Cervical cancer is the second most common cancer in women worldwide, according to the World Health Organization. It is estimated that 529,828 women are diagnosed with cervical cancer annually, and 275,128 die each year from the disease. The most common form is squamous cell carcinoma; adenocarcinoma is detected less frequently.
A discussion surrounding cervical cancer cannot occur without a concurrent discussion about human papillomavirus (HPV), the leading cause of cervical cancer. HPV has been detected in approximately 99.7% of cervical cancer cases.3

There are more than 100 subtypes of HPV, but the most well-known types and those covered by the currently available vaccines are HPV types 6, 11, 16, and 18. HPV types 6 and 11 have low malignant potential and are commonly associated with genital warts. HPV types 16 and 18 have a high malignant potential and are responsible for approximately 70% of the cervical cancer cases worldwide.1 There is also increasing evidence linking HPV types 16 and 18 to other anogenital cancers, including vaginal, vulvar, penile, and anal cancers.4 HPV does not solely infect mucous membranes, but rather has cutaneous presentations in the form of common warts and plantar warts.4 These warts are caused by subtypes other than the ones already listed.

There are 4 important steps in the development of cervical cancer from HPV: transmission of HPV to the host, persistence of the virus, progression of a clone of persistently infected cells to precancer, and invasion through the basement membrane.5 HPV is transmitted via skin-to-skin contact. Thus, transmission frequently occurs through genital contact, and HPV is the most common sexually transmitted infection in the United States.6 HPV most often causes a latent infection in which DNA from the virus is detectable within cells; however, no lesion or disease develops.7 Only about one-third of women with DNA-detectable HPV infection have any type of identifiable cytopathology.5 This, along with the fact that the human immune system can often clear an HPV infection over time without intervention, will be important to remember when discussing the new cervical cancer screening recommendations (described below), and why this information has been pivotal to the recent changes. An HPV infection that persists in the cervical cells can cause cellular changes over several years, which are identified with the Bethesda system as low-grade and high-grade intraepithelial lesions based on their cytopathology.8 High-grade squamous intraepithelial lesions are considered precancerous lesions and have the potential to develop into invasive carcinoma.9

Cervical cancer screening
To detect precancerous lesions and provide intervention to halt the development of cervical cancer, screening using cervical cytology, a Papanicolaou test, and HPV testing are employed. A commonly used office method for cervical cytology is the liquid-based, thin-layer preparation known as ThinPrep.9 A collection device, often a spatula, endocervical brush, or a combination of both, is used to obtain cells from the ectocervix and the endocervix.8 The collecting device is then placed in the liquid fixative solution, swirled several times within the solution, processed and filtered in the laboratory, and finally fixed in a single layer onto a glass slide.9 If the ThinPrep is utilized, then the same cervical cell sample can be used to perform an HPV assay, which detects high-risk (oncogenic) HPV subtypes.

New recommendations regarding cervical cancer screening were recently released this year by the United States Preventive Services Task Force (USPSTF). They recommend screening for cervical cancer begin at age 21 years, regardless of a woman’s sexual intercourse status.10 It was determined, after reviewing much of the literature and research surrounding HPV and cervical cancer, that more harm than benefit comes from screening before the age of 21.10 The progression of HPV-infected cervical cells to cervical carcinoma is slow, and often infection will regress on its own. The USPSTF hopes these new guidelines will decrease overdiagnosis and treatment and will decrease potential adverse physical and mental outcomes related to treatment of cervical cancer.10 It is recommended that women aged 21-65 years be screened for cervical cancer with cytology (i.e., Papanicolaou test) every 3 years.10 If a woman is within the age range of 30-65 years and wishes to lengthen the time between screenings, she can request a combination of cytology with HPV testing. This combination testing is performed every 5 years but is not recommended for women younger than 30 years, because no added benefit was found (see Table 1 on p. 7)10.
The USPSTF recommends screening for cervical cancer begin at age 21 years, regardless of a woman’s sexual intercourse status.

The USPSTF recommendations are similar to those recently released by the American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP). ACS, ASCCP, and ASCP state in their recommendations that the combination of HPV testing and cytology is the preferred method for screening women aged 30-65 years, but screening using cytology alone every 3 years is acceptable. The American Congress of Obstetricians and Gynecologists (ACOG) is in the process of evaluating these recommendations and determining their stance. The aforementioned groups recommend against annual screening with Pap tests, because there is no added benefit due to the slow development of disease from HPV infection.

Vaccination
Not only have efforts been made to change screening guidelines and improve detection of cervical intraepithelial lesions and cancerous cells, additional steps have been taken to prevent the development of cervical cancer. Two vaccines against specific HPV subtypes are now available. The quadrivalent HPV vaccine Gardasil provides immunity against HPV subtypes 6, 11, 16, and 18. The other vaccine that has been approved for use in the United States is a bivalent vaccine, Cervarix, which targets HPV subtypes 16 and 18 only. Several clinical trials have shown profound efficacy of both Gardasil and Cervarix at preventing cervical intraepithelial neoplasia and cervical cancer in women, with the greatest efficacy occurring in HPV-naive populations.

The efficacy of both Gardasil and Cervarix decreases significantly when all trial groups, not just the HPV-naive populations, were compared. The lower efficacy rate when comparing all women reflects the fact that many of the women enrolled in the trials were already sexually active and exposed to, or previously infected with, the HPV subtypes covered by the vaccine. These findings emphasize the importance of vaccinating a woman before she begins to engage in sexual intercourse. Nevertheless, adolescents should still be offered vaccination even if they have already commenced sexual activity. The vaccines can prevent cervical intraepithelial neoplasia and cervical cancer caused by the high-risk HPV subtypes 16 and 18, but they cannot treat or increase the clearance of pre-existing HPV infections or related disease.

Gardasil is given in 3 doses. The second dose is given 2 months following the first dose, and the third dose is given 6 months following the first dose. Cervarix is also administered in 3 separate doses, but the time between each dose is slightly different. The second dose is given 1 month after the first dose; the third dose is given 6 months after the first dose. The most common side effects of these HPV vaccines include swelling, redness, and soreness at the injection site. There have been rare reports of syncope occurring in women following vaccine injection.

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of females between the ages of 11 and 12 with either the bivalent or quadrivalent vaccine. Vaccination can start as early as 9 years of age in high-risk children, because the vaccine is approved for women aged 9-26 years. The recommendation is based on several conclusions drawn from data and findings from recent studies:

- The vaccine is safe and effective at preventing cervical intraepithelial neoplasia and genital warts (quadrivalent vaccine only).
- The average age of sexual debut in the United States.
- The high probability of HPV acquisition within several years following the start of sexual intercourse. ACIP also recommends females aged 13-26 years receive only “catch-up” vaccines.

The American Cancer Society guidelines differ only in the “catch-up” recommendations, which state that females aged 13-18 years (versus age 26 years per the ACIP guidelines) receive only “catch-up” vaccines. For patients older than 18 years,
they recommend a discussion of their potential previous risk of HPV exposure and benefits of vaccination with their health care provider before receiving the vaccine.\textsuperscript{15}

The use of quadrivalent vaccine also has been recommended for males. Studies have shown the quadrivalent vaccine to be effective against genital warts caused by the vaccine-HPV subtypes in male subjects 16-26 years of age.\textsuperscript{16} Newer studies have demonstrated protection against precancerous lesions of the anus in men who have sex with men. On the basis of effectiveness of the vaccine and the above findings, the ACIP and the American Academy of Pediatrics recommend boys aged 11-12 years be routinely immunized with the 3-dose schedule of quadrivalent HPV vaccine.\textsuperscript{16} The vaccine is approved for males as young as 9 years, and the “catch-up” vaccination is recommended for males aged 13-21 years.

Studies have shown that individuals under the age of 28 showed a significant decrease in incidence of genital warts in 2008 compared with 2004 to 2007, after the administration of the quadrivalent vaccine in 2007, to women aged 12-26 years.\textsuperscript{17} In addition, this decrease in incidence was not observed in the population of men who have sex with men, or in women older than 28 years.\textsuperscript{17} The expectation is that vaccination of males will not only decrease the rate of genital warts and anal cancer in males, but also decrease the transmission of HPV to females.\textsuperscript{13}

Males often do not know about their risk of or consequences from acquiring HPV infection. Approximately 85% of anal cancers are associated with HPV infection.\textsuperscript{18} Knowing that HPV causes genital warts,\textsuperscript{18} Television and Internet advertisements or communication with friends were the most common sources of HPV information.\textsuperscript{18} Only 4.5% of undergraduate males reported being concerned about HPV infection.\textsuperscript{18} A majority of males reported that they would be more likely and more comfortable talking to their health care provider about HPV and vaccination than with their parents.\textsuperscript{18} This highlights the need for physicians to put an emphasis on educating males about HPV and taking time to address issues related to their sexual health.

Males often do not know about their risk of or consequences from acquiring HPV infection. Approximately 85% of anal cancers are associated with HPV infection.

Even with the implementation of the HPV vaccine, it still is important for women to continue to undergo cervical cancer screening with cervical cytology. HPV vaccines will fail to prevent 25% to 30% of cervical cancers in HPV-naïve women, and the vaccine will not protect those women already infected with high-risk HPV types.\textsuperscript{13} Recommendations surrounding screening and the way in which screening is performed may change though, as more women and men are vaccinated, further research is done to evaluate the incidence of HPV and cervical cancer, and the impact of vaccination is revealed. Delay of screening to a later age is a possibility to be explored in the future, because there is a decrease in incidence of high-grade intraepithelial lesions following mass HPV vaccination.\textsuperscript{18} Increased elimination of highly oncogenic subtypes of HPV, such as HPV-16 and HPV-18, with mass vaccination should theoretically lead to a substantial decrease in high-grade cervical lesions. In the future, cytological screening may no longer have the same sensitivity or positive predictive value as before, and use of HPV DNA testing may become a popular screening method.\textsuperscript{19}

As the number of women becoming vaccinated against high-risk HPV subtypes 16 and 18 increases, questions have been raised regarding the financial benefits and cost-effectiveness surrounding vaccination and screening. Several studies have used mathematical methods and dynamic transmission models to predict the rates of cervical cancer and how screening could change in the future to be as cost-effective as possible. High costs to the health care system have the potential to be incurred if large-scale childhood HPV vaccination programs exist simultaneously with the current cervical cancer screening program.\textsuperscript{20} It will be important to continue research and follow the rates of cervical cancer and incidence of HPV infection in the postvaccination era to ensure the best and most cost-effective strategies for preventing cervical cancer are being implemented.

Norwegian data were used in one study to develop a dynamic HPV transmission model to assess possible cost savings in regard to screening after mass HPV immunization.\textsuperscript{20} The results suggested that the most beneficial area to target for cost-saving initiatives would be the more elderly population of women. Increasing the age of initial screening in Norway from 25 years to 30 years was found not to be beneficial.\textsuperscript{20} Diagnosis and treatment of women younger than 30 years still had tremendous preventive effects, which emphasized the need to continue cervical cancer screening in women younger than 30.\textsuperscript{20} It was found that high vaccine uptake will be a primary concern in the future for reducing the burden of cervical cancer, and will play a role in how cervical cancer screening can be changed to be most cost-effective.\textsuperscript{20} The study further emphasized that delaying any cost-saving initiatives until later, when the major effect of the vaccine has been achieved, will confer the best health benefits.\textsuperscript{20} The bottom line is that cervical cancer screening will need to continue to protect those women who are not
vaccinated and to protect women from HPV subtypes not covered by the currently available vaccines.21

Acceptance of the HPV vaccine has been an issue since its approval, and information available on the Internet and through other media can be biased and inaccurate. There has been some fear that providing the HPV vaccine to young people and decreasing their risk of a sexually transmitted infection may encourage them to be more sexually promiscuous because of a false sense of safety. This fear has been shown to be unfounded, as the National Survey of Family Growth from 2006-2008 found that when teenagers were questioned about why they had not engaged in sexual activity, they were least likely to choose “don’t want to get a sexually transmitted infection.”22 Physicians can help ease a parent’s fears by presenting them with this information and emphasizing the facts related to HPV, vaccination, and cancers associated with HPV infection.

A survey conducted in Greece between October 2005 and December 2010 investigated women’s attitudes toward their acceptance of the HPV vaccine.23 The survey was administered twice: the first survey was given before the HPV vaccine became available in Greece, and the second survey was given after the vaccine became widely accessible. Both surveys found that those who rejected the vaccine did so due to fear of side effects, which coincided with frequent negative publicity surrounding the vaccine and misinformation presented by the media.23

Nonpharmaceutical methods

It is important for young adults and the population as a whole to understand how to prevent exposure and infection with HPV. Genital warts and anogenital infections most commonly spread through genital contact, which occurs primarily during sexual intercourse.13 Identified risk factors include sex at a young age, sex with a new partner, multiple sexual partners, and a history of sexually transmitted diseases.4 Studies performed to identify the major risk factors surrounding HPV acquisition noted a direct correlation between an increased risk of HPV infection and the number of sexual partners. This risk includes not only the direct number of sexual partners, but also the indirect number, based on the number of sexual encounters their partner has had (ie, a person who has intercourse with a more sexually active person is at increased risk if their partner has themselves had multiple partners [number of male sex partners for females and the number of female sex partners for males]).4

Safe-sex practices are extremely important when trying to limit or avoid exposure to HPV, as with other sexually transmitted diseases. Avoiding skin-to-skin contact with the area of the body infected with HPV is the best way to prevent spread of disease.24 This can be accomplished through abstinence from sexual activities, such as sexual intercourse and oral sex, and use of condoms during sexual practice. Condoms cannot provide full protection against HPV, but one study found that if condoms were used correctly during every sexual encounter, the rate at which HPV infection occurred could be reduced by around 70%.24 Protection rates of 100% cannot be provided by condoms due to their inability to completely cover all parts of skin potentially infected with HPV.24 Other methods to help decrease HPV exposure include waiting to engage in sexual practice until later in life, limiting the number of sexual partners, monogamy, and avoiding sexual partners who have had multiple partners. These recommendations apply not only to women, but also to men.

Table 1. United States Preventive Services Task Force Recommendations

<table>
<thead>
<tr>
<th>Woman’s Age</th>
<th>USPSTF Recommendations</th>
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<tbody>
<tr>
<td>21-65 year</td>
<td>Screened for cervical cancer with cytology every 3 years</td>
</tr>
<tr>
<td>30-65 year</td>
<td>If wish to lengthen time between screening, can do combination of cytology AND HPV testing every 5 years</td>
</tr>
<tr>
<td>&gt;65 year</td>
<td>Screening no longer needed if prior screening was adequate and patient not considered high risk for cervical cancer</td>
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<tr>
<td></td>
<td>No screening necessary in women who have had a hysterectomy with complete removal of the cervix and who do not have a history of high-grade precancerous lesion or cervical cancer</td>
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Final notes
The role of the physician and other health care providers in educating patients about the facts and recommendations surrounding HPV, cervical cancer, and vaccination has become increasingly important in an era of misinformation. It also is important to spend time with youth, preteen, and teenage patients to educate them on ways to protect themselves. Frank discussions on safe sexual practices, routine screening to protect themselves. Frank discussions to teen patients to educate them on ways to spend time with youth, preteen, and young adults on erroneous, sources.

References

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