Human Papillomavirus and Cervical Cancer: Not Just a Sexually Transmitted Disease

Wendy M. Likes, APRN, BC, and Joanne Itano, RN, PhD, OCN®

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The human papillomavirus (HPV) is the cause of virtually all cancers of the cervix, the fourth most common cancer in women in the United States. HPV is sexually transmitted, and the lifetime risk of contracting the virus is estimated to be 75%–90%. New methods of detecting HPV infection and cellular changes (dysplasia) caused by HPV can greatly reduce the mortality associated with this virus. More than 100 types of HPV exist and may be classified as low-, intermediate-, or high-risk in terms of causing cancer. The virus can cause genital warts, subclinical dysplasia, and cancer. Nurses play an important role in educating patients regarding HPV and preventive measures as well as in screening and treatment. Most women diagnosed with HPV need emotional support and factual information provided in a supportive, nonjudgmental manner. Nurses can meet this challenge and make a difference in reducing the incidence and mortality of cervical cancer.

Key Words: papillomavirus, cervix neoplasms

What Is Human Papillomavirus?

HPV is a small, double-stranded DNA virus that is epitheliotropic, meaning it has a special affinity for epithelial cells (see Figure 1). HPV infects specific types of epithelium, such as the epithelium in the genital area and head and neck. Of the more than 100 types of papillomaviruses, about 40 affect the genital tract. The rest infect skin on other areas of the body, such as the hands and feet (Park, Fujiwara, & Wright, 1995).

Most individuals who get an HPV infection never know they have it because symptoms often do not develop. External genital warts (condylomata acuminatum) seen as small, flat, flesh-colored bumps or tiny, cauliflower-like bumps appear in a small percentage of those infected with HPV. This is associated with two HPV types, numbers 6 and 11. The time frame from HPV exposure to development of genital warts is six weeks to eight months, but HPV can remain latent for years or decades before warts or cervical disease is evident. Subclinical HPV infection (skin changes not visible to the “naked” eye) is 10–30 times more common than apparent infections. Thus, determining exactly when or from whom the exposure to the virus occurred often is not possible (Brentjens, Yeung-Yue, Lee, & Tyring, 2002; Wiley, 2002; Wiley et al., 2002; Wilson, 2002).

The various subtypes of HPV hold different levels of oncogenic potential. Types 6 and 11 (associated with genital warts) are examples of low-risk types, which rarely, if ever, are found in cervical cancer. These low-risk types are associated with benign lesions or low-grade dysplasia (i.e., abnormal changes in the size, shape, and organization of mature cells). In low-grade dysplasia, variability exists among cells, although the variability is less than in high-grade dysplasia. A low-grade dysplasia is unlikely to transform into cancer (Apgar, Spitzer, Brotzoman, & Ingnatavicius, 2002; Magnusson, Lichtenstein, & Gyllensten, 2000; Park et al., 1995).

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Nine intermediate HPV types exist: numbers 33, 35, 39, 51, 52, 56, 58, 59, and 68. These intermediate types are associated with high-grade dysplasia (has more variability among cells than low-grade) but rarely develop into invasive cancers (Apgar et al., 2002; Magnusson et al., 2000; Park et al., 1995).

Four high-risk types exist: numbers 16, 18, 31, and 45. High-risk HPV types are associated with high-grade dysplasia and are more likely to develop into cancer. HPV 16 is responsible for approximately 50% of cervical cancers worldwide (Apgar et al., 2002; Magnusson et al., 2000; Park et al., 1995).

The genomic organization of HPV contains 7,800–7,900 base pairs, a nonenveloped virion, and an icosahedral capsid with 72 capsomers (Sisk & Robertson, 2002). The HPV genome is comprised of six early and late proteins. The early proteins are E1, E2, E4, E5, E6, and E7. E1 and E2 are proteins involved in viral replication. E6 and E7 are the oncogenic proteins that are responsible for tumor progression and cell immortalization. E4 and E5 still are not well understood. The late proteins, L1 and L2, are involved in capsid formation and viral assembly. They are present during early, initial infection and interact with surface molecules to allow entry of viral DNA. The upstream regulatory region monitors transcription from the early and late proteins and controls the productions of viral proteins and infectious particles (Park et al., 1995). How strongly these proteins work depends on the HPV type. Knowledge about these proteins assists in understanding how future therapies will work. Future therapies will target the virus during the different phases.

**Risk Factors for Human Papillomavirus**

HPV is transmitted sexually, and certain sexual practices increase the risk for developing cervical cancer. The more sexual partners a woman has or the younger she begins sexual activity the greater the risk of acquiring a sexually transmitted disease such as HPV. The younger a woman becomes sexually active, the more likely she will be exposed to the virus. Infection with HPV is common, with 10%–15% of the sexually active population between the ages of 18–28 infected. Only 1% of this population shows evidence of genital warts, and approximately 4% have abnormal cervical cytology. Coinfection with other sexually transmitted diseases also is a risk factor (Castellsague, Bosch, & Munoz, 2002; Ferenczy & Franco, 2002; McLachlin, 2000).

Through a direct carcinogenic action, smoking may advance infected cells toward a neoplastic process and increases the risk for cervical cancer once patients are infected with the HPV virus. This has been found to be a comorbid risk factor in several studies (Lacey et al., 2001; Zivaljevic, Vlajinac, Adanja, Zivaljevic, & Kocev, 2001). The immune system recently has been implicated in playing a role in the progression from cervical dysplasia to cervical cancer. HPV-infected women have been shown to be four times more likely to be infected with HPV than women without HPV. This population also has been shown to have more persistent HPV infections, which is a key factor in progression to high-grade dysplasia or cancer (Castellsague et al., 2002; Coker, Bond, Williams, Gerasimova, & Pirisi, 2002; Kuper, Boffetta, & Adami, 2002).

HPV infection is common and usually transient, with 92% of HPV infections clearing spontaneously in two to five years. Persistence of a high-risk infection is necessary for the development, maintenance, and progression of a cervical cancer precursor lesion. Persistence is defined as repeated detection of an HPV infection every one to two years. A high viral load measured at the lesion may marginally (odds ratio = 1.80) increase the risk for high-grade dysplasia (Appar et al., 2002; Sisk & Robertson, 2002).

Long-term users of oral contraceptive pills have been shown to have a 2.2-fold increased risk for cervical cancer compared to the general population of women (McLachlin, 2000). The link between oral contraceptives and HPV is not well understood.

**Presentation of Human Papillomavirus**

Visible clinical presentation of HPV most commonly occurs in the form of genital warts. These lesions may involve the vaginal introitus, the vulva, the perineum, the anus, and, rarely, the cervix. They appear as well-circumscribed, multiple papillomatous growths (Appar et al., 2002). See Figure 2 for a normal cervix and Figure 3 for condyloma of the cervix. Low-risk HPV is associated with genital warts, but an underlying dysplasia or carcinoma may occur with or without these warts; therefore, biopsy is needed before a definite diagnosis can be made. Vulvar dysplasia may present itself with itching or erythema without warts. All women complaining of vulvar changes, such as redness or itching, without a known yeast infection should have a biopsy to determine if dysplasia is present.

The cervix is more susceptible to viral infection than other anogenital sites. This is because of the immaturity and hormone responsiveness of the transformation zone. The transformation zone is the area on the cervix between the mature epithelium of the exocervix and the columnar epithelium of the endocervix (Appar et al., 2002). HPV is associated with nearly 100% of cervical squamous cell carcinomas and 70% of cervical adenocarcinomas. HPV 16 is found in 50% of squamous cell carcinomas, and HPV 18 is found in 50% of adenocarcinomas (Sisk & Robertson, 2002). The cellular changes associated with HPV infection to the cervix are graded according to severity.
and include cervical intraepithelial neoplasia (CIN) 1, CIN 2, CIN 3, carcinoma in situ (CIS), and invasive carcinoma.

Screening and Diagnosis

Several methods have been developed to screen for HPV. The accuracy of cervical cytology is responsible for a 70% decrease in cervical cancer mortality over the past 50 years and is one of the most effective screening tests at present (Hagensee, 2000; Saslow et al., 2002). Conventional cervical cytology using a slide and fixative for a Pap test will detect premalignant lesions but not an HPV infection. The new liquid-based methods (versus the slide method) allow for not only the detection of premalignant conditions but also HPV. Liquid hybridization, Hybrid Capture® (Digene, Silver Springs, MD), or polymerase chain reaction methods can detect HPV in cervical samples and tissues (Chang, Chen, Lee, & Huang, 1997; Einstein & Goldberg, 2002). These are nucleic acid-based tests that can detect and type HPV. HPV screening is becoming more integrated into the care of women and is performed when an abnormality is detected by Pap test. Pap test results can fall into six major categories: normal and five abnormal categories. A normal result is the most frequent (90%–95%). A result of atypical squamous cells of undetermined significance (ASCUS) indicates that squamous cells are detected and do not look entirely normal but also are not entirely abnormal. Approximately 60% of the women with this result are HPV negative with no cervical disease and 40% are HPV positive with detectable cervical changes, mostly low-grade type changes (ARHP, 2001). A low-grade squamous intraepithelial lesion (LSIL) result is typically a result of an HPV infection in younger women (younger than 35) and in older women because of declining estrogen levels and other effects of the aging process on squamous cells. An estimated 75% of women with this result will test positive for HPV (ARHP). About 90% of women with a high-grade squamous intraepithelial lesion (HSIL) result will have cell changes because of HPV, the majority with high-grade cervical changes (ARHP). The atypical glandular cells of undetermined significance (AGCUS) indicate that glandular cells are detected and do not look entirely normal but also are not entirely abnormal. Upon further testing of women with AGCUS, approximately 50% will be found to have a normal histology (ARHP). However, high-grade squamous and glandular lesions may be found in 20%–50% of women with this result (ARHP). The fifth category is cancer (squamous or adenocarcinoma). Rarely will a Pap test result be cancer in women obtaining regular Pap tests because cervical cancer is a slow-growing disease and precursor changes will be identified first (ARHP). When a woman goes years between Pap tests, a precursor lesion may be missed.

Atypical Squamous Cells of Undetermined Significance

If a Pap test returns an ASCUS result, the standard of care is to repeat the Pap test in four to six months or test for HPV (Wright, Cox, Massad, Twigg, & Wilkinson, 2002). If HPV testing is positive for a high-risk type, then colposcopy is indicated. Colposcopy is the use of magnified illumination to distinguish normal from abnormal findings of the lower female genital system including the cervix, vagina, and vulva. The magnification allows the clinician to see whether areas turn white when acetic acid is applied. Some of these white areas contain abnormal cell changes, and biopsy is indicated. If HPV testing is negative, the Pap test is repeated in one year (Wright et al.).

Postmenopausal women with ASCUS may directly undergo colposcopy, have HPV testing, or receive estrogen therapy for three months and then repeat the Pap test one week after completion of the estrogen treatment. Postmenopausal women are at a lower risk for dysplastic changes than premenopausal women and may have abnormal squamous cells as a result of atrophy of the vaginal tissue rather than true dysplasia. Three months of estrogen therapy usually will resolve the atrophy and should then allow for a normal Pap test (Wright et al., 2002).

Low- and High-Grade Intraepithelial Neoplasia

HPV testing will decrease unnecessary colposcopies by screening for those who are at higher risk for dysplasia. If a patient has a Pap test result that is LSIL or HSIL, a colposcopy is indicated because the severity of dysplasia needs to be verified (Wright et al., 2002). The only exception is an LSIL Pap test result in adolescents or postmenopausal women because the likelihood of true dysplasia is lower in these women than in women of other ages. If a postmenopausal woman is not on estrogen therapy and has evidence of vaginal atrophy, she may be placed on estrogen therapy for three months if no contraindications exist and the Pap test is repeated one week after completion of the therapy. If no evidence exists of vaginal atrophy, the woman is treated as if the Pap test result is ASCUS. This involves either a repeat Pap test in four to six months or HPV testing. For adolescent patients, appropriate actions include colposcopy, a repeat Pap test in six months, or test for HPV based on the adolescent’s sexual history. If an adolescent has had multiple sexual partners or initiated sexual activity at a young age, colposcopy is indicated (Wright et al.).

Atypical Glandular Cells of Undetermined Significance

Management of AGCUS on a Pap test requires colposcopy for all ages and endometrial biopsy for those older than 35 or those with abnormal bleeding. An AGCUS Pap test result requires endometrial biopsy regardless of age if endometrial cells are present. AGCUS changes are a precursor to adenocarcinoma with substantially greater risk for the development of cervical cancer than the ASCUS or LSIL Pap test results (Wright et al., 2002).

Treatment

Treatment for the effects of HPV depends on the site affected. If mild dysplasia of the vulvar area exists (vulvar intraepithelial neoplasia [VIN] 1), observation for natural regression is sufficient. Aldara® (topical imiquimod, 3M Pharmaceuticals, St. Paul, MN) currently is being studied for use in vulvar dysplasia. Aldara is applied to the affected areas three times a week at bedtime and washed off in the morning for a maximum of 16 weeks. The drug is an immune response modifier that stimulates the body’s own immune response system to fight HPV (Syed, 2001).
Patients with VIN 3 lesions require surgical excision or cavitronic ultrasound surgical aspiration (CUSA). CUSA is performed in the operating room and uses water and vibration to excise the involved area and aspirates the tissue so that it may be analyzed by pathology (Santoso & Coleman, 2001). In patients with CIS or invasive disease, surgical excision is recommended with possible inguinal lymphadenectomy. All patients with VIN or invasive disease should be followed carefully for recurrence or progression every three months.

For vaginal involvement with mild dysplasia (vaginal intraepithelial neoplasia [VAIN] 1) options for treatment include observation or more aggressive treatment with 5-fluorouracil (5-FU) cream. This cream achieves significant penetration in areas of damaged or diseased skin to inhibit the formation of the DNA-specific nucleoside-based thymidine (Santoso & Coleman, 2001). Client education in the use of 5-FU cream is summarized in Figure 4.

With moderate to more severe dysplasia (VAIN 2–3), patients usually are placed on 5-FU cream or imiquimod cream (Davila & Shroyer, 1996; Jayne & Kaufman, 2002). With CIS of the vagina, the treatment of choice is a partial or total vaginectomy. In a nonsurgical client with CIS, 5-FU or intracavitary radiation is indicated. For invasive disease, whole pelvic radiation followed by brachytherapy is recommended. The exception to this is if the tumor is in the upper third of the vagina, in which case a radical hysterectomy with pelvic lymphadenotomy and partial or complete vaginectomy may be performed. Similar to vulvar dysplasia and cancer, follow-up is every three months (Davila & Shroyer; Kucera, Mock, Knocke, Kucera, & Potter, 2001; Stryker, 2000).

Women with low-grade cervical dysplasia (CIN 1) may be given the option of no treatment because an estimated 50%–70% of these lesions spontaneously resolve without treatment. A Pap test is necessary every six months. Low-grade lesions that do not spontaneously resolve over a period of up to two years of follow-up are more likely to progress to high-grade dysplasia and may be treated with cryotherapy, loop electrosurgical excision procedure (LEEP), or laser or cold conization. Cryotherapy is used to treat CIN 1 if indicated because of its reliability, ease of use, low cost, and low complication rate. The technique is an ablative procedure performed in the office in which the lesion and the entire transformation zone are destroyed by freezing. High-grade lesions (CIN 2–3, see Figure 5) may be treated with cryotherapy, LEEP, or laser ablation. LEEP uses a thin wire loop through which an electric current is passed that turns the loop into a very effective cutting tool. The advantages of LEEP are that the clinician is able to see the lesion while it is being excised and a tissue sample that can be evaluated is removed. Laser ablation is more costly than LEEP and cryotherapy and is indicated for lesions extending into the cervical canal. Cold conization uses a scalpel to remove the portion of the cervix with abnormal cells. The procedure requires general anesthesia and is used when the lesion is too far up the cervical canal or if glandular disease may be present in the canal (ARHP, 2001).

**Future Therapies**

Five approaches to producing HPV antigens (vaccines) and delivery of these antigens currently are being developed and tested. These include recombinant viral vectors, peptides and proteins, virus-like particles, DNA vaccines, and oral vaccines. These vaccines target proteins within HPV to eliminate the infection. More than 28 vaccines currently are under development. Clinical trials of these vaccines are difficult because of the slow and unpredictable nature of the course of HPV, as well as the multiple types of HPV. So far, all clinical trials for HPV vaccines have been phase I or II studies in which safety and immunogenicity are the main areas of interest. All of the vaccines employ genetic engineering to manipulate and transfer genes from one organism to another. This approach is safer and creates fewer side effects than vaccines made of whole organisms (Fausch, Da Silva, Eiben, Le Poole, & Kast, 2003; Moniz, Ling, Hung, & Wu, 2003; Onon & Kitchener, 1999). The HPV-16 vaccine recently was found to reduce the incidence of HPV-16 infection and HPV-16–related cervical intraepithelial neoplasia in a randomized double-blind study of 2,392 women who received either the HPV-16 vaccine or a placebo (Koutskey et al., 2002), and researchers have theorized that immunizing HPV-16–negative women eventually may reduce the incidence of cervical cancer (Hughes, Garnett, & Koutskey, 2002).

Four HPV proteins are potential targets for vaccines. Proteins L1 and L2 are targeted for prophylactic vaccines. This is a result of

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**5-Fluorouracil Cream (5-FU)**

You have been prescribed 5-FU cream to use in your vagina for vaginal dysplasia. Vaginal dysplasia is abnormal changes in cells in the vagina that have the potential to turn into cancer if left untreated.

**What is 5-FU?**

5-FU is a pyrimidine antagonist that prevents nucleic acid synthesis. It is used to treat intravaginal human papillomavirus infections and vaginal dysplasia. It is a cream.

**How is 5-FU cream used?**

1. First, apply petroleum jelly to cover the entire vulvar area to help prevent irritation from the cream.
2. Use an applicator (may use an estrogen cream or antifungal cream applicator) to insert 1.5 grams or one quarter of an applicator full of 5-FU cream into the vagina. Use gloves with application.
3. Wash your hands immediately after inserting cream. You may use a tampon to help reduce the risk of vulvar irritation if you wish.
4. You will use this cream once a week at night for 10 weeks.

**Side Effects**

Inflammation and redness to vulvar area may occur. You also may experience burning, stinging, soreness, swelling, and loss of hair to area.

**When to Call**

Please call ____________ if you experience open areas or sores, unmanageable discomfort, swelling, or rash. Please do not hesitate to call if you have any questions.

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**Figure 4. Patient Education Sheet**

*Note. Based on information from Wilkes et al., 2002.*
their involvement in the early stages of infection; they interact with surface molecules to provide entry for the virus. Oncoproteins E6 and E7 are the primary targets of therapeutic vaccines designed to treat later stages of disease. These oncoproteins are involved in the malignant transformation of HPV-infected cells and are thought to be required for continued tumor growth. Replication proteins E1 and E2 are expressed to a higher degree than E6 and E7 earlier in the disease process. These proteins are necessary for HPV replication within cells. E1 and E2 vaccines are being targeted to treat early stage disease such as low-grade dysplasias (Kols & Sherris, 2000).

**Nursing Implications**

An HPV infection has many implications for a woman’s health, but many women are unaware of HPV and its role in cervical and other cancers. Nurses have a significant role in educating women about HPV as an STD. Primary prevention strategies include education of women, especially adolescents, regarding the risk of early sexual activity, the number of sexual partners, and STDs. Sexual abstinence is ideal but often unrealistic; therefore, the use of a barrier contraception should be encouraged. Condoms can reduce but not eliminate the risk of HPV transmission, but because they are effective with other STDs, their use should be highly encouraged.

Nurses should advise patients of the risk that smoking has in relation to cervical and other cancers. Nursing strategies directed toward smoking cessation include counseling, support and encouragement, referral to smoking cessation programs, and written educational materials.

In secondary prevention, the need for regular Pap tests for all sexually active women regardless of age must be emphasized. Teaching and encouragement to perform vulvar self-examinations and seeking medical attention when vulvar irritation or genital warts develop is essential.

Once HPV is diagnosed or a Pap test result is abnormal, the nurse’s role is to assess the woman’s understanding of the diagnosis and options available for treatment. Because most women are unfamiliar with HPV, the diagnosis of an STD that may cause cancer often is frightening and filled with anxiety. Anger, confusion, and blame are common emotional responses to a diagnosis of any STD. Women may have feelings of shame and embarrassment and a loss of a positive body image. Providing education and emotional support is essential. This should be carried out without prejudice and with compassion. Emphasizing that HPV infection is quite common and the risk for the development of cancer is very low, especially with conscientious follow-up, is a very important message (ARHP, 2001).

A woman who has been in a monogamous relationship for many years may be most distressed by the STD nature of HPV infection. For example, Mrs. M, a 55-year-old woman who has been married for more than 23 years was seen for cervical dysplasia and HPV infection. When informed of the HPV infection, she questioned the faithfulness of her husband and began having difficulty with the thought of sexual intercourse with an infection that is sexually transmitted. The nurse must provide Mrs. M and her husband about the facts of HPV infection and inform them that although Mr. M likely has an HPV infection, relatively few health risks exist for him (penile cancer is very rare) and studies indicate that ongoing exposure to the same partner with HPV does not “reinfect” the woman (ARHP, 2001). The nurse may need to facilitate communication between the couple and refer them to counseling. Providing written materials to review at a later time may be useful to reinforce teaching. Follow-up visits often are necessary because many individuals have difficulty comprehending and remembering when first receiving the news about diagnosis. Nurses can help by being patient and understanding as questions are repeated. Concerns about sexuality also must be addressed.

Miss S is a 24-year-old female diagnosed with CIN 3 who recently completed a successful LEEP treatment. She has questions regarding intercourse with past and future partners and the possibility of transmitting the virus to others. The nurse must listen to her concerns and identify how the disease and treatment have affected her perceptions of herself as a sexual being and her ability to form relationships with others. Regular Pap tests are needed to monitor for recurrence of cervical changes. Providing women with information about practicing abstinence, having fewer sexual partners, and getting to know their partners and the partners’ sexual history before intercourse may reduce the risk of HPV infection.

Nurses should reinforce the importance of follow-up to all women. If a woman has a history of abnormal Pap tests, she should follow up as indicated; this usually is every three to four months. Nurses should take the initiative to send reminder cards or call women with reminders when they are scheduled to return. One good way of doing this is to have cards already made when a woman makes her appointment. This card is filled out by the woman before she leaves the office and mailed to the woman several weeks before her next appointment.

**Conclusions**

A relationship between HPV and cervical cancer had been established. Nurses must educate the public regarding this risk. Optimal, 100% of women who are at risk should obtain regular Pap tests. The morbidity and mortality associated with cervical cancer can be reduced. Research continues toward the development of HPV immunizations, but, at present, regular Pap tests and conscientious follow-up of abnormalities and HPV infections is the standard of care.

**Author Contact:** Wendy M. Likes, APRN, BC, can be reached at wlikes@utcancerinstitute.com.

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Subclinical HPV is 10–30 times more common than apparent infections.

Cervical cytology is responsible for a 70% decrease in cervical cancer mortality during the past 50 years and is one of the most effective screening tests at present.