their own; however, some infections can have serious health consequences. In fact, certain strains of genital HPV are responsible for nearly all (99.7%) cases of cervical cancer worldwide.⁷

Genital HPV is classified as low-, intermediate-, and high-risk for cervical cancer. Although all types of HPV are largely asymptomatic, where the majority of people

who carry the virus will never know that they have it,⁵ some classic manifestations of genital HPV can be detected. Among the types that affect the genital area, only a few are tumor-producing, and thus, are considered to be high-risk types. For example, whereas HPV types 6 and 11 are low-risk genital wart-causing agents and are not associated with cervical cancer, types 16, 18, 31 and 45 are high-risk types and, therefore, have potential to develop into cervical cancer.⁸

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Genital HPV & Cervical Cancer

Certain types of genital HPV account for almost all cases of cervical cancer.² Cervical cancer is the third most common cancer in the world,⁹ and the tenth most common cancer among women in the United States.¹⁰ Whereas an estimated 230,000 deaths occur annually from cervical cancer worldwide, most of these cases (80%) occur in developing countries.⁹ In the past, cervical cancer was one of the most common causes of cancer deaths for women in the U.S.; however, the advent of the Papanicolaou test (Pap test) has allowed for early detection of cervical cell changes and treatment, which has prevented cervical cancer development.¹¹

Nonetheless, in 2003, an estimated 4,100 deaths resulted from cervical cancer in the U.S. and many of these deaths could have been prevented through appropriate screening mechanisms.¹² In fact, half of all women who develop cervical cancer in the U.S. have not had a Pap test.¹³ When detected early through screening, mortality from cervical cancer is controllable.⁸

It is unacceptable that over 4,000 women are dying from cervical cancer annually in the U.S. If over 4,000 American civilians were killed this year due to terrorism, this kind of loss of life would not be tolerated by the government or the American people. Why is it that we tolerate death from cervical cancer when we know how to prevent it? Clearly, more emphasis should be placed on the surveillance, detection and treatment of genital HPV, as no woman should be dying of cervical cancer in the U.S.

Prevalence of HPV

The Association of Reproductive Health Professionals (ARHP) estimates that the lifetime risk of acquiring HPV is between 75% and 90%.¹⁴ It is, therefore, incongruent that the lifetime risk is so great yet 70% of people have never heard of it.¹⁵ It is estimated that in the United States alone, 24 million people are infected with genital HPV,⁸ and 5.5 million people become infected with genital HPV each year.¹⁶ And, whereas the virus never actually leaves the body, 92% of all HPV infections have been

shown to clear up by themselves within two to five years.⁸

Contracting Genital HPV

Both men and women are at risk for contracting genital HPV. Because the primary mode of transmission of genital HPV is through sexual (vaginal, anal and oral) penetration or genital-to-genital contact, certain sexual practices increase the risk for HPV acquisition.¹⁷ Persons with multiple sexual partners and people who begin sexual activity at a young age are most at risk for contracting HPV.⁸ It also has been shown that people with comorbid factors such as having concurrent STIs are at higher risk for HPV.¹⁸

Immune system response is directly related to the persistence, spread or remission of an already-established HPV infection. Individuals with a suppressed immune system are more likely to experience a repetitive and active HPV infection.¹⁹ It is not surprising then that women with Human Immunodeficiency Virus (HIV) are more likely than HIV-negative women to have HPV and are, therefore, at a higher risk for cervical cancer. In fact, women living with HIV are four times more likely to have HPV than women without HIV.¹⁸

Circumcision in men has been shown to reduce the likelihood of HPV infection among women. Therefore, the risk of cervical cancer is slightly reduced in female partners who engage in sexual activity with circumcised men.¹⁸ Another interesting epidemiologic development is the connection among smoking, HPV and cervical cancer. Once a person already has HPV, smoking cigarettes has been shown to be a catalyst, increasing a person's risk for cervical cancer.²⁰

New studies are being conducted to assess the relationship between a potential genetic link that increases a person's vulnerability to HPV. People with this genetic link may be predisposed to cervical cancer and may, therefore, be at a higher risk.⁸

Symptoms of Genital HPV

There are symptoms associated with genital HPV, although in most cases the virus is asymptomatic.⁵ Genital HPV can

present itself as genital warts for both men and women or abnormal cells that reside on the cervix for women. Genital warts vary in shape and size and can be anywhere from 1mm to greater than 10mm in size. Genital warts can be raised or flat, or can exist alone or as multiple warts. They can appear as flesh-colored or white or they can be present but undetectable with the naked eye. Non-visible warts are referred to as subclinical. In general, warts do not itch or burn. Warts can appear on a woman's vulva, in or around the vagina, anus or on the groin and cervix. Warts on men can appear on the penis, scrotum, groin, or in and around the anus.²¹

Symptoms for HPV that are not wart-producing for women includes cervical dysplasia, which can usually be detected through a Pap test. Because most high-risk HPV resides on the cervix and cannot be detected without screening, screening mechanisms are critical to the detection of high-risk HPV and the prevention of cervical cancer.²¹

Genital HPV Transmission

As stated previously, the primary mode of transmission of HPV is through sexual intercourse.¹⁷ However, HPV can be transmitted person-to-person through any skin-to-skin contact with an HPV-infected area of the body such as the genitals or anus.²² A few recent studies have documented the transmission of HPV through non-sexual pathways, such as fomites or vertical transmission.²² One study looked at HPV in virgins and attributed their genital infection to non-sexual pathways.¹⁷ Although non-sexual routes of transmission are deemed less significant than sexual modes of transmission, further research in this area is warranted.

Another notable mode of transmission is the passing of HPV from mother to infant during pregnancy²³ and childbirth.²⁴ Although literature on this topic is inconclusive, the consensus is that babies can contract HPV from the mother *in utero*.²³ However, the actual mode of *in utero* transmission is unclear. It has been suggested that HPV transmission *in utero* could occur



through semen at fertilization, through an infection from the mother,²³ through the placenta or through the process of vaginal birth.²⁵

The influence of mode of delivery in childbirth on HPV transmission is an additional area that requires further research. Some studies show that babies are less likely to acquire HPV through cesarean section delivery compared to vaginal delivery,²⁶ whereas other studies show that amniotic fluid *in utero* can transmit HPV, and therefore, a cesarean birth does not offer any protective factors.²⁷ More research is needed to sift through these inconsistencies. However, it is important to understand routes of transmission, especially in conjunction with new vaccination program planning and implementation.

Genital HPV Prevention

The main way to avoid HPV is not to engage in sexual intercourse or skin-to-skin contact with a HPV-infected person. But, because the majority of people are sexually active at some point in their lives, there are ways to reduce the risk of acquiring HPV when sexually active. Having only one sexual partner reduces the risk of HPV. Using condoms correctly can help prevent the spread of HPV, although this method of protection is not 100% effective.²¹

One new and currently unfolding HPV prevention strategy is vaccination. Vaccines work through a targeting of proteins in HPV to eradicate infection.⁸ The results of a recent randomized double-blind study indicated that a vaccine provided protection of HPV type 16 in a group of 2,392 women aged 16-23.²⁸ This finding indicates that immunizing women who do not have type 16 HPV could potentially decrease the incidence of cervical cancer.²⁸ Larger studies are awaited to prove vaccination success among HPV types 6, 11, 16, and 18.⁵ However, because there are so many different types of HPV and because HPV is known for its slow and ever-changing nature, vaccine research and vaccine success are slow and lengthy processes.⁸

Koutsky et al. postulate that if future vaccines do as well as current vaccines, vac-

ination will not only prevent genital warts but also will prevent over 70% of dysplasias and cancers, greatly reducing the costs associated with HPV detection and treatment.²⁸ In addition, McNeil postulates that because HPV is present in almost all cases of cervical cancer, effective vaccination could eliminate cervical cancer worldwide.²⁹ Moreover, if vaccination proves to be effective, projected challenges include vaccine delivery, vaccine awareness and destigmatization of the concept of HPV.⁵

Sanders and Taira evaluated the cost-effectiveness of vaccinating female teens against high-risk HPV.³⁰ They found the vaccination of adolescent girls to be cost-effective when compared to other health interventions. The particular high-risk HPV vaccine used in this study prevented a substantial number of lifetime cases of HPV and cervical cancer and, by implication, a large number of cancer-related deaths.

Sanders and Taira project that an effective vaccination could prevent 1,300 cervical cancer-related deaths annually in the U.S. if all 12-year-old girls residing in the U.S. were given the vaccination.³⁰ This analysis by Sanders and Taira is one of only two cost-effective analyses on a HPV vaccine. The only other study on cost-effectiveness was published by the Institute of Medicine (IOM) and offered similar cost-effective results.³¹ However, because the vaccine may not provide immunity for all types of HPV and may not be 100% effective, vaccination should not replace other prevention strategies such as Pap tests and protective sexual practices.

Genital HPV Detection

The primary mode of detection of HPV in women is through Pap tests. According to the American Social Health Association, there are currently three ways to screen for genital HPV.²¹ The first and most common method for screening is utilizing the conventional Pap test to look for abnormal cells. This procedure involves retrieving a sample of cells taken from the cervix and subsequently placing the cells on glass to be viewed under a microscope. If results are normal, the recommendation is to conduct

follow-up with a similar Pap test in one calendar year.²¹ This type of Pap test has been shown to be 70% to 80% sensitive in detecting HPV.³²

The second method used is a liquid-based Pap test called a Thin Prep™ where cells are sampled from the cervix and then placed in a container filled with a liquid solution. If results are normal from this type of test, the recommendation is to test again with a similar Pap test in two calendar years. The longer period of time for this second test is due to the higher accuracy of the liquid-based test.²¹ The liquid-based test has been shown to be 85% to 95% sensitive in detecting HPV.³³

The third method, a combination Pap-HPV DNA test, is used only to test women over the age of 30. If results are normal, then new recommendations suggest that women can wait three years before undergoing another screen.²¹ The induction of screening mechanisms for HPV has proven invaluable in that these screening methods have been attributed to a 70% decrease in cervical cancer deaths over the last 50 years.³⁴

Another method used for screening for genital warts for both men and women is through acetowhiting or a highlighting of HPV lesions with acetic acid (vinegar). With this method, acetic acid is placed on the genitals, causing warts to give a white appearance allowing the HPV to be detected and typed.^{21,22} However, American Social Health Association warns that this type of screening can be misleading as acetic acid may highlight normal bumps on the genitals as well.²¹

A limitation of existing screening mechanisms is that tests available for men are highly inadequate. As Schiffman and Castle confirm, "there is currently no reliable way of measuring HPV infection of the entire cornified epithelium of the penis."²² Because it is difficult to get a sufficient cell sample from the thick skin of the penis, HPV tests for men tend to produce a certain percentage of false negatives.²¹ Moreover, because HPV is so frequently a sub-clinical virus, most men do not know that they have it, and can infect their partners



unknowingly. Fortunately research has not shown any great risks for men with HPV that compare to cancer in women. However, further research on screening mechanisms for men should not be disregarded.²¹

Pap tests are insufficiently implemented to women in the U.S. as demonstrated by the unacceptable number of deaths (4,100) as a result of cervical cancer in 2003. Half of all women with cervical cancer in the U.S. have never had a Pap smear and another 10% of women with cervical cancer have not been screened within the past five years.¹³ In addition, another more recent national survey showed that 18% of women in the U.S. have not had a Pap smear in the last three years.³⁵ Because Pap tests are a preventative method of discovering cervical cancer, every woman should have Pap smears as recommended by the screening guidelines.

HPV Screening Guidelines

In 2003, new screening recommendations for cervical cancer were presented by three reputable groups: the American Cancer Society (ACS), the U.S. Preventive Health Services Task Force (USPHSTF), and the American College of Obstetricians and Gynecologists (ACOG).^{11,36,37} However, the specific recommendations that are advocated vary slightly across these organizations.

All three guidelines recommend setting the age to begin screening at age 21 or three years after onset of sexual activity, whichever comes first. Whereas ACOG does not establish an upper age limit for screening, ACS and USPHSTF set age limits of age 65 and 70 respectively as long as women have a previous history of normal cytology tests.

Whereas the ACOG recommends *annual* screening intervals for women under 30 regardless of screening technology, the ACS recommends *annual* screening with conventional cytology or *every two years* with liquid-based cytology (i.e., Thin Prep™) and the USPHSTF recommends screening *every three years* regardless of screening technology. All three groups agree that screening intervals for women over age 30 should be conducted every 2-3 years based on cytology history. All three sets of guide-

lines also agree that women with a total hysterectomy for benign indications could discontinue screening.

In terms of the use of HPV testing in conjunction with screenings, the ACS recommends the use of high-risk HPV typing following Pap smear results of atypical squamous cells of undetermined significance (ASCUS). An ASCUS Pap smear result means that cells from the cervix were slightly abnormal. The ACS also recommends a colposcopic evaluation with high-risk HPV and a negative result for HPV can resume annual screening protocol. The ACOG recommends reflex HPV testing as follow-up to ASCUS test results but does not recommend use if the results are LSI (low-grade squamous intraepithelial lesion) or higher. The USPHSTF discourages the use of HPV testing for primary screening. The Missouri Family Health Council has created a useful comparative chart of these three sets of guidelines. The chart is included as Figure 1.

Treatment Options for Cervical Dysplasia

Although there is currently no "cure" for HPV, there are various treatment alternatives for cervical dysplasia. Treatment options are enumerated here in no particular order. The first treatment option is for women with mild cervical dysplasia to undergo *no* treatment as 50% to 70% of cases of mild dysplasia subside on their own.⁸ A second commonly used treatment option is to have cryotherapy performed. Cryotherapy involves freezing the affected cells with liquid nitrogen.²¹ Cryotherapy is commonly used for its low cost, low complication rate and reliability.⁸

A third treatment option is to have a loop electrosurgical excision procedure (LEEP) involving a wire loop that becomes a cutting tool when an electric current is passed through it. In this way, clinicians are able to use this tool to successfully remove lesions.⁸

A fourth treatment option is to have cold conization performed in which a portion of the cervix that contains the abnormal cells is removed with a scalpel.⁸ A fifth treat-

ment option is to have a laser procedure to remove abnormal cells. However, the laser option is used infrequently as not all clinicians are trained for this type of procedure.²¹

Treatment Options for Genital Warts

There are various treatment options available for the removal of genital warts. Some treatment options can be performed at a physician's office, whereas others can be administered at home. Treatment options for genital warts include the following:

- *Cryotherapy*: With cryotherapy, warts are frozen off with liquid nitrogen. This procedure is inexpensive but must be performed by a trained professional.
- *Podophyllin*: A chemical compound that is applied to the wart by a clinician. However, this treatment option is rarely used anymore.
- *Trichloroacetic acid (TCA)*: Acid is applied to the wart.
- *Excision* of the lesion by a clinician.
- *Electrocautery*: Warts are burnt off with an electrical current.
- *Laser therapy*: Laser therapy is costly and medical professionals must be well trained in the procedure. Most medical professionals do not have laser equipment in their offices. Laser therapy is most typically used for larger warts or in circumstances where patients have not succeeded in other treatment procedures.
- *Interferon* is injected into the wart. This procedure is costly and has side effects that have led to it rarely being performed anymore.

• *Prescription creams* such as Podofilox cream (Condylox®) and Imiquimod cream (Aclara®). Podofilox cream is applied to external warts for four weeks and is relatively inexpensive, easy and safe to use. Imiquimod cream is also applied to external warts and is easy and safe to use; however, instead of working by destroying warts like other treatments, Imiquimod cream works by boosting the immune system, and thus, suppressing the HPV.

Persistence vs. Clearance

HPV persistence refers to the reemergence or continuation of a HPV infection after treatment and HPV clearance refers to

**Figure 1. Cervical Cancer Screening Guidelines**

A Comparison of Recommendations Compiled by Erin Spears, Clinical Program Coordinator Missouri Family Health Council

Age to begin screening	Age 21, or three years after onset of sexual activity	Age 21, or three years after onset of sexual activity	Age 21, or three years after onset of sexual activity
When to discontinue screening	ACOG does not set an upper age limit for screening	Age 65, if they have adequate previous screenings and are not high risk	Age 70, with an intact cervix, and who have had 3 consecutive satisfactory normal/negative cytology tests. They must have no abnormal tests within the last 10 years
Screening intervals	Annually for all women under 30 regardless of screening technology (conventional vs. liquid-based?)	Annually with conventional cytology or Every two years with a liquid-based cytology	At least every three years
Screening intervals for women over 30	Women who have had three consecutive negatives screening results, and who have no hx of CIN 2 or CIN 3, are not immunocompromised, are not HIV infected, and have not had DES exposure may extend the screening to every 2-3 years.	Every 2-3 years, at the discretion of the provider, after 3 consecutive normal cytology results (unless high risk or immunosuppressed)	Does not change screening recommendations for women over 30
Screening intervals for women with total hysterectomy	Women who have undergone hysterectomy with removal of the cervix for benign indications and who have no prior history of CIN 2 or CIN 3 or worse may discontinue routine screening	May discontinue all screenings (cervical/vaginal) if hysterectomy was done for a benign condition	May discontinue routine Pap screenings if hysterectomy was done for a benign condition
Use of HPV testing in conjunction with screenings	ACOG acknowledges the benefit of reflex HPV testing as a follow-up to ASC-US test results, but does not advocate using if the results are LSIL or higher. FDA has approved a combo cervical screening/HPV test for women	Recommends the use of high-risk HPV typing following an ASCUS pap. (+) high risk warrants colposcopic evaluation, while (-) results can resume annual screening protocol	Discourages use of HPV testing for a primary screening. Does not address its use in follow-up testing

a HPV infection that becomes undetectable by tests either with or without treatment. However, little information is available on why HPV persists in some and subsides in others although factors associated with persistence include older age, high-risk types

of HPV, immune suppression and infection with multiple types of HPV.³⁸ Like warts on other parts of the body, warts on the genitals tend to subside on their own. HPV on the cervix does not always do this, however.

Cervical HPV is detectable for approxi-

mately one year and HPV type 16 tends to persist even longer. One of the unresolved questions about HPV is the issue of viral latency. Almost all HPV infections become undetectable by HPV DNA tests within a period of two years except infections that



lead to precancerous states. More research is needed on viral latency as little else is known about what causes reemergence of a HPV infection.²²

Public Awareness and HPV

Public knowledge about HPV is generally poor. One U.S. study surveyed all first-year students at a private university and found that approximately 96% of both males and females had heard of genital warts, but only 4.2% of males and 11.6% of females knew that HPV caused genital warts.³⁹ A second study also surveyed university students and found that in a random sample of 500 students, 63% had never heard of HPV.⁴⁰ A third study assessed knowledge among a group of inner-city high school students and found that 87% had never heard of HPV.⁴¹ Other studies conducted in the U.S. have found similar low rates of HPV knowledge.^{42,43,40}

Low HPV awareness is not only common to people living in the U.S., but also to women in the U.K. Among a sample of well-educated women attending a women's clinic, 70% had never heard of HPV. Even among the 30% who had heard of HPV, fewer than half were able to link HPV to cervical cancer.⁴⁴

Implications for Health Educators

Health educators are a vital component of community health education. They strive to promote and improve healthy lifestyles and prevent disease through a provision of information to both individuals and communities. In their critical role, health educators can influence the level of knowledge and subsequently increase prevention of HPV within the community.

Health educators must first acknowledge the vastness of the prevalence of the infection and stress the existence of HPV in their own work. Further, health educators must work to increase knowledge about HPV in the general public. Specifically, health educators should educate regarding the need for screening mechanisms for early detection and treatment of HPV and the use of prevention methods such as condom use, abstinence or having only one sexual partner. Not only can health educators raise

awareness about HPV prevention, detection and treatment, which will subsequently save lives, they can also aid in the decision-making process of picking a treatment option and prevention method that is acceptable for each individual. In addition, health educators can play a role in the education of pregnant mothers and supporting fathers on routes of HPV transmission in childbirth and can assist in the decision-making process for these families.

In the future, when a successful HPV vaccination is developed, health educators will again play an integral part in the education of the public about the vaccination and in facilitating the administration of this important development. As the guidelines on Pap smear screening change, health educators can assure that women are educated on the new screening guidelines, thereby making an important commitment to keeping women healthy throughout their lifespan.

Health educators should work to educate and organize community coalitions about HPV, should include current and relevant information in their educational materials, newsletters, public information reports and grant writing and should develop informational campaigns stressing important HPV prevention messages. While health educators raise awareness about HPV, they must also remember to simultaneously decrease the stigma that surrounds HPV. Although health educators must work to increase knowledge about HPV, heighten public awareness of the threat and consequences of contracting HPV and increase preventive behaviors among women and men, they can not be expected to do this alone. They will need the help of nurses, public health social workers, physicians and other health-related professionals.

SUMMARY

Genital HPV is a highly prevalent virus that can cause genital warts, cervical dysplasia, and cancer. Given the state of scientific knowledge, there clearly are steps that public health agencies, health care professionals, health educators and the general

public can take to ensure the reduction of cervical cancer incidence and mortality in the U.S. through the prevention, detection and treatment of HPV.

Public health agencies should collaborate to increase awareness about prevention of HPV and cervical cancer among health care professionals, health educators and the public. Outfitted with the current knowledge about genital HPV, health care professionals and health educators play an important role in the promotion of cervical cancer screening for all women as well as the promotion of preventive measures for both men and women. In addition, health care professionals and health educators can educate both men and women on methods that can lower their risk of HPV infection such as monogamy, abstinence, condom and dental dam use.

Public health agencies as well as researchers can ensure that epidemiologic, laboratory and behavioral research is conducted on HPV infection through the support of federal funding. To begin, it would be helpful to develop a national surveillance system where genital HPV infections are routinely reported. In addition, public health agencies and professionals can work together to advocate for the speedy development of an effective HPV vaccine.

As the general public is provided the knowledge about genital HPV, they can ensure that they are screened appropriately and that they make informed decisions about their sexual health. It is a failure of the public health and medical system that women continue to die of cervical cancer, as cervical cancer is largely preventable. This kind of loss of life is not permissible. How many women must die before something is done? It is time to start caring about HPV.

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