Cervical Cancer Remains One of the Most Prevalent Diseases

Cervical Cancer

ABSTRACT: Cervical cancer remains one of the most prevalent diseases affecting women worldwide. Essentially, the human papillomavirus (HPV) infection causes all cervical cancer, and two high-risk subtypes, HPV 16 and HPV 18, account for about 70 percent of all cases. Risk factors include multiple sex partners, early age at first intercourse, multiparity, immuno-deficiency, and smoking. Screening programs for cervical cancer in the United States have markedly reduced the incidence of the disease. The Papanicolaou test (Pap test) has been the mainstay of screening; liquid-based cytology is the most common. HPV testing has two major roles in the clinical setting: triage of atypical squamous cells of undetermined significance (ASC-US) cytology and combination screening in patients older than 30 years. Prevention of cervical cancer involves not only screening but also education, safe sexual practices, and use of the HPV vaccines.

The introduction of human papillomavirus (HPV) vaccines and the availability of a DNA test for the virus are exciting developments in the detection and prevention of cervical cancer. They represent a unique opportunity to continue to reduce the number of cases of cervical cancer in the United States and worldwide.

Epidemiology

Cervical cancer remains one of the most prevalent diseases affecting women worldwide, second only to breast cancer in terms of malignancy-related morbidity and mortality. Worldwide, cervical cancer continues to affect more than 530,000 women annually and results in more than 275,000 deaths.

In the United States, screening programs have markedly reduced the incidence and prevalence of cervical cancer over the past 50 years. The American Cancer Society estimates that there will be about 12,170 new cases of invasive cervical cancer in the United States in 2012, with 4220 deaths. In addition, the lifetime probability that an American woman will develop cervical cancer is approximately 1 in 147.

Risk Factors

Many risk factors contribute to the development of cervical cancer. It’s now known that essentially HPV causes all cervical cancer. This virus is transmitted sexually, and although HPV infection is not a re-portable disease, it’s estimated to be the most common or second most common sexually transmitted infection in the United States. Management of risk

factors primarily involves lessening the risk of HPV transmission.

Modification of sexual behavior is the best way to prevent HPV infection and cervical cancer. Patients with multiple partners are at greater risk for the development of cervical cancer; in fact, those patients with seven or more partners have a relative risk of 8.1. Patients who engage in intercourse at a younger age or with more high-risk sex partners are also at greater risk for the development of cervical cancer. Other sexually transmitted infections, such as chlamydia, may also be co-factors in the development of invasive cervical cancer.

Multiparity is an additional known risk factor, although the physiologic reason for the increased risk is not clear. The increased risk may stem from the vaginal trauma during delivery, the effects of the hormone changes on the cervix, or nutritional variations during pregnancy. Immunodeficiency, either secondary to systemic disease such as HIV infection or long-term immunosuppressant medications, also increases the risk of cervical cancer. Screening intervals and strategies should reflect this increased risk. There’s also some evidence that long-term (greater than five years) use of oral contraceptives increases the risk of cervical cancer in patients who test positive for HPV.

Smoking has been shown in numerous studies to be a co-factor in the development of cervical cancer. Among HPV-positive patients, the risk increases for those who have ever smoked. Although the definite cause of this association isn’t clear, the cervical mucus of smokers reveal metabolites of cigarette smoke, where these metalbolites likely damage host cell DNA and facilitate cervical cancer progression.

HPV can be found in approximately 99.7 percent of all HPV infections. This family of double-stranded DNA viruses includes more than 100 subtypes. The viruses infect only humans, and they have a variety of clinical manifestations. In

addition to cervical cancer, HPV causes common warts, plantar warts, genital warts, and Bowen’s disease.

Certain subtypes have been implicated in the development of cervical cancer. The subtypes that cause cancer are stratified into low-, high-, and intermediate-risk groups. Most of the attention focuses on the most high-risk subtypes, especially HPV 16 and HPV 18. These two high-risk types account for about 70 percent of all cervical cancer.

HPV infection is extremely common in young sexually active women. One study found a prevalence of 64 percent among urban adolescent girls, while the overall prevalence among women aged 18 to 40 years is 40 percent. Typically, young women acquire the infection during their late teenage or college years. A study of college-age women showed that 43 percent of those who were initially HPV-negative tested positive for the virus within the next three years.

HPV is transmitted through skin to skin contact, the majority of which is intimate contact or intercourse. The transmission of HPV subtypes may be genital-genital, oral-genital, or manual-genital. Fomite transmission, though unlikely, is possible. Most HPV infections clear within 24 to 36 months, especially in younger women.

HPV causes cervical cancer by incorporating into the host DNA. The oncogenes E6 and E7 incorporate into host DNA and encode proteins that then interact with host proteins to dysregulate the cell cycle.

Screening Methods

Screening programs for cervical cancer in the United States have markedly reduced the incidence of the disease. Because cervical cancer arises from a precancerous state, cervical intra-epithelial neoplasia (CIN), we are able to detect and appropriately treat these changes before invasive cervical

cancer develops. From the detection of CIN class 2 or 3, it takes an average of about 10 years for invasive cervical cancer to develop. This lead time allows detection and treatment for most cases in the early stages.

Although screening programs are very successful, the current system still has inadequacies and inefficiencies. In 2010, 76.4 percent of adult women reported having a Papanicolaou (Pap) test in the past three years. Most commonly, cervical cancer develops because a patient had no screening at all or missed screening tests.

Papanicolaou test. Cervical cancer screening has had widespread use in the United States since the 1950s. Dr. George Papanicolaou originally developed the Pap smear in 1941. A standardized reporting system, the Bethesda System, was developed in 1988 and revised in 2001.

The conventional Pap smear has some disadvantages. The test has a low sensitivity of 60 percent to 80 percent, and therefore annual testing was necessary to increase the likelihood of detecting early cervical changes. The test itself also has inherent disadvantages, since it requires individual interpretation by cytopathologists. In addition, the quality of the samples collected is highly variable, and the differentiation of the cell types can be technically difficult.

Most cytology done in the United States today is liquid-based cytology. As opposed to smearing the cells directly onto a microscope slide, the cells are placed into a vial with preservative liquid and processed to separate the cells from the microscopic debris. The sensitivity of the liquid-based test has been reported to be 85 percent to 95 percent. Another benefit of the liquid-based testing is that the remainder of the sample can be used for additional testing for HPV, chlamydia, or Neisseria gonorrhoeae. Use of the liquid-based test reduces the false-negative rate by 60 percent.

HPV DNA test. The newest test available for screening is the HPV DNA test. This test screens for the 13 high-risk HPV subtypes that are most likely to cause cervical cancer. The test employs RNA probes that bind to the HPV DNA strand. Antibodies then capture the hybrids and produce light, which is measurable. This test is more sensitive (88 percent to 100 percent) than cytology methods but is also less specific for the detection of cervical dysplasia.

HPV testing basically has two major roles in the clinical setting:

- Triage of atypical squamous cells of undetermined significance (ASC-US) cytology
- Combination screening in patients older than 30 years

The HPV DNA test has some advantages, including increased sensitivity (up to 100 percent), the lack of inter-observer variability, and the possibility for self-collection. Disadvantages to the test include the high prevalence of the disease, especially in women younger than 30 years. In addition, a test with high sensitivity and relatively lower specificity for high-grade squamous intra-epithelial lesion (HSIL) (86 percent) could lead to increased false-positive tests and more colposcopy. Moreover, in younger women, a majority of the HPV infections are transient and will be cleared by the immune system without any appreciable cellular cervical changes.

For women older than 30 years of age – among whom the prevalence of HPV infection is lower than in younger women, but the infections are less transient – the HPV DNA test in combination with liquid-based cytology has a negative predictive value of 99 percent to 100 percent, and the likelihood that the patient has undetected CIN 2 or higher is 1 in 1000. This approach is also cost-effective.

The HPV DNA test has an important role in the triage of

patients with ASC-US cytology on conventional or liquid-based tests. A large, multicenter trial from the National Cancer Institute, the *Atypical Squamous Cells of Undetermined Significance/Low Grade Squamous Intraepithelial Lesion Triage Study* (ATLS), ended in 2001. This study randomized patients with ASC-US or low-grade squamous intra-epithelial lesion (LSIL) to one of three management arms: HPV DNA testing, immediate colposcopy, or repeated cytology. This study found that HPV testing was more sensitive for CIN 2 or 3 and fewer patients were referred for colposcopy.

In order for patients and physicians to adopt new screening practices involving the HPV test, we need to correct some of the myths about the virus, the infection, and the test. First, the infection is extremely common and affects more than 80 percent of women at some point in their lives. Patients also need to know that most positive HPV infections are transient, and that the immune system will clear most infections without any additional treatment. Patient education should also emphasize that a positive HPV test does not indicate unfaithfulness in a relationship.

Guidelines for Screening

The table [See original article] lists the three major cervical cancer screening guidelines issued by the American Cancer Society (ACS), the United States Preventive Services Task Force (USPSTF), and the American College of Obstetrics and Gynecology (ACOG).

All of the current guidelines recommend initiation of screening at age 21 regardless of sexual history. Although screening for patients who are truly abstinent isn’t necessary, screening patients older than age 21 ensures the screening of women with either incomplete or unreliable sexual histories. We don’t recommend screening those younger than age 21 because adolescents are at very low risk for cervical cancer and any cervical cell abnormalities detected are

probably transient and will resolve on their own.

Annual screening is no longer recommended. The USPSTF and the ACS recommend screening women ages 21 to 65 with the Pap test every three years. Women ages 30 to 65 can be screened with the HPV DNA test and the Pap test (co-testing) every five years. In this age group, the ACS preferred co-testing over the Pap test alone, whereas the USPSTF considered co-testing an acceptable alternative. All current guidelines advise against using the HPV DNA test alone in women of any age or using co-testing in women younger than 30 years.

ACOG recommends screening women ages 21 to 29 with the Pap test every two years; women ages 30 to 65 may increase the interval between Pap tests to every three years if they have a history of three consecutive negative Pap tests. Co-testing is acceptable in women ages 30 to 65 every three years if the Pap test is normal and the HPV test is negative.

All current guidelines have exceptions for patients who are at increased risk for cervical cancer, including those who are immuno-compromised or have a history of cervical dysplasia or cancer.

The recommendations vary with regards to the discontinuation of screening, ranging from 65 years (USPSTF and ACS) to 70 years (ACOG) depending on the results of previous tests. ACOG recommended the continuation of routine screening in older women who have multiple sex partners. Total hysterectomy is also a reason to discontinue screening, but the reason for the surgery (benign versus malignant conditions) should dictate the necessity of screening. For example, depending on risk factors, sampling of cells in the vaginal vault may be done to screen for vaginal cancers and/or confirm the absence of any remnant cervical cells. Pap tests should continue after a supra-cervical hysterectomy (cervix remains). In either case, regular pelvic and rectal examinations are necessary. Women who have received the HPV vaccine should continue

screening because the overall effect of vaccination on high-grade precancerous cervical lesions and cervical cancer remains unknown.

Risk Management

Incorporating the HPV test into a primary screening role in conjunction with Pap testing could also prove to be a wise risk management decision. Although the Pap test has been an extremely effective screening tool, the test still has some inherent legal risks. There are several steps in Pap testing that increase the likelihood of error. First, the tests require collecting an adequate sample, and invariably the samples are of inconsistent quality. Then, cytopathologist, who's reading up to 100 slides per day, needs analyze and read the tests. There are additional steps in physician and patient notification of results and appropriate follow-up testing that make the Pap test an imperfect test.

Beyond the potential pitfalls in performing the Pap test, physicians must realize that most women believe the test is 100 percent accurate even though there are significant false-negatives. In addition, if a patient does develop cervical cancer and the screening protocol wasn't followed closely or there was an error, most juries will empathize with a young otherwise healthy patient. The HPV test has higher sensitivity, does not rely on human interpretation, and leaves less room for error and potential malpractice claims.

Prevention

Prevention of cervical cancer certainly involves screening, but it also includes education, safe sexual practices, and HPV vaccination. At this point, abstinence is the only certain way to prevent the acquisition of the HPV subtypes that lead to cervical cancer. Long-term monogamous relationships also play a role in the prevention of the spread of the virus, because patients with multiple partners are at increased risk for HPV

infection.

Although condoms are not entirely effective at preventing the transmission of HPV, they do appear to decrease the likelihood of developing a genital HPV infection. A study of 82 college-age women engaging in their first sexual intercourse showed a significantly lower incidence of HPV infection in those whose partners used condoms 100 percent of the time. These patients also had no cases of intra-epithelial lesions during the course of the study. Another study showed that proper condom use facilitates the clearance of an HPV infection.

The most significant development in the prevention of HPV infection and cervical cancer has been the HPV vaccine. Two vaccines have received approval for the prevention of the most common types of HPV infection that cause cervical cancer: Gardasil and Cervarix.

In 2006, the FDA approved the use of Gardasil for girls and women ages 9 to 26. This quadrivalent vaccine is designed to prevent infection with HPV 6, 11, 16, and 18. HPV 16 and 18 cause about 70 percent of all cases of cervical cancer, and HPV 6 and 11 are subtypes responsible for genital warts. The vaccine uses the viral capsid protein (L1) and does not include any HPV DNA. The phase IIb trial of this quadrivalent vaccine showed an efficacy of 90 percent with regard to persistent infection or disease associated with any of the 4 subtypes (6, 11, 16, 18) through 36 months. Gardasil is also approved for use in boys and men ages 9 to 26.

In 2009, the FDA approved the use of Cervarix for girls and women ages 10 through 25 years; this bivalent vaccine was developed to prevent HPV 16 and 18 infections. The study of the bivalent vaccine enrolled 1113 women and was shown to be effective at reducing persistent infections with HPV 16 and HPV 18 in 100 percent of patients.

The CDC’s Advisory Committee on Immunization Practices

recommends routine vaccination of girls aged 11 or 12 years with three doses of either Cervarix or Gardasil. The vaccination series can be started beginning at age 9. Vaccination is also recommended for girls and women aged 13 through 26 years who have not received vaccinations previously or who have not completed the three-dose series. If a woman reaches age 26 before the vaccination series is complete, remaining doses can continue after age 26. The CDC also recommends Gardasil for all boys age 11 or 12, and for males 13 through 21 who did not get any or all of the three doses when they were younger. All men, including those who have sex with other men (e.g., bisexual men), may receive the vaccine through age 26 if they did not get fully vaccinated when they were younger.

Ideally, vaccine should be administered before potential exposure to HPV through sexual contact. The median age of first sexual intercourse in the United States is 15 years, so the recommended age range for vaccination would capture most patients before their initial sexual encounter.

These vaccines could drastically reduce the number of biopsies and invasive procedures associated with abnormal Pap and HPV tests; however, routine cervical cancer screening remains important. Screening will be necessary to prevent cancer in patients who did not receive the vaccine, who had HPV before they were vaccinated, or who are infected with other HPV subtypes. In addition, the long-term efficacy of the vaccines has not been established.

The acceptance of the HPV vaccine by physicians, patients, and parents is also a concern. Although the initiation of the HPV vaccination series among girls in the United States aged 13 to 17 years increased from 25 percent in 2007 to 48.7 percent in 2010, only one in three completed the entire three-dose series. Furthermore, a recent study showed that the number of insured females aged 13 to 27 years completing the HPV vaccination series dropped overall from 50 percent in 2006 to

approximately 20 percent in 2009. The study also found that obstetricians/gynecologists were more successful in having patients complete the series compared to pediatricians and family medicine practitioners, with family medicine practitioners the least successful. Because the infection is sexually transmitted, continued education about cervical cancer and HPV is necessary to convince people of the efficacy and appropriateness of the vaccine, especially in the preteen population before sexual activity occurs.

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