Cervical cancer is responsible for more than 7% of all cancer-related deaths in women worldwide.\(^1\) Most cases of cervical cancer (85%) occur in developing countries that have ineffective screening programs.\(^2\) Total cancer-related deaths in American women declined by more than 80% from 1930 to 2012, primarily because of widespread use of cytology (Papanicolaou [Pap] test).\(^3\) The annual incidence and mortality rate of cervical cancer have decreased nearly 50% since 1975; there were reportedly 7.5 cases per 100,000 women from 2009 to 2013, and 2.3 deaths per 100,000 women in 2011.\(^4,5\) The most common types of cervical cancer are squamous cell carcinoma and adenocarcinoma.\(^2\) The American Cancer Society projected that there would be 12,820 new cases of cervical cancer diagnosed in 2017 in the United States, with 4,210 deaths.\(^3\)

Nearly one-half of women with cervical cancer were not screened before diagnosis, and another 10% were not screened within the previous five years.\(^4\) Although the rates of cervical cancer in U.S. women who have adequate access to screening are decreasing, patients who lack regular preventive health care services continue to be at higher risk.\(^6\)

Types of human papillomavirus (HPV) are categorized as low risk (wart-causing) and high risk (oncogenic, cancer-causing). Precancerous cervical lesions, called cervical intraepithelial neoplasias (CINs), and cervical carcinomas are strongly associated with sexually transmitted infections. The American Academy of Family Physicians and the U.S. Preventive Services Task Force recommend starting screening in immunocompetent, asymptomatic women at 21 years of age. Women 21 to 29 years of age should be screened every three years with cytology alone. Women 30 to 65 years of age should be screened every five years with cytology plus HPV testing or every three years with cytology alone. Screening is not recommended for women younger than 21 years or in women older than 65 years with an adequate history of negative screening results. The U.S. Preventive Services Task Force is in the process of updating its guidelines. In 2015, the American Society for Colposcopy and Cervical Pathology and the Society of Gynecologic Oncology published interim guidance for the use of primary HPV testing. (Am Fam Physician. 2018;97(7):441-448. Copyright © 2018 American Academy of Family Physicians.)

See related article on cervical cancer evaluation and management on page 449.
CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 439.

Author disclosure: No relevant financial affiliations.
Patient information: A handout on this topic is available at https://familydoctor.org/condition/cervical-cancer/.
CERVICAL CANCER SCREENING

There are more than 200 types of HPV strains, of which about 40 types commonly infect the anogenital region. Types 16 and 18 are high-risk strains that cause 70% of all cervical cancers. Table 1 summarizes cervical cancer risk based on HPV genotype.

Risk factors for high-risk HPV infection include early onset of sexual activity, multiple sex partners, long-term use of oral contraceptives, low socioeconomic status, micronutrient deficiency, immunosuppression, and tobacco use.

Most cervical HPV infections are transient, although a small percentage are persistent. It takes the immune system six to 24 months to clear a transient HPV infection.

High-risk HPV infection is more likely to resolve in younger women. Other HPV-induced cancers include vaginal, vulvar, anal, penile, and oropharyngeal cancers. It is unknown if previously resolved HPV infection produces immunity toward future infection with the same HPV genotype.

Screening with cytology can detect early cervical cancer precursors and early-stage disease. Precursors include atypical squamous

---

**Table 1**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Pathogenesis</th>
<th>Commonly used FDA-approved HPV tests for genotype detection and specification*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk (oncogenic)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 16</td>
<td>Causes 50% of all squamous cell carcinomas of the cervix and 55% to 60% of all cervical cancers worldwide</td>
<td>Pooled detection by Hybrid Capture II HPV DNA test, Cervista HPV DNA test, and Aptima HPV mRNA test Specific detection by Cobas HPV DNA test</td>
</tr>
<tr>
<td>Type 18</td>
<td>Causes 20% of cervical adenocarcinomas</td>
<td>Pooled detection by Hybrid Capture II HPV DNA test, Cervista HPV DNA test, and Aptima HPV mRNA test Specific detection by Cobas HPV DNA test</td>
</tr>
<tr>
<td>Other: types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, (66), 68</td>
<td>All types combined cause 25% of cervical cancers</td>
<td>Results are not differentiated by type and are reported as positive or negative for these 12 high-risk HPV strains Pooled detection of all types except for type 66 by Hybrid Capture II HPV DNA test Pooled detection of all 14 oncogenic types by Cervista HPV DNA test, Cobas HPV DNA test, and Aptima HPV mRNA test</td>
</tr>
<tr>
<td><strong>Low risk (wart-causing)</strong></td>
<td></td>
<td>Testing is not recommended</td>
</tr>
<tr>
<td>Types 6 and 11</td>
<td>Cause 90% to 95% of anogenital warts</td>
<td></td>
</tr>
</tbody>
</table>

*FDA = U.S. Food and Drug Administration; HPV = human papillomavirus.

Information from references 4, 8, and 9.
cells of undetermined significance and low-grade squamous intraepithelial lesions on cytology, and mild dysplasia, also known as CIN1, on histology. Precancerous cervical lesions include high-grade squamous intraepithelial lesions and atypical glandular cells on cytology, and CIN2 and CIN3 (i.e., moderate and severe dysplasia) on histology.

Cervical Cancer Screening Methods

Cervical cancer screening includes cytology and HPV testing, alone or in combination. Conventional cytology (a Pap test sample affixed to a slide at the time of testing) and liquid-based cytology (a newer method for collecting, transporting, and preparing cells collected by the Pap test in a liquid medium [e.g., ThinPrep Pap test]) provide comparable results. Both methods are acceptable and have nearly equivalent sensitivity and specificity for detection of high-grade CIN.4,11-14

HPV testing, alone or in combination with cytology, is more sensitive than cytology alone in detecting CIN2 and CIN3.15 There are a variety of tests approved by the U.S. Food and Drug Administration (FDA) for detecting cervical HPV, including HPV DNA and HPV mRNA tests (Table 1). Current methods for using cervical HPV testing in the United States include triage testing for patients with abnormal findings on cytology (reflex testing), adjunct testing with cytology (cotesting), and primary testing.

Screening Recommendations

The decision of when, how, and how often to screen for cervical cancer depends on a woman’s age, screening history, risk factors, and the choice of screening tests available. Current screening recommendations from the U.S. Preventive Services Task Force, the American Academy of Family Physicians, and other national organizations are summarized in Table 2.15-21 and Table 3.4,16,18-20,22 Women with symptoms or visible cervical lesions on speculum examination should undergo diagnostic testing rather than screening.

Primary HPV testing was not previously recommended, largely because of concerns about low specificity and insufficient data to determine when positive HPV test results require diagnostic evaluation.4 However, a large U.S. study has since shown that primary HPV screening has equivalent or superior effectiveness to cytology alone.4,15,23

Additionally, an effective algorithm for managing patients with positive findings on primary HPV screening has been validated4,15,23 (Figure 1). As a result, the FDA approved the Cobas HPV DNA test in August 2014 for primary cervical cancer screening in women. In 2015, the American Society for Colposcopy and Cervical Pathology and the Society of Gynecologic Oncology provided interim guidance on the use of primary HPV testing4,15 (Table 2).4,15-21 The U.S. Preventive Services Task Force is currently reviewing the evidence regarding primary HPV testing.18 The American Academy of Family Physicians suspended its Choosing Wisely recommendation against primary HPV testing in women younger than 30 years because of the uncertainty around the effectiveness of HPV testing alone.17

Although primary testing for high-risk HPV infection can be considered as an alternative to cytology-based screening methods, cytology alone or cotesting is recommended in major guidelines.4,14,15,17,18,20

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer screening in women before 21 years of age leads to more harms than benefits and does not reduce cervical cancer incidence or mortality.</td>
<td>A</td>
<td>4, 14, 16, 18, 20</td>
</tr>
<tr>
<td>Average-risk women 21 to 29 years of age should be screened every three years with cytology alone.</td>
<td>A</td>
<td>4, 16, 18, 20</td>
</tr>
<tr>
<td>Average-risk women 30 to 65 years of age should be screened every three years with cytology alone or every five years with a combination of cytology and HPV testing.</td>
<td>A</td>
<td>4, 16, 18, 20</td>
</tr>
<tr>
<td>Cervical cancer screening should be discontinued in women older than 65 years with an adequate history of negative screening results.</td>
<td>C</td>
<td>4, 16, 18, 20</td>
</tr>
<tr>
<td>Annual cervical cancer screening is not recommended for average-risk women of any age.</td>
<td>A</td>
<td>4, 16, 18, 20</td>
</tr>
<tr>
<td>Women with a hysterectomy unrelated to cancer should not be screened for cervical cancer.</td>
<td>C</td>
<td>4, 16, 18, 20</td>
</tr>
<tr>
<td>Women with a hysterectomy related to a history of cancer should be screened for cervical cancer for 20 years after the hysterectomy.</td>
<td>C</td>
<td>4, 16, 18, 20</td>
</tr>
<tr>
<td>Primary HPV testing may be considered for cervical cancer screening every three years in women 25 years and older.</td>
<td>B</td>
<td>4, 15, 23</td>
</tr>
</tbody>
</table>

HPV = human papillomavirus.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.
Primary HPV screening should not be performed in women younger than 25 years or older than 65 years, or in women who are immunocompromised. Rescreening after a negative primary HPV test result should occur no earlier than three years later, and patients with positive results should be tested for specific HPV genotype. If testing is negative for HPV types 16 and 18 but positive for other high-risk genotypes, then cytology should be performed. If cytology results are negative, then follow-up testing should be performed in 12 months (Figure 1). The type of follow-up testing to perform is not specified in the interim guideline, but the American College of Obstetricians and Gynecologists recommends cotesting.

It is likely that primary HPV testing in 25- to 29-year-old women will lead to increased CIN3 detection, but the actual impact on cervical cancer prevention in this age group...
The optimal cervical cancer screening program maximizes the benefit to women and minimizes harms and the costs of screening. Harms are related to both screening tests and the procedures required for diagnosis, management, and follow-up of patients with abnormal screening results. Screening tests and subsequent diagnosis and management can lead to psychological harms such as distress and anxiety. The pelvic examination and Pap test can cause mild bleeding and cramping in some women. Additionally, inadequate sampling may necessitate repeat procedures. Abnormal screening test results can lead to more frequent testing, out-of-pocket expenses, and invasive procedures such as colposcopy with cervical biopsy.

Weighing the Benefits and Harms of Screening
The primary goal of cervical cancer screening is to decrease mortality by detecting precancerous lesions and intervening to prevent the progression to cervical cancer. It is important to recognize that the risk of HPV infection is highest among those who are newly sexually active, and that the risk decreases with age. The peak incidence of high-risk HPV infection is in teenagers and in women in their early 20s. The progression from persistent high-risk HPV infection to invasive cervical disease takes an average of 10 to 20 years (Figure 2). Because of this slow oncogenesis, persistent high-risk HPV infections that manifest as abnormalities of the cervix can be detected early, resulting in less-invasive treatments and overall fewer adverse outcomes.

The harms of diagnostic testing with colposcopy or endocervical curettage include bleeding, pain, infection, and failure to diagnose from inadequate sampling. Short-term risks of treatment methods include bleeding, pain, and infection. Long-term risks of treatment include subsequent preterm delivery and neonatal mortality because of severe needs further investigation. Some believe that the harms of excessive diagnostic testing will outweigh the benefits. Primary HPV testing is a rapidly evolving area of preventive medicine. Randomized controlled trials are global and ongoing, and include studies on patient-collected HPV samples. Primary polymerase chain reaction–based HPV testing via self-sampling has similar sensitivity to that of an in-office collection method, with reportedly wider acceptability and positive feedback, especially in underscreened and unscreened patient populations.

### TABLE 2

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Screening is not recommended in women older than 65 years with an adequate history of negative screening results</th>
</tr>
</thead>
<tbody>
<tr>
<td>‡</td>
<td>Not addressed</td>
</tr>
<tr>
<td>§</td>
<td>Annual screening is not recommended patients should be counseled that annual well-woman visits are recommended even if cervical cancer screening is not performed at each visit</td>
</tr>
<tr>
<td>†</td>
<td>Not addressed</td>
</tr>
<tr>
<td>†</td>
<td>Screening is not recommended by primary testing for high-risk HPV infection</td>
</tr>
<tr>
<td>ACOG 2016</td>
<td>ASCCP and SGO 2015: interim guidance on primary testing for high-risk HPV infection</td>
</tr>
<tr>
<td>Screening is not recommended</td>
<td>Screening is not recommended</td>
</tr>
<tr>
<td>Cytology alone every three years</td>
<td>Primary HPV testing every three years (alternative to cytology alone or cotesting) for women 25 years and older; not recommended in women 21 to 25 years of age</td>
</tr>
<tr>
<td>Cotesting every five years (preferred)</td>
<td>Primary HPV testing every three years (alternative to cotesting or cytology alone)</td>
</tr>
<tr>
<td>Cytology alone every three years (acceptable)</td>
<td>Primary HPV testing every three years (alternative to cotesting or cytology alone)</td>
</tr>
</tbody>
</table>

Information from references 4, and 15 through 21.
CERVICAL CANCER SCREENING

Overdiagnosis and overtreatment are common; the treatment threshold in the United States is CIN2, and about 40% of CIN2 lesions regress over six months without intervention. To reduce harms from cervical cancer screening, guidelines recommend against screening women before 21 years of age and in patients who have had a hysterectomy for reasons unrelated to cancer. Screening should be stopped after 65 years of age in women with an adequate history of negative screening results. Annual screening is not recommended for average-risk women of any age; screening too frequently has been proven to have greater harms than benefits.

Prevention
Preventing high-risk HPV infection is the key to the prevention of cervical dysplasia and cancer. Barrier contraceptives, such as condoms, are only about 70% effective at preventing HPV transmission. In 2016, the Centers for Disease Control and Prevention recommended that all women aged 13 to 26 years receive the HPV vaccine as part of their routine vaccination schedule. The vaccine is effective at preventing HPV infection and subsequent cervical dysplasia and cancer.

TABLE 3
Other Cervical Cancer Screening Recommendations

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>ACS, ASCCP, and ASCP 2012</th>
<th>USPSTF and AAFP 2012</th>
<th>ACP 2015</th>
<th>ACOG 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppression* (includes solid organ transplant recipients; those with auto-immune conditions or HIV infection; and those taking immunosuppressive medications; does not include otherwise healthy pregnant women†)</td>
<td>Not addressed; recommends referring to CDC/NIH/IDSA guidelines22</td>
<td>Not addressed; recommends referring to CDC/NIH/IDSA guidelines22</td>
<td>Not addressed</td>
<td>Initiate screening within one year of onset of sexual activity or, if already sexually active, within the first year after HIV diagnosis but no later than 21 years of age; continue screening throughout the woman’s lifetime—annually until sufficient negative screenings are achieved, then every three years; screening is not stopped at 65 years of age and cotesting is not recommended for women younger than 30 years</td>
</tr>
<tr>
<td>Total hysterectomy (with removal of the cervix) unrelated to cancer‡</td>
<td>Screening should be stopped</td>
<td>Screening should be stopped</td>
<td>Screening should be stopped</td>
<td>Screening should be stopped</td>
</tr>
<tr>
<td>Total hysterectomy (with removal of the cervix) related to cancer</td>
<td>Continue screening for 20 years after hysterectomy with cotesting every five years (preferred) or cytology alone every three years (acceptable)</td>
<td>Not addressed</td>
<td>Not addressed</td>
<td>Continue to screen for 20 years after hysterectomy with cytology every three years§</td>
</tr>
<tr>
<td>Received human papillomavirus vaccine</td>
<td></td>
<td>Follow age-specific recommendations</td>
<td>Follow age-specific recommendations</td>
<td>Follow age-specific recommendations</td>
</tr>
</tbody>
</table>

**ACFP = American Academy of Family Physicians; ACOG = American College of Obstetricians and Gynecologists; ACP = American College of Physicians; ACS = American Cancer Society; ASCCP = American Society for Colposcopy and Cervical Pathology; ASCP = American Society for Clinical Pathology; CDC = Centers for Disease Control and Prevention; CIN = cervical intraepithelial neoplasia; HIV = human immunodeficiency virus; IDSA = Infectious Diseases Society of America; NIH = National Institutes of Health; USPSTF = U.S. Preventive Services Task Force.

*—There are limited data and no consensus regarding how to routinely screen women who are immunocompromised because of a condition other than HIV. Recommendations have been extrapolated from data in women with HIV infection. Annual cytology beginning at 21 years of age traditionally has been performed.

†—Pregnant women should continue to be screened using age-specific recommendations.

‡—Applies to women without a cervix and without a history of CIN2 or a more severe diagnosis in the past 20 years or cervical cancer ever.

§—Women should continue to be screened if they have had a total hysterectomy and have a history of CIN2 or higher in the previous 20 years or cervical cancer ever. Continued screening for 20 years is recommended in women who still have a cervix and a history of CIN2 or higher. Therefore, screening with cytology alone every three years for 20 years after initial posttreatment surveillance for women with a hysterectomy is reasonable per ACOG.

||—The possibility that vaccination might reduce the need for screening has not yet been established.

Information from references 4, 16, 18 through 20, and 22.
and Prevention changed the recommendations for HPV vaccination to include vaccinating boys and girls before 15 years of age, and as early as nine years of age. A two-dose series is used when initiated before 15 years of age, whereas a three-dose series is required if initiated at 15 years or older or if the individual is immunocompromised. Vaccination is recommended through 26 years of age for females and 21 years of age for males.

Gardasil-9 (9-valent) is the only FDA-approved HPV vaccine (eTable A). If Cervarix (bivalent, no longer available in the United States) or Gardasil (quadrivalent, no longer available in the United States) has already been given, there is no evidence that the patient should be revaccinated using Gardasil-9. Additionally, the HPV vaccination series should be finished with whichever vaccine type is available. Because long-term effectiveness of the vaccine is unknown, all patients with a cervix should undergo age-based cervical cancer screening regardless of vaccination status.

This article updates a previous article on this topic by Nuovo, et al. Data Sources: A PubMed search was conducted using the key terms cervical intraepithelial neoplasia, low-grade squamous intraepithelial lesion, Pap smear, cytology, colposcopy, human papillomavirus, HPV, HPV testing, and HPV vaccination. The search included retrospective studies, prospective studies, meta-analyses, and reviews. Essential Evidence Plus, Google Scholar, the National Institute for Health and Care Excellence guidelines, and the Cochrane database were also searched. Search dates: August 2016, February 2017, May 2017, and October 2017.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of Defense, the U.S. Army Medical Department, or the U.S. Army Service at large.

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**FIGURE 1**

Algorithm for primary human papillomavirus (HPV) screening. If primary HPV testing is used for cervical cancer screening, it is recommended that this algorithm be used for management of positive results.


**FIGURE 2**

Natural history of high-risk cervical human papillomavirus (HPV) infection. Cervical carcinogenesis starts with sexual transmission of high-risk HPV (infection is transient [90% of cases] or persistent [10%]). High-risk cervical HPV infections are considered persistent if cervical abnormalities or HPV type 16 or 18 is present for more than two years. Persistent infections can progress to invasive cervical cancers if precancerous lesions are not identified and treated.

CERVICAL CANCER SCREENING

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References
### Comparison of HPV Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>HPV genotypes covered</th>
<th>Indications</th>
<th>Age-based recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardasil-9</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, and 58</td>
<td>Prevent cervical cancer in females&lt;br&gt;Prevent genital warts in all individuals</td>
<td>Females&lt;br&gt;Give at 11 to 12 years; may be given as early as nine years&lt;br&gt;&lt;br&gt;Two-dose series if started &lt; 15 years&lt;br&gt;&lt;br&gt;Three-dose series if started ≥ 15 years or if the patient is immunocompromised*&lt;br&gt;&lt;br&gt;Vaccinate through 26 years</td>
</tr>
<tr>
<td>Gardasil (no longer available in the United States)</td>
<td>6, 11, 16, and 18</td>
<td>Prevent cervical, vaginal, and vulvar cancers in females&lt;br&gt;Prevent penile cancer in males&lt;br&gt;Prevent genital warts, oropharyngeal cancer, and anal cancer in all individuals</td>
<td>Females&lt;br&gt;Give at 11 to 12 years; may be given as early as nine years</td>
</tr>
<tr>
<td>Cervarix (no longer available in the United States)</td>
<td>16 and 18</td>
<td>Prevent cervical cancer in females</td>
<td>Females&lt;br&gt;Give at 11 to 12 years; may be given as early as nine years</td>
</tr>
</tbody>
</table>

CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus.

*—Includes those with human immunodeficiency virus infection, cancer, or autoimmune disease, or those taking immunosuppressant medications. This excludes children with asthma, diabetes mellitus, and other conditions that would not suppress immune response to HPV vaccination.

**Information from:**
### CERVICAL CANCER SCREENING

<table>
<thead>
<tr>
<th>Injection schedule</th>
<th>Effectiveness</th>
<th>Common adverse effects</th>
</tr>
</thead>
</table>
| 0, and 6 to 12 months or 0, 2, and 6 months | HPV susceptibility  
90% for invasive cervical cancer  
Up to 93.6% for CIN2 and CIN3 lesions  
Disease reduction  
42.5% for high-grade squamous intraepithelial lesions | Pain, swelling, and redness at injection site (20% to 89%)  
Headache (11% to 14%)  
Fever (0.7% to 5%) |
| 0, and 6 to 12 months or 0, 2, and 6 months | HPV susceptibility  
100% for external vaginal lesions  
98% to 100% for CIN2 or CIN3 lesions  
Disease reduction  
34% for external vaginal lesions  
17% to 20% for cervical lesions | Pain, swelling, and redness at injection site (13% to 83%)  
Headache (12% to 28%)  
Fever (8% to 13%) |
| 0, 2, and 6 months | HPV susceptibility  
98% for CIN2 or CIN3 lesions associated with HPV types 16 and 18  
Disease reduction  
30% for CIN2 or CIN3 lesions associated with all HPV types | Pain, swelling, and redness at injection site (44% to 91%)  
Headache (53%)  
Fever (12%) |

Information from: