Cervical cancer

Screening, management, and prevention

Abstract: Cervical cancer incidence in the United States is estimated to affect 12,900 women in 2016, with 4,100 deaths. Screening for this cancer with Pap test and adjunct human papillomavirus testing has made cervical cancer a treatable disease. This article reviews screening, treatment recommendations, and prevention for cervical cancer.

By Barbara A. Wuerthner, NP-C and Maria Avila-Wallace, RNC, WHNP

Cervical cancer screening via the Pap test has made it possible for this cancer to be a treatable disease. Cervical cancer in the United States is estimated to affect 12,990 women in 2016, with an estimated 4,100 deaths.[1] The literature reveals that 50% of women diagnosed with cervical cancer never had screening done, and 10% had not been screened within the last 5 years.[2] It is important for NPs to have a good foundation and understanding regarding cytohistologic abnormalities, the role of human papillomavirus (HPV) in the development of cervical dysplasia and cancer, and the current recommended guidelines for cervical cancer screening and prevention.

Cervical cancer screening test

Dr. Papanicolaou originally introduced the cervical cytology test in 1941 using morphologic classifications.[3] The Bethesda system for reporting cervical cancer was later established in 1988.[4] This system changed the classification to one based on cervical carcinogenesis related to HPV.[2] At that time, there was wide variability in reporting cervical cytology. A recommendation was made that the terminology should communicate relevant information from the lab to the healthcare provider.[4]

The second recommendation declared that terminology must be uniform and reproducible across different pathology labs, and it must reflect the most current understanding of cervical neoplasia (see *Bethesda terminology for cytology*).

The role of high-risk HPV

One cannot discuss the abnormal Pap result without including the role of high-risk HPV in cervical cancer. When HPV is detected on cervical cytology, a concurrent cytologic abnormality is seen one-quarter to one-third of the time.[3] The identification of this DNA virus in the 1980s determined

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it to be the etiologic agent responsible for virtually all cases of cervical cancer in addition to a significant proportion of other epithelial cancers of the genital tract.[5]

Approximately 200 HPV genotypes have been identified.[5] The oncogenic high-risk HPV genotypes include strains 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.[6] HPV 16 is the most oncogenic, followed by HPV 18. Of the 12 known oncogenic types, HPV 16 is linked to most high-grade cervical intraepithelial neoplasia (CIN 2-3) at the transformation zone (TZ) and is considered a precursor to cervical cancer.[3]

HPV 18 is also a concerning oncogenic high-risk type, more often associated with adenocarcinomas, which are found less commonly in the glandular cells present in the endocervical canal. These two high-risk HPV genotypes account for approximately 66% to 70% of cervical cancers.[3] Infection by approximately 12 other types account for the remaining 30%.[2]

Ninety percent of genital warts are caused by low-risk HPV genotypes 6 and 11, whereas other types are responsible for nongenital warts and asymptomatic infections.[5] Genotypes 6 and 11 are considered low risk because they do not lead to cervical cancer. One-half of new HPV infections are undetectable within 6 to 12 months, and approximately 90% will clear within a few years.[6] However, patients with persistent infection 1 to 2 years after initial infection have a higher risk of CIN.[5]

A persistent high-risk HPV infection is necessary to develop invasive cancer. Persistent HPV infections cause virtually all of the more than 500,000 cases of invasive cervical cancer diagnosed annually worldwide.[3] Cervical cancer occurs primarily at the TZ, which is the ring of tissue located where the squamous epithelium meets, and eventually replaces the glandular epithelium of the endocervical canal. Several steps are involved for cervical cancer to develop from a high-risk HPV infection. There must be acute infection from the more oncogenic types followed by viral persistence (rather than clearance), which leads to precancerous cell changes and finally invasion.[3]

In some cases, women may have difficulty clearing the HPV infection due to inherited or acquired deficiencies. For example, women who have coinfection of HIV will take longer to clear HPV, as HIV-induced immunosuppression impairs cell-mediated immune control of HPV infections.[3] There can be latency and reappearance of HPV, although this state of viral infection is not well understood.[3] The persistence of detectable high-risk HPV over years can increase the cancer risk.

Cervical cancer screening guidelines

The guidelines for cervical cancer screening were updated by a number of professional groups in 2012 and incorporated HPV testing. The American Cancer Society, the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology collaborated to create practicable guidelines for cervical cancer screening based on the most current data.[7]

The U.S. Preventive Services Task Force published screening guidelines in 2012 (www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cervical-cancer-screening), and the guidelines are currently under revision. The American College of Obstetricians and Gynecologists (ACOG) published similar guidelines, which were updated in 2016.[2] In all guidelines, initiation of screening is recommended at age 21 with cytology only. If results are negative in women age 21 to 29, the recommendation is against annual screening in favor of 3-year interval screening for cytology-only tests.[2,7]

Because only 0.1% cases of cervical cancer are detected before age 20, it was determined that regardless of age of sexual debut, the risk of cancer is low (with the exception of HIV-positive women).[2] The recommendation to add HPV cotesting with cytology should begin for women at age 30 because the presence of an incidental HPV infection is so common in the under-30 age group.[2,7] This is based on the knowledge that nearly all cases of HPV infection are cleared by the immune system in 1 to 2 years without causing neoplastic changes.

The recommended screening interval for women with both negative cytology and HPV cotesting is 5 years, as there is increased sensitivity when compared with cytology alone, allowing for greater detection of precancerous changes while allowing longer screening intervals without adding significant risk.[2,7,8] The ACOG guidelines suggest discontinuing cervical cancer screening at age 65 if the woman has had three negative prior cytology results or two consecutive cotesting results within the last 10 years, with the most recent performed in the last 5 years.[2]

Screening may also be discontinued for women post-hysterectomy with benign findings. If a hysterectomy was performed for moderate-to-severe cervical dysplasia, vaginal cytology is continued for 20 years posttreatment due to the potential risk of vaginal precancerous changes.[9]

More frequent screening is required for specific populations. For women who are immune-compromised, such as those with HIV or organ transplant patients receiving immunosuppressive treatment, screening remains yearly. This recommendation also applies to women with a history of diethylstilbestrol exposure in utero or those who have had a history of moderate or severe cervical dysplasia in the past.[2]

Bethesda terminology for cytology[4]

Interpretation of squamous epithelial cell abnormalities	
NILM	Negative for intraepithelial lesion or malignancy
ASCUS	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells of undetermined significance; cannot exclude HSIL
LSIL	Low-grade squamous intraepithelial lesion
HSIL	High-grade squamous intraepithelial lesion
Glandular cell	Endocervical or endometrial or glandular not specified

Management of cytologic abnormalities

The ASCCP responded to the terminology standardization with comprehensive, evidence-based guideline algorithms for managing abnormal Pap test results. These algorithms were last updated in 2012 and are available at www.asccp.org. The Pap and HPV test results were reviewed within the concept of cervical cancer prevention as a process with benefits and harms.[10] The guidelines represent the review of screening for cervical cancer and high-risk HPV subtypes detected on cytology.

The optimum strategies were then determined by identifying and relating those HPV abnormalities that are likely to progress to invasive cancer while avoiding destructive treatment of abnormalities unlikely to become cancerous. For women with higher-grade abnormalities or the presence of the oncogenic HPV subtypes, a colposcopic evaluation is recommended (see *Management guidelines for abnormal Pap test results*).

Diagnosis and treatment

Colposcopy is the accepted diagnostic test for evaluating abnormal Pap tests to determine the presence, location, grade, and extent of CIN.[11] The cervical epithelium is bathed with 3% to 5% acetic-acid solution and examined under magnification with a colposcope. As indicated in the ASCCP guidelines, if the results of the colposcopy are negative or

consistent with a low-grade abnormality, the Pap test should be repeated in 1 year.[10] The colposcopy should be repeated if the subsequent Pap test results remain abnormal.[10]

If moderate or high-grade cervical dysplasia is confirmed, ablation, cryotherapy, loop electrosurgical excision procedure (LEEP), and cervical cone biopsy (also known as conization or cold knife cone biopsy) are acceptable options for treating CIN. A LEEP and cervical cone biopsy have the advantage of examining the excised tissue by a pathologist to determine if margins are clear (although there may be an associated risk of preterm delivery for women with history of either or both procedures). A cervical cone biopsy is recommended when adenocarcinoma in situ is confirmed with colposcopy and if residual dysplastic tissue is seen with LEEP.[11]

HPV vaccines

The identification of HPV as the agent responsible for virtually all cases of cervical and genital tract cancer led to the development of three FDA-approved multivalent prophylactic HPV vaccines shown to be effective at preventing HPV infection.[5,6,12] The first-generation vaccines specifically target 70% of infections that may lead to cervical cancer, and the second-generation, nine-valent vaccine targets those additional 15% to 25% potentially oncogenic infections not addressed by the quadrivalent and bivalent vaccines (offering the potential to prevent almost 90% of cervical cancers).[5,6,12] (See *HPV vaccines.*)

HPV vaccines are the only preventive therapy available for young women and men, but they are underutilized in the United States. The literature identified the following reasons for the underutilization of the vaccines:

- The three-dose schedule[5,13]
- Accessibility and cost[14]
- Lack of state mandates for school vaccination[1,5,14]
- Provider discomfort discussing sexual health with parents and young patients[13]
- Lack of urgency conveyed by pediatricians due to the long, natural history of HPV-related disease[13]
- The notion that vaccination against HPV will encourage unsafe sexual activity among adolescents.[2,13]

All the multivalent vaccines have well-established efficacy in the prevention of cancers and its precursors; the vaccines have minimal systemic adverse reactions, positive safety profiles, long-term immune response, and the selective reduction in the prevalence of HPV types and genital warts.[3,6,12,13] Still, after the debut of the vaccines 9 years ago, vaccination coverage is substantially below the Healthy People 2020 target of 80%.[13,14]

In 2013, only 37.6% and 13.9% of adolescent girls and boys, respectively, had received all three vaccine doses, and 57% of girls and 34.6% of boys had received at least one of the recommended three doses of the HPV vaccine (with the majority of doses being the quadrivalent vaccine).[5,6,12-14] If vaccination rates were to increase to the targeted 80% by 2020, the CDC estimates that an additional 53,000 cases of cervical cancer could be prevented, and every year that vaccination rates do not increase, approximately 4,400 women would develop cervical cancer.[6]

HPV vaccines cannot prevent infection after the fact, which is why immunization is recommended before sexual debut.[13] Testing for HPV is not recommended before vaccination; however, if an individual tests positive for HPV, vaccination is still recommended, as it is unlikely that an individual would have been exposed to all of the other strains covered by the vaccine.[6] Revaccination with the HPV nine-valent vaccine, recombinant in previously vaccinated individuals with the quadrivalent or bivalent vaccines is not recommended.[6]

For individuals who have not completed the series with either of the two first-generation quadrivalent or bivalent vaccines, available data demonstrate no safety concerns if they were to complete the immunization schedule with the nine-valent vaccine.[6] Although studies show that HPV vaccines do not cause problems for infants born to women who were vaccinated while pregnant, they are not recommended for pregnant women, as more research is still needed.[15,16] The vaccines may be administered to lactating women, as inactivated HPV vaccines do not affect the safety of mothers or infants.[6]

Management guidelines for abnormal Pap test results[10]

Cytology results	HPV results	Management
Negative cytology	Positive high-risk HPV (+hrHPV non 16, 18)	Repeat cotesting in one year
Negative cytology	+hrHPV 16, 18	Colposcopy
ASCUS	–hrHPV	Repeat cotesting in 3 years or 1 year if cytology only
ASCUS	+hrHPV all types	Colposcopy
LSIL	–hrHPV	Repeat cotesting in 1 year
LSIL	+hrHPV or unknown	Colposcopy
HSIL	+/– or unknown hrHPV	Either colposcopy or LEEP

Primary high-risk HPV screening

The established causative relationship of cervical cancer development via a persistent, high-risk HPV infection also led to the development of a variety of FDA-approved,

HPV vaccines

Vaccine	Year released	HPV types	Age group
HPV quadrivalent (types 6, 11, 16, and 18), recombinant (www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf)	2006; revised 2012	6, 11, 16, and 18	Females: ages 9 through 26 Males: ages 9 through 26
HPV bivalent (types 16 and 18), recombinant (www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Cervarix/pdf/CERVARIX-PI-PIL.PDF)	2009	16 and 18	Females: ages 9 through 25
HPV nine-valent, recombinant (www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf)	2014; revised 2015	6, 11, 16, 18, 31, 33, 45, 52, and 58	Females: ages 9 through 26 Males: ages 9 through 26

high-risk HPV tests, which are currently recommended to be used in conjunction with cytology. As a rational consequence, questions have been raised regarding their use in primary screening.[17-20] Studies have shown that high-risk HPV testing is safe and has high sensitivity.[8,17] The test does not provide protection against invasive cancer; however, it may help reduce cancer risk and may aid in early cancer diagnosis.[20,21]

The most contemporary trial information available, which has evaluated the performance and use of primary HPV screening, is limited to a small number of trials in the United States and others conducted in Europe.[17-20,22] Follow-up data were restricted to 3 and 6 years, respectively. However, important observations were reported as a result of these trials:

- High-risk HPV primary screening had the highest sensitivity for cervical intraepithelial neoplasia grade 2+ but the lowest specificity (this referring to the possibility of a false negative result).[17]
- Cotesting had an intermediate specificity.
- Safety reassurance provided by the cotesting was derived from the HPV test component.
- The use of genotyping for HPV strains 16 and 18 as a way to triage HPV-positive women was supported.
- The incidence of cervical cancer was lower in women initially screened with HPV testing compared with cytology alone.
- HPV primary screening provided greater protection against invasive adenocarcinomas given the known limitations of cytology in identifying glandular lesions.[20,21]

Due to a well-designed study that provided the FDA with a reasonable assurance of safety and effectiveness when used as a primary screening tool for cervical cancer, the HPV DNA test for women ages 25 and older is the only FDA-approved test available at this time.[23] Interim guidelines have been put forth by ASCCP for applying primary HPV screening in the clinical setting. However, the need for further study makes it too early to adopt HPV primary screening for all women over age 25 as the primary screening intervention for cervical cancer in the United States at this time.[17,19]

Implications for practice

Cervical cancer screening saves womens' lives, but a number of women remain unscreened or underscreened.[2] Since the introduction of the Pap test, advances in cervical cancer screening and prevention include high-risk HPV testing and HPV vaccination. The advent of a uniform reporting system, known as the Bethesda System, improved the reporting process for cervical cytology results across different pathology labs.

Algorithms created and updated by the ASCCP provide a guide for managing abnormal Pap test results by assessing benefits and harms and include decisions taking into consideration both cytology and high-risk HPV types found in cotesting.[10] Avoiding unnecessary excision or ablation of the cervix in young women is advisable, even though the association between LEEP and preterm birth has been challenged.[2]

Future trends may move toward HPV as the primary screening test for detection of women more at risk for cervical cancer.[17] However, it does not change current medical practice guidelines for cervical cancer screening. HPV DNA testing has superior sensitivity (greater than 90%) in contrast to 50% for cytology; however, studies are necessary to fully evaluate its efficacy as primary screening in a variety of clinical settings.[9,17,19]

Studies suggest that up to 62% of women do not comply with the follow-up guidelines recommended by the ASCCP.[15] As clinicians, the role of patient education and other interventions, such as telephone counseling or written education material, were found to be effective strategies to improve adherence.[15]

The HPV vaccine is safe and effective in the reduction in the prevalence of HPV infections in young men and women.[5,6,12] HPV vaccination currently is only required as standard vaccination for middle-school children in two states (Rhode Island and Virginia) and the District of Columbia.[13,14] HPV vaccination rates must improve in order to meet the 2020 Healthy People objective of 80% of fully immunized boys and girls with all three HPV doses.[13,14]

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Barbara A. Wuerthner is an NP at Massachusetts General Hospital, Boston, Mass.

Maria Avila-Wallace is a gynecological oncology NP at Massachusetts General Hospital, Boston, Mass.

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