Reducing the Economic Burden of HPV-Related Diseases
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Human papillomavirus (HPV) infection is a common sexually transmitted infection that is often acquired at the onset of sexual activity. Risk factors include younger age at time of sexual debut, sexual behavior, intact foreskin, and immunologic status. Persistent infection with high-risk oncogenic HPV types (especially 16 and 18) is associated with cervical cancer, other anogenital diseases, as well as some head and neck cancers. Infection with low-risk HPV types is associated with genital warts, low-grade dysplasias, and recurrent respiratory papillomatosis. Screening and management of HPV-related diseases incur high healthcare costs. Whereas routine screening of female patients with Papanicolaou tests helps prevent advanced stages of cancer through early detection and treatment, the recently developed HPV L1 capsid protein virus-like particle vaccines offer an option for prevention of HPV-related diseases, including cervical cancer.

For a long time, a need has existed for more research in women’s health. Over time, new data have been emerging on such women’s health issues as heart disease prevention, and early detection, prevention, and treatment of breast cancer. Many advances have also been made related to cervical disease, cervical cancer, and other diseases related to the human papillomavirus (HPV).

This review provides the latest thinking and data related to HPV. Many presentations at symposia may discuss conditions or diseases that physicians do not often see, especially in primary care–type practices. However, HPV is not one of those entities. Current estimates show that approximately 20 million people are infected with HPV in the United States.1 The annual incidence of sexually transmitted HPV infection is 6.2 million.2 In 2005, an estimated 10,370 new infections and 3710 deaths occurred.3 Worldwide HPV infection is a major issue as well.

In the United States, the total direct medical expenditures for HPV, at $1.6 million annually,4 are the highest of all other STDs except the human immunodeficiency virus infection. During their lifetime, about 75% of sexually active individuals will be exposed to HPV.4 One of the most common STDs is genital warts, with 1.4 million individuals (1%) currently affected, and the incidence is increasing.5

Genital Warts
Between 500,000 and 1 million new cases of genital warts occur annually in the United States,6,7 and approximately 316,000 initial office visits in the United States are for genital warts.7 A high number occurs in the later teenaged and early college-aged population. Genital...
warts, like most warts, have about a 3-month latent epithelial phase. In a study by Winer et al, visible, obvious condylomata acuminata (genital warts) developed in about two thirds of women within 3 years from first sexual intercourse and exposure to HPV type 6 or HPV type 11. The median time to progression from infection to overt clinical warts was 2.9 months, and the median time to wart clearance in response to treatment was 5.9 months. Therefore, changing the paradigms for transmission and prevention of genital warts could make a great difference.

Most HPV is spread by sexual contact. Therefore, proscribing sexual contact obviously would prevent HPV transmission. Compliance with abstinence, however, would be difficult to achieve, especially among teenagers. It is also known that even with abstinence, some documented cases of fomite transmission have occurred, as infection with HPV can be spread by other means (ie, fingers, tampons, swabs, biopsy forceps, and other devices). Also, documented cases of nonpenetrative sexual activity have been implicated as a cause of genital warts.

Unfortunately, many teenagers may be confused about what constitutes “having sexual relations” and “not having sexual relations.” Cancer can occur in the throat; so clearly, oral sex also is a means of HPV transmission. It is therefore essential to use clear definitions when determining which individuals or populations are at risk for HPV-associated diseases. Although nonssexual routes of HPV transmission exist, the sexual route is by far the most common. Transmission of HPV infection does not require penetrative intercourse.

Diagnosis of Genital Warts
Visual inspection with magnification is usually sufficient for diagnosing genital warts. Acetic acid application is insensitive and nonspecific and should not be used for routine screening or diagnosis. It is used mainly for identifying cervical lesions for biopsy. Biopsy is rarely necessary, but it should be done if diagnosis is in doubt, the patient is immunocompromised, the lesion worsens with therapy, or the lesion is pigmented or fixed.

Treatment Options for Genital Warts
The patient may self-treat with topical application of podofilox or imiquimod. Modalities administered by a physician include the following:
- cryotherapy, recommended for vaginal, anal, and oral warts
- podophyllin resin
- trichloroacetic or bichloroacetic acid, recommended for vaginal and anal warts
- surgery (shave biopsy, laser, electrosurgery), recommended for anal, vulvar, and oral warts.

All these modalities have 60% to 80% short-term efficacy and high rates of recurrence. Their effect on transmission is unknown.

Diagnosis of Cervical Abnormalities
Cytology (Papanicolaou [Pap] smear test) is a useful screening test for detecting cervical dysplasia. It provides indirect evidence of HPV infection because it detects squamous epithelial cell changes typically caused by HPV. The US Food and Drug Administration has approved high-risk HPV testing for triaging women with atypical cells of undetermined significance (ASCUS) detected with the Pap test and as an addition to the Pap test for cervical cancer screening in women 30 years or older. This test is unnecessary for women who have had a Pap test finding of low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL) because we know most are infected with HPV.

Currently in the United States, testing for high-risk HPV is done in two major settings. One is a reflex test used when a Pap test shows ASCUS. Newly recommended is high-risk testing. Women who have both tests showing no abnormality can be reliably screened at 3-year intervals because of the high negative predictive value of negative HPV tests combined with cytology.

About 25% of the HPV-infected population has no evidence of infection, whereas the largest proportion of the 75% of sexually active individuals with HPV infection comprise those who have serologic evidence (ie, antibodies to HPV) of having been infected sometime in the past but who do not currently have active infection.

Many women have HPV infection detected by colposcopy, the use of which is determined by the findings of the physical examination and Pap test (exclusive of HPV test findings). When a woman has a Pap test showing abnormal cells, follow-up biopsy is used to histologically establish the level of disease.

Indications for cervical biopsy include visible exophytic lesions on the cervix, an HSIL Pap test result, a Pap test showing atypical squamous cells that cannot exclude HSIL, or LSIL with abnormal colposcopic findings.

Treatment Options for Cervical Abnormalities
Treatment options for patients with cervical abnormalities start with observation. Cryotherapy may be used to destroy precancerous lesions by freezing them with a metal probe. The loop electrosurgical excision procedure (LEEP) is another option, in which an electric current is passed through a thin wire loop to act as a very sharp knife. Laser therapy directs a narrow beam of intense light to destroy or remove abnormal cells. In cervical conization, or cone biopsy, a knife, laser, or LEEP probe is used to remove a cone-shaped piece of tissue from the center of the uterine cervix.

Transmission of Human Papillomavirus
One medical myth is that once individuals have had sex, they will automatically have an HPV infection. The median number of sexual partners that an individual must have to reach the 50% infection mark for a particular HPV type is four to five. If young male patients are given this information, they will likely think, “I could have four partners, and I’ll be safe.” Of course, that conclusion is erroneous. One’s personal risk is determined by one’s choice of a sexual partner. For specific populations, it takes more exposures on average to reach the 50% infection rate. That myth about four to five sexual partners is important in the discussion regarding the design of studies, particularly regarding inclusion and exclusion criteria, by Susan Mayeaux • Reducing the Economic Burden of HPV-Related Diseases JAOA • Supplement 2 • Vol 108 • No 4 • April 2008 • 53

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In most cases, sexual contact with an infected partner is necessary for transmission. Men are implicated as the “vectors,” or “carriers.” The incubation period for genital warts ranges from 3 weeks to several months, whereas it may take decades for development of cervical cancer. The source contact often has subclinical infection and is asymptomatic.

Once individuals become sexually active, the incidence of HPV infection increases. In a study looking at a college-aged population, it was found that once sexual activity was initiated—even without intromissive intercourse—the incidence of infection increased over time.

**Human Papillomavirus Types**

There exist high-risk, or oncogenic, genotypes of HPV, and low-risk, or benign, genotypes of HPV (Figure 1). Basically, HPVs are categorized into groups based on the sequences of certain proteins, mainly the L1 protein, which is the major structural protein in the viral coat. The vaccine-type virus-like particles and the live virus look alike on the outside.

With wild-type HPV infection, an individual who is exposed to a certain type (e.g., HPV 16) will become immune to that type, without having immunity to other HPV types. Thus, each HPV-type infection is almost a different disease as far as its effect on the body.

Some types of HPV have a greater association with cancer than others, whereas some HPV types, mainly types 6 and 11, generally do not cause cancer. However, they can still cause disease. These HPV types are only slightly associated with cancer, mainly vulvar cancer.

Type 6 and type 11 HPV cause an extremely rare, but serious, syndrome termed recurrent respiratory papillomatosis (RRP). Although only about 3000 cases occur per year in the United States, RRP is a devastating disease. Treatment of children with RRP requires multiple ablations and noxious chemicals placed in the airway to control the disease until such time as these children can outgrow the disease.

Juvenile onset of RRP is thought to be the result of vertical transmission from HPV-infected mothers to infants during delivery. Adult onset occurs less frequently and is the result of transmission through sexual contact.

Condoms may not be universally effective in preventing HPV-associated cervical dysplasia but may prevent genital warts.

**HPV-Related Cancers**

The two HPV types posing the highest risk associated with cervical cancer are HPV 16 and HPV 18. Figure 1 shows the common HPV types associated with malignant disease. The top five high-risk HPV types are 16, 18, 31, 33, and 45, with HPV 16 and HPV 18 causing the greatest proportion of cervical cancer worldwide. Minor variations occur in prevalence of HPV types from country to country. In general, the ranking of these types holds fairly true.

Vaginal and vulvar cancers are also associated with HPV infections, and other sites of malignant involvement also have been identified. An extremely rare cancer of the nail fold and some oropharyngeal cancers are related to HPV 16. New data have shown HPV 16 is associated with up to 70% of lower tongue and pharyngeal cancers. Clearly, the HPV in general is involved in malignant disease in multiple regions. Data, however, are still insufficient to determine exactly how effective any particular preventive methods or treatment modali-
using will not be sufficient to accomplish the paradigm and adopting a totally new approach.

Cervical cancer is directly related to HPV infection, but it is not necessarily sufficient by itself to cause all cervical cancers; 99.7% can be proved related to HPV, the other 0.3\%,\textsuperscript{11} is suspected but cannot be proved to be related to HPV. Potential cofactors exist in cervical carcinogenesis (Figure 2).\textsuperscript{16,23,24} If cervical cancer is an infectious disease, a new paradigm is warranted, one that parallels the current one for preventing hepatitis B, poliomyelitis, rubella, and other diseases that are becoming less common and having reduced morbidity and mortality in the United States.

Several malignancies are attributable to HPV infection (Figure 3).\textsuperscript{25,26} Each year, 6\% of 9 million new cases of all cancers worldwide, excluding nonmelanoma skin cancers, and 20\% to 24\% of all cancers in women in Latin American, Southwest Asia, and sub-Saharan Africa are attributable to HPV infection.\textsuperscript{26}

### Risk Factors for HPV Transmission

Several factors are known to pose higher risk for transmission of HPV (Figure 4).\textsuperscript{5,11,27-30} The debate continues about whether circumcision poses a risk. The latest data indicate that a small effect exists in males who are not circumcised, probably related to the full exposure of the inner mucosal surface of the prepuce to vaginal secretions.\textsuperscript{31} The greatest risk factor clearly is the number of an individual’s sexual partners, especially the lifetime number of sexual partners. The more sexual partners an individual has, the more likely the exposure to a high-risk HPV type. The following description of a public service announcement spot, though not about HPV, is apropos and provides a visual concept illustrating the exponential increase in risk of disease transmission.

A beautiful woman is running through a field of beautiful flowers. A very handsome man is running toward her, and she is running toward him. Then, the camera pans back and reveals two men behind the woman. Next, the camera pans back to the handsome man, and three women standing behind him. The camera pans back even farther, and behind each woman stand another three men. The camera then zooms up into space to provide a wide-angle shot of a huge pyramid of people behind the original two attractive individuals.

The significance of this pyramid is important when considering risk of HPV transmission because, as the study by Castellsagué et al\textsuperscript{32} shows, when one partner is monogamous, risk is directly related to previous exposure, but when the partner is not monogamous, risk is multiplied. Figure 4 outlines factors associated with higher risk of HPV transmission.

### Screening and Prevention

Vast sums of money are spent in the United States for screening and prevention. Inisinga et al\textsuperscript{33} examined the health-care cost of cervical HPV-related disease (in 2002 dollars). Approximately 1 million of the 50 million Pap tests done per year in the United States show an abnormality. The cost of workup for a Pap test showing an HSIL was about $2400.

In a study by Alam and Stiller,\textsuperscript{34} the total direct costs (including costs of initial and subsequent physician visits) per complete clearance of simple and extensive condylomata acuminata via medical modalities ranged from $424 for podofilox to $6665 for interferon-alfa 2b. The

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### Figure 2. Potential cofactors in cervical carcinogenesis

- **Other Infectious Agents**
  - Herpes
  - Chlamydia
  - HIV (and other immunosuppression)
- **Diet**
- **Smoking**
- **Hormonal Contraceptives**
  - Weak immunomodulatory effect
  - Eversion of columnar epithelium
  - Decrease in blood folate levels
  - Progesterone effect on human papillomavirus expression

### Figure 3. Malignancies attributable to human papillomavirus infection

- **Cervical cancers** approximately 100%*
- **Anal cancers** (85%)†
- **Vulvar, vaginal, penile cancers** (50%)†
- **Oropharyngeal cancers** (20%)†
- **Laryngeal and esophageal cancers** (10%)†
- **Nonmelanoma skin cancers** (unknown but likely substantial proportion)*

### Figure 4. Risk factors for HPV transmission

- **Cancer risk by lifetime number of sexual partners**
- **Cancer risk by number of sexual partners**
- **Cancer risk by number of sexual partners per day**
- **Cancer risk by number of sexual partners per month**
- **Cancer risk by number of sexual partners per year**

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direct costs for surgical modalities ranged from $285 to $951.24 Thus, effective prevention of HPV-related disease—even by reducing the number of abnormalities detected on Pap tests by 10% to 30%—could lead to substantial healthcare cost savings.

Generally, antibodies develop in individuals who are infected with the low-risk types of HPV—types 6 and 11—just as they do in those persons infected with HPV type 1, which causes the common warts of the finger. The same thing commonly occurs in individuals with the high-risk types of HPV, but not always.

The good news is that in most women who become infected with the worst HPV types, the infection clears by itself. The bad news is that no one can predict in which women the infection will clear. Thus, HPV of the high-risk types may persist, and as the infection persists, the virus forms proteins that interfere with DNA transcription, pre-programmed cell death (or apoptosis), and the cell’s ability to enter the resting cell phase.

Uncontrolled cell growth, DNA errors, and persistent HPV infection lead to cancer. High-risk types of HPV are known to be associated with cancer. Ability to predict in whom this threat exists would allow directly targeting prevention for those women at highest risk of cancer. However, despite the best diagnostic tests available, research findings, and recognition of immunomodular effects of cofactors (eg, smoking, nutrition, oral contraceptives), physicians still lack such predictive ability.

It was once thought that HPV infections progressed in an orderly fashion to cervical intraepithelial neoplasia grade 1 (CIN-1), next to grade 2 (CIN-2), and then to grade 3 (CIN-3). It is now recognized, however, that CIN-1 and HPV infection are much the same and not where the real risk for cancer lies. Somewhere in CIN-1 HPV infection, one cell becomes abnormal and clones itself and becomes the CIN grades 2 and 3, which ultimately lead to cancer.

New evidence-based algorithms for management of abnormalities detected on Pap tests are now available at http://www.asccp.org.

Factors

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<tr>
<th>Women</th>
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<tbody>
<tr>
<td>Age†</td>
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<tr>
<td>Sexual behavior‡</td>
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<tr>
<td>— increased risk associated with greater number of sexual partners‡</td>
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<tr>
<td>— risk increases with earlier age of first sexual intercourse§</td>
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<tr>
<td>Sexual behaviors of previous male sexual partners‡</td>
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<td>Immunologic status‡</td>
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<td>HPV more likely in immunosuppressed women</td>
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<th>Men</th>
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<tr>
<td>Lifetime number of sexual partners</td>
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<td>Number of recent sexual partners</td>
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<tr>
<td>Uncircumcised</td>
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<td>Same sex encounters</td>
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Genital warts are easier to identify, but if they do not respond to treatment as expected, a tissue biopsy is warranted. If the patient has already been treated for genital warts, it is essential to alert the pathologist to avoid using chemicals that are noxious and alter the appearance of the cell sample.

Comment

Human papillomaviruses are associated with a wide spectrum of disease, ranging from noncancerous lesions to cancer diseases, including invasive and in situ cancers of the cervix, vulva/vagina, anus, and penis, as well as invasive conjunctival and tonsillar cancers. All treatment of patients with HPV infection is directed toward high-grade disease and prevention of cancer disease.

The question has always been, How can we treat patients with HPV-related diseases more effectively? But now, the question has become, How can we prevent these diseases more effectively? The answer may be the HPV L1 capsid protein virus-like particle vaccines. These vaccines are designed to prevent genital infections, genital warts, and anogenital neoplasia. The bivalent and quadrivalent HPV vaccines are not live; they contain no viral DNA, so they are neither infectious nor oncogenic.

References


