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Cervical cancer update: The latest on screening & management

Here are updated guidelines for prevention, testing, and treatment. Elimination of causative HPV continues to hold center stage in the global effort to curb disease.

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PRACTICE RECOMMENDATIONS

› *Encourage eligible patients to be vaccinated against human papillomavirus (HPV) because the vaccine is highly effective for preventing cervical dysplasia, especially when given to patients previously unexposed to the virus.* (A)

› *Screen for cervical disease with either cytology plus HPV testing or primary HPV testing with secondary triage for cytology; both protocols are more accurate than screening with cervical cytology alone, and allow you to widen the screening interval.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

The World Health Organization estimates that, in 2020, worldwide, there were 604,000 new cases of uterine cervical cancer and approximately 342,000 deaths, 84% of which occurred in developing countries.[1] In the United States, as of 2018, the lifetime risk of death from cervical cancer was 2.2 for every 100,000, with a mean age of 50 years at diagnosis.[2]

In this article, we summarize recent updates in the epidemiology, prevention, and treatment of cervical cancer. We emphasize recent information of value to family physicians, including updates in clinical guidelines and other pertinent national recommendations.

Spotlight continues to shine on HPV

It has been known for several decades that cervical cancer is caused by human papillomavirus (HPV). Of more than 100 known HPV types, 14 or 15 are classified as carcinogenic. HPV 16 is the most common oncogenic type, causing more than 60% of cases of cervical cancer[3,4]; HPV 18 is second, causing 16.5% of cases—taken together, the 2 types account for more than 75% of cervical cancers.

HPV is the most common sexually transmitted infection, with as many as 80% of sexually active people becoming infected during their lifetime, generally before 50 years of age.[5]

A NOTE FROM THE EDITORS

The Editors of *The Journal of Family Practice* recognize the importance of addressing the reproductive health of gender-diverse individuals. In this article, we use the words "women," "men," "girls," and "boys" in limited circumstances (1) for ease of reading and (2) to reflect the official language of the US Food and Drug Administration and the Advisory Committee on Immunization Practices. The reader should consider the information and guidance offered in this discussion of cervical cancer and other human papillomavirus-related cancers to speak to the care of people with a uterine cervix and people with a penis.

CONTINUED

TABLE 1

Variables associated with cervical cancer[7]

Cigarette smoking[a]
Early onset of sexual activity
Genetic predisposition to persistent human papillomavirus infection
History of other sexually transmitted infection
Immunosuppression
Multiple sexual partners or a high-risk sexual partner

[a] Associated with an increased risk of squamous cell carcinoma but not an increased risk of adenocarcinoma.

HPV also causes other anogenital and oropharyngeal cancers; however, worldwide, more than 80% of HPV-associated cancers are cervical.[6]

Risk factors for cervical cancer are listed in **TABLE 1**.[7] Cervical cancer is less common when partners are circumcised.[7]

Most cases of HPV infection clear in 1 or 2 years. In approximately 1% of untreated cases, cancer develops. Once infection progresses to high-grade dysplasia (ie, cervical intraepithelial neoplasia [CIN] 3), further progression to invasive cervical cancer occurs in approximately 30% of untreated cases.[8] Patients who develop cervical cancer generally test positive for a high-risk HPV genotype for at least 3 to 5 years before infection progresses to cancer.[9]

At least 70% of cervical cancers are squamous cell carcinoma (SCC); 20% to 25% are adenocarcinoma (ADC); and < 3% to 5% are adenosquamous carcinoma.[10] Almost 100% of cervical SCCs are HPV+, as are 86% of cervical ADCs. The most common reason for HPV-negative status in patients with cervical cancer is false-negative testing because of inadequate methods.

Primary prevention through vaccination

HPV vaccination was introduced in 2006 in the United States for girls,[a] and for boys[a] in 2011. The primary reason for vaccinating boys is to reduce the rates of HPV-related anal and oropharyngeal cancer. The only available HPV vaccine in the United States is Gardasil 9 (9-valent vaccine, recombinant; Merck), which provides coverage for 7 high-risk HPV types that account for approximately 90% of cervical cancers and 2 types (6 and 11) that are the principal causes of condylomata acuminata (genital warts). Future generations of prophylactic vaccines are expected to cover additional strains.

Vaccine studies have been summarized in a Cochrane review,[11] showing that vaccination is highly effective for prevention of cervical dysplasia, especially when given to young girls and women[a] previously unexposed to the virus. It has not been fully established how long protection lasts, but vaccination appears to be 70% to 90% effective for ≥ 10 years.

Dosing schedule. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends a 2-dose schedule 6 to 15 months apart, for both girls and boys between 9 and 14 years of age.[12] A third dose is indicated if the first and second doses were given less than 5 months apart, or the person is older than 15 years or is immunocompromised. No recommendation has been made for revaccination after the primary series.

In 2018, the US Food and Drug Administration approved Gardasil 9 for adults 27 to 45 years of age. In June 2019, ACIP recommended vaccination for men[a] as old as 26 years, and adopted a recommendation that unvaccinated men and women between 27 and 45 years discuss HPV vaccination with their physician.[13]

The adolescent HPV vaccination rate varies by state; however, all states lag behind the CDC's Healthy People 2020 goal of 80%.[14] Barriers to vaccination include cost, infrastructure limitations, and social stigma.

Secondary prevention: Screening and Tx of precancerous lesions

Cervical cancer screening identifies patients at increased risk of cervical cancer and reassures the great majority of them that their risk of cervical cancer is very low. There are 3 general approaches to cervical cancer screening:

- cytology-based screening, which has been implemented for decades in many countries

[a] See "A note from the Editors" on page 499 regarding the gender-based terminology used in this article.

TABLE 2

US Preventive Services Task Force recommendations for cervical cancer screening[15]

Patients < 21 y: screening is not recommended
Patients 21-29 y: cytology alone
Patients 30-65 y: • cytology alone every 3 y *or* • cytology plus high-risk type HPV co-testing every 5 y *or* • primary high-risk type HPV testing
Patients > 65 y: screening is *not* recommended unless they: - have had inadequate prior screening *or* - are in follow-up surveillance after abnormal screening results, with or without treatment *or* - are otherwise at increased risk of cervical cancer
Screening is *not* recommended for any patient, at any age, who has had a hysterectomy with removal of the cervix, unless they have a history of high-grade dysplasia or cervical cancer.

HPV, human papillomavirus.

- primary testing for DNA or RNA markers of high-risk HPV types
- co-testing with cytology-based screening plus HPV testing.

USPSTF guidance. Recommendations of the US Preventive Services Task Force (USPSTF) for cervical cancer screening were updated in 2018 (**TABLE 2**[15]). The recommendations state that high-risk HPV screening alone is a strategy that is amenable to patient self-sampling and self-mailing for processing—a protocol that has the potential to improve access to testing for patients who are inadequately screened.

ASCCP guidance. The American Society of Colposcopy and Cervical Pathology (ASCCP) makes nearly the same recommendations for cervical cancer screening. An exception is that ASCCP guidelines allow for the possibility of screening using primary high-risk HPV testing for patients starting at 25 years of age.[16]

Screening programs that can be initiated at a later age and longer intervals should be possible once the adolescent vaccination rate is optimized and vaccination registries are widely implemented.

Cervical cytology protocol

Cervical cytologic abnormalities are reported using the Bethesda system. Specimen adequacy is the most important component of quality assurance,[17] and is determined primarily by sufficient cellularity. However, any specimen containing abnormal squamous cells of undetermined significance (ASCUS) or atypical glandular cells (AGCs) is considered satisfactory, regardless of the number of cells. Obscuring factors that impair quality include excessive blood; inflammation; air-drying artifact; and an interfering substance, such as lubricant. The presence of reactive changes resulting from inflammation does not require further evaluation unless the patient is immunosuppressed.

Abnormalities are most often of squamous cells, of 2 categories: low-grade squamous intraepithelial lesions (LSILs) and high-grade squamous intraepithelial lesions (HSILs). HSILs are more likely to be associated with persistent HPV infection and higher risk of progression to cervical cancer.

Cytologic findings can be associated with histologic findings that are sometimes more, sometimes less, severe. LSIL cytology

specimens that contain a few cells that are suspicious for HSIL, but that do not contain enough cells to be diagnostic, are reported as atypical squamous cells, and do not exclude a high-grade intraepithelial lesion.

Glandular-cell abnormalities usually originate from the glandular epithelium of the endocervix or the endometrium—most often, AGCs. Less frequent are AGCs, favor neoplasia; endocervical adenocarcinoma in situ; and ADC. Rarely, AGCs are associated with adenosquamous carcinoma. Endometrial polyps are a typical benign pathology that can be associated with AGCs.

In about 30% of cases, AGCs are associated with premalignant or malignant disease.[18] The risk of malignancy in patients with AGCs increases with age, from < 2% among patients younger than 40 years to approximately 15% among those > 50 years.[19] Endometrial malignancy is more common than cervical malignancy among patients > 40 years.

AGC cytology requires endocervical curettage, plus endometrial sampling for patients ≥ 35 years. Patients with a history of AGCs are at higher risk of cervical cancer for as long as 15 years.

Cytology-based screening has limitations. Sensitivity is relatively low and dependent on the expertise of the cytologist, although regular repeat testing has been used to overcome this limitation. A substantial subset of results are reported as equivocal—ie, ASCUS.

High-risk HPV screening alone is amenable to patient self-sampling and self-mailing for processing—a protocol that has the potential to improve access to testing.

Primary HPV screening

Primary HPV testing was approved by the US Food and Drug Administration in 2015 and recommended as an appropriate screening option by professional societies.

In contrast to cytology-based screening, HPV testing has high sensitivity (≥ 90%); the population-based negative likelihood ratio is near zero.[20] This degree of sensitivity allows for extended screening intervals. However, primary HPV testing lacks specificity for persistent infection and high-grade or invasive lesions, which approximately doubles the number of patients who screen positive. The potential for excess patients to be referred for colposcopy led to the need for secondary triage.

Instituting secondary triage. Cytology is, currently, the primary method of secondary triage, reducing the number of referrals for colposcopy by nearly one-half, compared to referrals for all high-risk HPV results, and with better overall accuracy over cytology with high-risk HPV triage.[21] When cytology shows ASCUS, or worse, refer the patient for colposcopy; alternatively, if so-called reflex testing for HPV types 16 and 18 is available and positive, direct referral to colposcopy without cytology is also appropriate.

In the future, secondary triage for cytology is likely to be replaced with improved technologies, such as immunostaining of the specimen for biomarkers associated with cervical precancer or cancer, or for viral genome methylation testing.[22]

Management of abnormal cervical cancer screening results

Routine screening applies to asymptomatic patients who do not require surveillance because they have not had prior abnormal screening results. In 2020, ASCCP published risk-based management consensus guidelines that were developed for abnormal cervical cancer screening tests and for cancer precursors.[16] Guiding principles, and screening situations in which the guidelines can be applied, are summarized in **TABLE 3**.[16]

ASCCP guidelines provide a framework to incorporate new data and technologies without major revision. The web-based ASCCP resource can be obtained at no cost at http://asccp.org; there is also a smartphone app resource ($9.99).

Some noteworthy scenarios in ASCCP risk-based management are:

- For unsatisfactory cytology with a negative HPV test or no HPV test, repeat age-based screening in 2 to 4 months. (Note: A negative HPV test might reflect an inadequate specimen; do *not* interpret this result as a true negative.)
- An absent transformation zone (ie, between glandular and squamous cervical cells) with an otherwise adequate specimen should be interpreted as satisfactory for screening in patients 21 to 29 years of age. For those ≥ 30 years and with no HPV testing in this circumstance, HPV testing is preferred;

TABLE 3

ASCCP guiding principles for 2019 recommendations[16]

New guiding principles
HPV-based testing, alone or as co-testing, is the basis for risk estimation
Risk-based management should be personalized, with knowledge of current results *and* history
These principles will be updated • based on new test methods • as risk decreases with more HPV-vaccinated patients who reach screening age
Colposcopy should be performed according to colposcopy standards of ASCCP
Preserved 2012 guiding principles
The goal of screening is cancer prevention through detection and treatment of cervical cancer precursors
Guidelines apply to all patients who have a cervix
Equal management of equal risk
Balancing benefits and harms with both consideration of maximization of prevention with minimization of harms due to overtreatment
Guidelines apply to asymptomatic patients who have abnormal cervical cancer screening results (eg, not abnormal bleeding)
Guidelines are intended for use in the United States
Risk estimates are available for several circumstances
Current abnormal screening results and patient age with unknown history
Abnormal screening with documentation of preceding negative HPV test or co-test
Surveillance of previous abnormal results that did not require colposcopy
Follow-up surveillance after prior colposcopy (with or without biopsy) without treatment
After treatment for a high-grade abnormality

ASCCP, American Society of Colposcopy and Cervical Pathology; HPV, human papillomavirus.

repeating cytology, in 3 years, is also acceptable.

- After a finding of LSIL/CIN1 without evidence of a high-grade abnormality, and after 2 negative annual screenings (including HPV testing), a return to 3-year (not 5-year) screening is recommended.
- A cytology result of an HSIL carries a risk of 26% for CIN3+, in which case colposcopy is recommended, regardless of HPV test results.
- For long-term management after treatment for CIN2+, continue surveillance testing every 3 years after 3 consecutive negative HPV tests or cytology findings, for at least 25 years. If the 25-year threshold is reached before 65 years of age, continuing surveillance every 3 years is optional, as long as the patient is in good health (ie, life expectancy ≥ 10 years).
- After hysterectomy for a high-grade abnormality, annual vaginal HPV testing is recommended until 3 negative tests are returned; after that, surveillance shifts to a 3-year interval until the 25-year threshold.

Treatment of cancer precursors

Treatment for cervical dysplasia is excisional or ablative.

Excisional therapy. In most cases, excisional therapy (either a loop electrosurgical excision procedure [LEEP; also known as *large loop excision of the transformation zone*, *cold knife conization*, and *laser conization*] or cone biopsy) is required, or preferred. Excisional treatment has the advantage of providing a diagnostic specimen.

The World Health Organization recommends LEEP over ablation in settings in which LEEP is available.[23] ASCCP states that,

In about 30% of cases, atypical glandular cells (AGCs) found on cytology are associated with premalignant or malignant disease. The risk of malignancy with AGCs increases with age.

TABLE 4

Cervical lesions and other patient factors that require a diagnostic specimen[16]

Lesion extends into the cervical canal, where it cannot be fully visualized
Lesion covers ≥ 75% of the exocervix or extends beyond the reach of the cryoablation tip, or both
Endocervical curettage shows CIN2+ or ungraded CIN
Patient had prior excision for CIN2+
Treatment is for glandular disease
Diagnostic uncertainty because of inadequate colposcopy or discordant cytology and biopsy results

CIN, cervical intraepithelial neoplasia.

in the relatively few cases in which treatment is needed and it is for CIN1, either excision or ablation is acceptable. **TABLE 4**[16] lists situations in which excisional treatment is required because a diagnostic specimen is needed.

Ablative treatments are cryotherapy, CO_2 laser ablation, and thermal ablation. Ablative therapy has the advantage of presenting less risk of adverse obstetric outcomes (eg, preterm birth); it can be used if the indication for therapy is:

- CIN1 or CIN2 and HPV type 16 or 18 positivity
- concordant cytology and histology
- satisfactory colposcopy
- negative endocervical curettage.

The most common ablative treatment is liquid nitrogen applied to a metal tip under local anesthesia.

Hysterectomy can be considered for patients with recurrent CIN2+ who have completed childbearing or for whom repeat excision is infeasible (eg, scarring or a short cervix), or both.

Cost, availability, and convenience might play a role in decision-making with regard to the treatment choice for cancer precursors.

Is care after treatment called for? Patients who continue to be at increased risk of (and thus mortality from) cervical and vaginal cancer require enhanced surveillance. The risk of cancer is more than triple for patients who were given their diagnosis, and treated, when they were > 60 years, compared to patients treated in their 30s.[1] The excess period of risk covers at least 25 years after treatment, even among patients who have had 3 post-treatment screenings.

Persistent HPV positivity is more challenging. Patients infected with HPV type 16 have an increased risk of residual disease.

Cancer management

Invasive cancer. Most cervical cancers (60%) occur among patients who have not been screened during the 5 years before their diagnosis.[24] For patients who have a diagnosis of cancer, those detected through screening have a much better prognosis than those identified by symptoms (mean cure rate, 92% and 66%, respectively).[25] The median 5-year survival for patients who were not screened during the 5 years before their diagnosis of cervical cancer is 66%.[2]

In unscreened patients, cervical cancer usually manifests as abnormal vaginal bleeding, especially postcoitally. In approximately 45% of cases, the patient has localized disease at diagnosis; in 36%, regional disease; and in 15%, distant metastases.[26]

For cancers marked by stromal invasion < 3 mm, appropriate treatment is cone biopsy or simple hysterectomy.[27]

Most patients with early-stage cervical cancer undergo modified radical hysterectomy. The ovaries are usually conserved, unless the cancer is adenocarcinoma. Sentinel-node dissection has become standard practice. Primary radiation therapy is most often used for patients who are a poor surgical candidate because of medical comorbidity or poor functional status. Antiangiogenic agents (eg, bevacizumab) can be used as adjuvant palliative therapy for advanced and recurrent disease.[28]

After treatment for invasive cervical cancer, the goal is early detection of recurrence, although there is no consensus on a protocol. Most recurrences are detected within the first 2 years.

Long-term sequelae after treatment for advanced cancer are considerable. Patients report significantly lower quality of life, comparatively, across multiple dimensions, including mental health, physical health, and sexual function.[29]

Hormone replacement therapy is gener-

ally considered acceptable after treatment of cervical cancer because it does not increase replication of HPV.

Recurrent or metastatic cancer. Recurrence or metastases will develop in 15% to 60% of patients,[30] usually within the first 2 years after treatment.

Management depends on location and extent of disease, using mainly radiation therapy or surgical resection. Recurrence or metastasis is usually incurable.

Last, there are promising areas of research for more effective treatment for cervical cancer precursors and cancers, including gene editing tools[31] and therapeutic vaccination,[32] which is intended to target and kill infected cells.

Prospects for better cervical cancer care

Prevention. HPV vaccination is likely to have a large impact on population-based risk of both cancer and cancer precursors in the next generation.

Screening in the foreseeable future will gravitate toward reliance on primary HPV screening, with a self-sampling option.

Surveillance after dysplastic disease. The 2019 ASCCP guidelines for surveillance and intervention decisions after abnormal cancer screening results will evolve to incorporate introduction of new technology into computerized algorithms.

Treatment. New biologic therapies, including monoclonal antibodies and therapeutic vaccines against HPV, will likely be introduced for treating cancer precursors and invasive cancer. JFP

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