MAYO CLINIC

Screening Women at High Risk for Cervical Cancer: Special Groups of Women Who Require More Frequent Screening

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Learning Objectives: On completion of this article, you should be able to (1) identify high-risk groups of women who need more frequent cervical cancer screening, (2) understand the association between human papillomavirus infection and cervical cancer in women with immunosuppression, and (3) be cognizant of cervical cancer screening recommendations for high-risk groups of women.

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Abstract

The updated cervical cancer screening guidelines recommend that women at average risk who have negative screening results undergo cervical cytological testing every 3 to 5 years. These recommendations do not pertain to women at high risk for cervical cancer. This article reviews recommendations for cervical cancer screening in women at high risk.

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Since the advent of cervical cytological testing for cervical cancer screening, the incidence and mortality rates associated with cervical cancer have significantly decreased.[1] In the United States in 1975, the incidence of cervical cancer was 14.8 and the mortality rate was 5.55 per 100,000 women; these statistics have improved to an incidence of 6.7 and a mortality rate of 2.3 per 100,000 in 2011.[2] This improvement was seen in women receiving regular cervical cancer screening.

In 2012, the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology provided consensus guidelines for

cervical cancer screening.[3] These guidelines recommend that women aged 21 to 29 years be screened with cervical cytological testing every 3 years and with reflex human papillomavirus (HPV) testing for women older than 25 years.[4] Reflex HPV testing is an easily performed add-on test of the residual cytology liquid, if the cytological results indicate abnormalities. It is preferred that women aged 30 to 65 years undergo *cotesting*—cervical cytological testing and testing for high-risk HPV—every 5 years. If cotesting is not available, cervical cytological testing every 3 years is an acceptable alternative.[2,3,5] Cervical cancer screening can be discontinued in women at age 65 years if they had adequate negative results of screening on 3 consecutive tests or 2 negative cotesting results in the past 10 years.[3,6]

These guidelines, however, are for women at average risk for cervical cancer and do not pertain to women who are at increased risk. Certain medical conditions place women at a higher risk for cervical cancer, such as solid organ or stem cell transplants, human immunodeficiency virus (HIV) infection, in utero exposure to diethylstilbestrol (DES), personal history of cervical dysplasia or cervical cancer, and immunosuppression from other causes. Several existing guidelines provide recommendations for screening in some of these high-risk women. With regard to immunosuppression, only HIV-positive women have been evaluated extensively enough to provide data-driven recommendations; recommendations for other women with immunosuppression are extrapolated from those for HIV-positive patients. The aim of this concise review is to discuss the screening recommendations for these women at higher risk for cervical cancer.

HPV INFECTION IN HIGH-RISK WOMEN

Human papillomavirus is transmitted by skin and genital contact and is found in 99.7% of all invasive cervical cancers, and it is considered to be essential for cervical cancer development.[7] Persistent infection with the highly oncogenic types of HPV is strongly associated with the development of cervical cancer.[8,9] High-risk HPV subtypes 16, 18, 31, 33, and 35 are most commonly associated with genital carcinomas (cervical, vaginal, vulvar, and anal), with subtypes 16 and 18 causing more than 70% of the cervical cancers.[10] Fortunately, this infection is transient in most immunocompetent women, clearing in 70% by 12 months and in 91% by 24 months (median duration, 8 months).[11] As in women at average risk, the individual risk of HPV infection in women at high risk depends on sexual behavior and the number of sexual partners.[8] Of note, HPV infection has been identified in many women in lifelong monogamous relationships and is now considered the most common sexually transmitted infection.

CERVICAL CANCER SCREENING IN WOMEN WITH SOLID ORGAN OR STEM CELL TRANSPLANTS

Recipients of solid organ and stem cell transplants now have longer life expectancy. As a result, secondary cancers are becoming more common in this patient population.[12] Carcinomas found to occur most commonly in the stem cell transplant group are those associated with HPV (cancers of the vulva, vagina, cervix, and anal area).[9]

Although women who require immunosuppressant medications after transplant are not at a higher risk for acquiring new HPV infections,[8] they have decreased capacity for viral clearance if they are newly infected with HPV and have an increased risk of reactivation of latent infection.[8-14] Several factors affect immunity and viral clearance, including the duration of immunosuppressant therapy, number and dosing of immunosuppressant medications, history of ionizing radiation and/or chemotherapy, and age.[8,9,12] Once infected with HPV, immunosuppressed women have higher viral loads than immunocompetent women.[12]

Renal transplant recipients have a higher prevalence of both cervical and anal dysplasia.[11] After kidney transplant, women are at a 50-fold increased risk for vulvar cancer and a 15-fold increased risk for cervical cancer.[13] DNA damage caused by most immunosuppressants, altered DNA repair, and reduced immunologic tolerance account for the increased incidence of cancers in posttransplant patients.[1] The calcineurin inhibitor class of medications (cyclosporine and tacrolimus) most likely increases cancer incidence through promotion of angiogenesis and production of cytokines.[1] Therefore, cervical cytological testing and HPV testing are recommended

before transplant, and HPV vaccination should be offered to eligible women.[1,14] After transplant, women should have more frequent screening for vulvar, vaginal, and anal carcinomas with annual pelvic examinations that include thorough visual inspection and palpation.[14,15] It is preferred that women older than 30 years undergo cotesting every 3 years, but if cotesting is not available, cervical cytological testing every year is an acceptable alternative. Routine testing for high-risk HPV is not recommended for women younger than 30 years.[2] The goal of more frequent screening is to identify low-grade lesions and avoid progression to irreversible and high-grade lesions, such as high-grade squamous intraepithelial lesions, or carcinoma.[14]

CERVICAL CANCER SCREENING IN HIV-POSITIVE WOMEN

Human immunodeficiency virus infection generally causes a progressive deterioration of the immune system. Worsening immunity is associated with higher HIV viral load and an increase in HPV infection rates.[16] In women with concomitant HIV and HPV infection, changes in the cervical mucosa are seen even before evidence of systemic immunosuppression. The innate and adaptive immune responses that help clear the HPV infection are impaired, which leads to increased vulnerability to persistent HPV infection and later to cervical intraepithelial neoplasia (CIN).[16]

Human papillomavirus is more frequently isolated from cervical and anal swabs obtained from HIV-positive women than HIV-negative women.[11,17] Women who are HIV positive often have an increased HPV viral load and concomitant infection with several genotypes.[15] In general, immunocompetent women infected with high-risk HPV have progression to high-grade cervical dysplasia (CIN 3) over 7 to 8 years, and invasive cervical cancer develops in an additional 5 to 7 years. In women with AIDS, the rate of progression from CIN 3 to invasive cervical cancer is much faster—estimated at 3.2 years.[15]

In HIV-infected women, regardless of the mode of infection (eg, perinatal exposure, sexual activity), initiation of cervical cancer screening is recommended within 1 year of sexual debut but no later than age 21 years (Table 1). Women aged 21 to 29 years with newly diagnosed HIV infection should have cervical cancer screening completed at the time of HIV diagnosis. Repeated testing should be completed in 12 months. After 3 annual consecutive cervical cytologic tests with normal results, the interval can be extended to every 3 years. Cotesting is not recommended for these women until age 30 years.[2,18]

In women older than 30 years with HIV infection, cotesting is preferred, most commonly at the time of HIV diagnosis. If the results are negative, cotesting can be completed

TABLE 1. Screening Recommendations for Cervical Cancer in HIV-Positive Women

Population	Recommended screening method	Comment
Age ≤21 y and sexually active	Cervical cytologic testing alone every 3 y	
Age 21-29 y	Cervical cytological testing alone every 3 y	
Age ≤29 y, HIV newly diagnosed	Annual cervical cytological testing alone	If 3 consecutive cervical cytological results are normal, return to age-based screening
Age ≥30 y	HPV and cervical cytological testing (cotesting) every 3 y (preferred) Cervical cytological testing alone every 3 y (acceptable)	
Age ≥30 y, HIV newly diagnosed	HPV and cervical cytological testing (cotesting) every 3 y (preferred) Annual cervical cytological testing alone (acceptable)	If 3 consecutive cervical cytological results are normal, return to age-based screening
Patients with total hysterectomy	No screening necessary	Applies to women with no cervix and no history of CIN 2/3, adenocarcinoma in situ, or cervical carcinoma in the past 20 y

CIN = cervical intraepithelial neoplasia; HIV = human immunodeficiency virus; HPV = human papillomavirus.
Data from the US Department of Health and Human Services.[18]

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every 3 years. If high-risk HPV testing is unavailable, cervical cytological testing is recommended at the time of diagnosis and then every 12 months. Screening intervals can be changed to every 3 years after 3 consecutive normal cervical cytological test results. Cervical cancer screening should be continued for the lifetime of a woman with HIV infection and should not be stopped at age 65 years.[2,18]

Women infected with HIV also have increased rates of vaginal cancer compared with the general population. However, if a hysterectomy is performed for benign reasons, routine screening for vaginal cancer with vault cytological testing or HPV testing is not recommended. In patients who have undergone hysterectomy for cervical dysplasia or cervical carcinoma, vaginal vault cytological testing should be continued (Table 1).[2,18]

The effect of antiretroviral therapy (ART) on the incidence of invasive cervical cancer is not clear,[15] but CD4 counts are inversely related to the rates of invasive cervical cancer. Some studies suggest that women compliant with ART have improved regression of precancerous cervical lesions.[19] However, the incidence of cervical carcinoma in HIV-infected women is unchanged since the introduction of ART. Current recommendations are to follow the same screening frequency for these women, regardless of ART.[18]

CERVICAL CANCER SCREENING IN WOMEN EXPOSED TO DES IN UTERO

DES is a potent synthetic estrogen that was prescribed until the early 1970s to prevent premature births and maintain pregnancies.[20,21] This practice was discontinued when the link between in utero exposure to DES and development of clear cell cancer of the vagina and cervical adenocarcinoma was firmly established.[20] In 1994, the American College of Obstetricians and Gynecologists recommended that women exposed to DES in utero should have annual cervical cytological testing and a thorough vaginal examination (Table 2).[2] Daughters of women exposed to DES during their early weeks of pregnancy were found to have a wider cervical transformation zone, leading to the increased incidence of high-grade squamous neoplasia of the cervix.[22] The National Cancer Institute DES cohort follow-up study found that the risk appears to be highest during adolescence and peaks at around age 25 years but persists up to age 39 years.[21] There is no reported increased incidence of breast, ovarian, or endometrial cancer in this population.[21]

Currently, there are no screening guidelines or society recommendations for women exposed to DES in utero who undergo total hysterectomy for benign causes. However, given that they are at higher risk for clear cell cancer of the vagina, it is reasonable to

TABLE 2. Screening Recommendations for Cervical Cancer in Women Who Are Immunocompromised (Non-HIV) or Have DES Exposure[a,b]

Population	Recommended screening method	Comment
Age ≤21 y and sexually active	Annual cytological testing alone	
Age 21-29 y	Annual cytological testing alone	
Age ≥30 y	HPV and cytological testing (cotesting) every 3 y (preferred) Annual cytological testing alone	
Patients with total hysterectomy	Non-HIV immunocompromised women: no screening DES-exposed women: vaginal HPV and cytological testing (cotesting) every 3 y (preferred) Annual cytological testing alone	Women with no cervix and no history of CIN 2/3, adenocarcinoma in situ, or cervical carcinoma in past 20 y

[a]CIN = cervical intraepithelial neoplasia; DES = diethylstilbestrol; HIV = human immunodeficiency virus; HPV = human papillomavirus.
[b]For women who are immunocompromised for non-HIV causes or have in utero exposure to DES, there are currently no major society recommendations guiding cervical cancer screening. These recommendations are extrapolated from known risks and guidelines for similar populations.
Data from *Obstet Gynecol.*[2]

continue vaginal vault cytological testing every 3 years until age 65 years.[2] In addition, if the woman has a history of severe cervical dysplasia or carcinoma, screening should be continued (Table 2).[2]

CERVICAL CANCER SCREENING IN WOMEN WITH A HISTORY OF CERVICAL DYSPLASIA OR CERVICAL CANCER

The incidence of invasive cervical cancer is increased 2.8-fold in women previously treated for cervical dysplasia (CIN 2 or CIN 3) or cervical adenocarcinoma.[6] This rate is the same for women who have been treated with hysterectomy, cervical excision procedures, or cervical ablative procedures.[23] It is unclear whether the increased risk is due to development of new invasive cancer or growth of minor residual disease that was undetected at the time of treatment.[23] The risk remains substantial for the first 10 years and then decreases.[23] However, the risk remains slightly increased for up to 20 years after initial treatment.[23] These women should continue to receive routine age-based screening for 20 years after completion of the initial posttreatment surveillance (Table 3).[2] Screening can extend beyond 65 years of age for some women, depending on their age at diagnosis.[3] These women are also at increased risk for recurrent intraepithelial neoplasia or cancer at the vaginal cuff.[2] They are one of the few groups of women who should be considered for vaginal Papanicolaou tests (vault cytology) after a hysterectomy.[3] The role of HPV testing in these women has not been well established.[2]

CERVICAL CANCER SCREENING IN WOMEN WITH OTHER CAUSES OF IMMUNOSUPPRESSION

Women with autoimmune diseases have several immune system defects, and some undergo immunosuppressant therapy. These patients have a higher rate of abnormal Papanicolaou test results than those without autoimmune disease.[19,24] The rate of cervical dysplasia is increased in women with vs without systemic lupus erythematosus, and the use of immunosuppressive medications increases this risk even further.[6,24] Women with inflammatory bowel disease have an increased incidence of cervical dysplasia and cervical cancer, possibly from the inflammatory bowel disease itself or from the associated immunomodulator and immunosuppressive medications.[25] Women with primary immunodeficiencies are also considered to be at higher risk for cervical cancer. Women who are immunosuppressed are at a greater risk for HPV-related cancers (cervical, vaginal, vulvar, and anogenital areas). In an immunocompromised state, viral clearance is reduced and progression from precancerous lesions to invasive cancer is more rapid.[6,15] With certain immunosuppressants, the risk of cancer is directly related to the cumulative dose of the medication.[19] Studies are limited in these groups of women, but in general they are considered to be at a higher risk for cervical cancer. Clear-cut guidelines do not exist regarding the frequency of cervical cancer screening for these women (Table 2). Until such guidelines are available, it is reasonable

TABLE 3. Screening Recommendations for Cervical Cancer in Women With a History of CIN 2, CIN 3, or Adenocarcinoma in Situ[a,b]

Population	Recommended screening method
Age 21-29 y	Cervical cytological testing alone every 3 y
Age 21-29 y with total hysterectomy	HPV and cervical cytological testing (cotesting) every 5 y (preferred) Cervical cytological testing alone every 3 y (acceptable)
Age ≥30 y	HPV and cervical cytological testing (cotesting) every 5 y (preferred) Cervical cytological testing alone every 3 y (acceptable)
Age ≥30 y with total hysterectomy	HPV and cervical cytological testing (cotesting) every 5 y (preferred) Cervical cytological testing alone every 3 y (acceptable)

[a]CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus.
[b]Routine age-based screening should be initiated after completion of initial posttreatment surveillance. It should be continued for a total of 20 years after spontaneous regression or appropriate management.
Data from *Obstet Gynecol.*[2]

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to offer all women who are immunocompromised due to various causes annual cervical cytological testing or cotesting every 3 years.[6,25]

Women who are immunocompromised for various other reasons and who undergo hysterectomy for benign reasons can discontinue vaginal cytological or HPV testing (Table 2).[2] If an immunocompromised woman undergoes hysterectomy for treatment of severe cervical dysplasia or cervical carcinoma, screening should continue for 20 years after hysterectomy (Table 3).[2]

CONCLUSION

Current cervical cancer screening recommendations are available only for women at average risk for cervical cancer. It is important to remember that women at high risk for cervical cancer need more frequent cervical cancer screening. Annual cervical cytological testing with age-appropriate reflex HPV testing or cotesting every 3 years has been found to decrease the incidence of invasive cervical cancer in high-risk groups of women.[9]

Abbreviations and Acronyms: **ART** = antiretroviral therapy; **CIN** = cervical intraepithelial neoplasia; **DES** = diethylstilbestrol; **HIV** = human immunodeficiency virus; **HPV** = human papillomavirus

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