

NCCN Guidelines® Insights

Cervical Cancer Screening

Featured Updates

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Abstract

These NCCN Guidelines Insights focus on recent recommendations for cervical cancer screening and management of abnormal screening tests. When the NCCN Panel convened to update the NCCN Guidelines for Cervical Cancer Screening, they decided to adopt and endorse guidelines from other organizations to avoid duplication of effort. Therefore, in July 2013, after review and validation of consensus guidelines from the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology, the NCCN Guidelines for Cervical Cancer Screening were discontinued. (*J Natl Compr Canc Netw* 2014;12:333–341)

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Release date: March 10, 2014; Expiration date: March 10, 2015

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Inform clinicians of recent changes to cervical cancer screening recommendations and management of abnormal screening test results
- Describe the rationale behind the recent changes in management for cervical cancer screening

Disclosure of Relevant Financial Relationships**Editor:**

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Supported by an independent educational grant from Prometheus Laboratories, Inc., and by education grants from Bayer HealthCare, Onyx Pharmaceuticals, Inc., and Algeta US; Exelixis, Inc.; Genentech; Genomic Health, Inc.; NOVOCURE; and Merck Sharp & Dohme Corp.

Cervical Cancer Screening

Overview

Cervical cytology screening has been proven to decrease the incidence and mortality of cervical squamous cell cancer and to increase the cure rate of cervical cancer.¹⁻⁴ Despite this, an estimated 12,340 women will be diagnosed with cervical cancer in the United States in 2013, with 4030 expected deaths.⁵ High-risk groups include women without access to health care and those who have immigrated to the United States from countries where cervical cancer screening is not routinely performed. Risk factors for cervical cancer include persistent infection with high-risk subtypes of human papillomavirus (HPV), such as HPV 16 and HPV 18, which account for approximately 70% of cervical cancer.⁶⁻¹⁰ However, most HPV 16/18 infections in women are not persistent, especially those in young women (age <30 years).¹¹⁻¹³ Other epidemiologic risk factors associated with cervical cancer are a history of smoking, parity, contraceptive use, early age of onset of coitus, larger number of sexual partners, history of sexually transmitted disease, and chronic immunosuppression. Squamous cell carcinomas account for approximately 80% of all cervical cancers, and adenocarcinomas for approximately 20%.¹⁰

Cervical cytology screening is the predominant method for early detection of cervical cancer and its precursors, such as high-grade squamous intraepithelial lesions (HSILs). Use of DNA testing for high-risk subtypes of HPV is a useful adjunct to cervical cytology screening in select patients. Cervical cytology screening techniques include liquid-based cervical cytology or conventional Papanicolaou (Pap) smears; data suggest that the 2 techniques are similar.^{1,2} These techniques are collectively referred to as *cervical cytology*. Most cervical cytology testing in the United States is now performed with liquid-based cytology.¹⁴ When compared with conventional Pap testing, advantages of liquid-based cervical cytology include the fact that (1) testing for HPV can be performed using the same sample, referred to as *cotesting* (if done at the same time) or *reflex testing* (if done later on); and (2) it is easier to read.¹⁴ Testing that includes HPV is more sensitive than cervical cytology alone, but is less specific.^{15,16}

When the NCCN Cervical Cancer Screening Panel convened to update the NCCN Guidelines,

they decided to adopt and endorse guidelines from other organizations to avoid anticipated significant overlap and duplication of effort.^{1,17} Therefore, in July 2013, after review and validation of consensus guidelines from the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology, the NCCN Guidelines for Cervical Cancer Screening were discontinued.^{1,17} Development of the screening guidelines involved a systematic review of the evidence and input from working groups, which focused on devising the best screening strategies to balance the benefits and harms of screening.¹ Revising the guidelines for the management of abnormal screening tests involved use of the new screening guidelines, thorough review of the evidence (including evidence weighting, abstraction of risk/outcomes data from the Kaiser Permanente Northern California database, input from NIH statisticians), and an inclusive consensus development process (including Web posting for comment before presentation, voting, and revision at a meeting involving representatives from 26 stakeholder organizations).¹⁷ The panel feels that these consensus guidelines represent an accurate and thorough evaluation of the data, the recommendations are appropriate, and it is appropriate to endorse these guidelines.

Cervical Cancer Screening Guidelines

In 2012, revised screening guidelines for cervical cancer and its precursors were developed and approved by the ACS, ASCCP, and ASCP (Table 1).⁶ The panel endorses these new screening guidelines, which have been widely adopted. These revised screening guidelines also include recommendations for special populations, such as (1) young women aged 21 to 24 years; (2) pregnant women; (3) postmenopausal women; and (4) women aged 65 years and older. These new screening guidelines do not provide recommendations for populations at higher risk for cervical cancer, such as women who are immunocompromised (eg, HIV infection), were exposed to diethylstilbestrol in utero, or have a history of cervical cancer; more frequent screening may be appropriate for these patients.^{1,15}

The new recommendations involve longer screening intervals and cotesting (using liquid-

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based cervical cytology plus HPV testing).¹⁸ A few of the recommendations for cervical screening are as follows: (1) annual screening is not recommended for any age group; (2) HPV testing should not be used as a stand-alone test for screening; (3) cotesting every 5 years is preferred for women aged 30 to 65 years; (4) screening with cervical cytology alone every 3 years is recommended for all women aged 21 to 65 years if cotesting is not recommended or not available; (5) cotesting is not recommended for screening women aged 21 to 29 years; (6) women younger than 21 years should not be screened for cervical cancer; (7) women who have been vaccinated against HPV need to be screened using the same recommendations for unvaccinated women; and (8) screening is not recommended in women aged 65 years and older if they have had adequate prior screening with normal results.

Cotesting is preferred for women aged 30 to 65 years, because cervical cytology alone is not as sensitive and cotesting decreases the number of follow-up visits.^{6,15,16} In general, women with high-risk HPV are at greater risk for precursors to cervical cancer (eg, cervical intraepithelial neoplasia 3 [CIN 3]) than those who are HPV-negative. Women should begin screening at 21 years of age, regardless of whether sexual intercourse has already occurred.¹ Data indicate that cervical screening should be avoided in women younger than 21 years, because they are at very low risk of cervical cancer and because treatment can lead to complications; a significant increase in premature births has been noted in women previously treated for dysplasia.^{19–25} Although a few adolescents or young adults may have CIN 3, progression to cervical cancer is extremely rare in women younger than 21 years; most women with CIN 3 are identified on subsequent screening.^{26–29} A high percentage of young women will be HPV-positive within several years of initial sexual activity.^{30–32} Thus, adolescents or young women (<21 years) who are sexually active have a high prevalence of high-risk HPV infection; however, many infections will regress.^{12,26,27,33,34} Cotesting is not recommended for screening women younger than 30 years because of the high prevalence of HPV in young women and the consequent poor specificity of cotesting. Therefore, HPV DNA screening is not recommended for women aged 21 to 29 years.^{1,22,26} HPV

is often a transient infection and typically does not cause CIN 3 or cervical cancer; persistent infection with high-risk HPV is required to cause cervical cancer.^{6,7,12,13,33,35}

Management of Abnormal Cervical Cancer Screening Tests

Cervical cytology test results are reported using the 2001 Bethesda System.³⁶ Test results may be normal (ie, negative for intraepithelial lesion or malignancy), unsatisfactory, or positive for abnormalities (eg, HSILs) or invasive carcinoma. Unsatisfactory cervical cytology tests should be repeated even for women with HPV-negative results; however, colposcopy is also an option for women aged 30 years or older. Abnormalities from cervical cytology testing range from lowest to highest risk of cancer as follows: (1) atypical squamous cell of undetermined significance (ASC-US); (2) low-grade squamous intraepithelial lesion (LSIL); (3) atypical squamous cell suspicion of high-grade dysplasia (ASC-H); (4) HSIL; and (5) invasive carcinoma. Colposcopy, along with colposcopically directed biopsies, may be indicated for evaluating women with abnormal results (eg, positive HPV test results and ASC-US or worse). In general, the guiding principle for managing abnormal test results is similar management for similar risks.

During a colposcopic examination, the cervix is viewed through a long focal-length dissecting-type microscope (magnification, 10x–16x). A 3% to 5% solution of acetic acid is applied to the cervix before viewing. The coloration induced by the acid and the observance of blood vessel patterns allow a directed biopsy to rule out invasive disease and determine the extent of preinvasive disease. For example, the biopsy may show precursors of cancer, such as CIN 3. If the entire squamocolumnar junction of the cervix is visualized (ie, the entire transformation zone is seen), the examination is considered adequate and endocervical curettage is not required.^{26,37,38} Techniques for definitive treatment of cervical abnormalities include excision with the loop electrosurgical excision procedure, cold-knife conization, or total hysterectomy. Ablative procedures include laser ablation or cryotherapy. Clinicians should inform

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patients that treatment may be associated with adverse pregnancy outcomes.^{19,20,24,25}

Because new screening guidelines were recently adopted, the ASCCP updated their guideline for managing abnormal cervical screening tests and follow-up.^{1,17} Management is now more complex, because cotesting and HPV genotyping have increased the number of possible test results (Table 2; see article by Massad elsewhere in this issue).⁶ Some of the new recommendations are as follows: (1) conservative management is recommended for women aged 21 to 24 years and those who are pregnant; (2) although cotesting is not recommended for screening in women aged 25 to 29 years, HPV testing may be recommended for management of abnormal tests in certain circumstances, because the risk for cervical cancer begins to increase in this age group; (3) women older than 65 years should continue to be screened if they have ACS-US, even if they are HPV-negative; and (4) cotesting is often used for follow-up to decrease the number of return visits.

Cotesting is not recommended for cervical cancer screening in women aged 21 to 29 years. However, reflex HPV testing is preferred to assess women aged 25 to 29 years with abnormal cervical

cytology results of ASC-US, but repeating cytology is also an option.¹⁷ Recently, clinicians have been concerned about overtreatment of young women whose precancerous lesions may regress. Therefore, more conservative management of young women aged 21 to 24 years is now recommended.¹⁷ Although repeat cytology is preferred for assessing abnormal results in women aged 21 to 24 years, reflex HPV testing is also acceptable, but only for ASC-US. For women aged 21 to 24 years with HSIL, colposcopy is recommended but immediate treatment is not recommended. CIN 1 should not be treated in any age group unless persistent for 2 years. Observation is recommended for CIN 2. Young women aged 21 to 24 years with CIN 3 should not be observed; they should be treated with a diagnostic excisional procedure, but hysterectomy is not the primary treatment.

Colposcopy and cervical biopsy are not acceptable in pregnant women unless high-grade neoplasia or invasive cancer is suspected. Colposcopy is preferred for pregnant women with LSIL, but deferring colposcopy until 6 weeks after childbirth is also an option. Treatment of CIN 1 is not recommended for pregnant women. For pregnant women with LSIL who do not have CIN 2, postpartum

Table 1 Cervical Cancer Screening Guidelines^a

Population	Screening Recommendations
Age group	
<21 y	Do not screen
21–29 y	Perform cytologic testing alone every 3 y
30–65 y	Perform cytologic and HPV cotesting every 5 y (preferred), or perform cytologic testing alone every 3 y (acceptable) ^b
>65 y	Discontinue screening if there has been an adequate number of negative screening results previously (3 consecutive negative cytologic tests or 2 consecutive negative cotests in the past 10 y, with the most recent test in the past 5 y) and if there is no history of HSIL, ^c adenocarcinoma in situ, or cancer
Women who have undergone hysterectomy	Discontinue screening if the patient has undergone a total hysterectomy with removal of cervix and if there is no history of HSIL, adenocarcinoma in situ, or cancer

Abbreviations: HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesions.

^aThe 3 major sets of screening guidelines were issued by the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Multisociety Guidelines Group¹; the American College of Obstetricians and Gynecologists²⁹; and the U.S. Preventive Services Task Force (USPSTF).² The guidelines agree on most recommendations, including the recommended age at the start of screening (21 y), the age at which screening can be discontinued if the history of negative screening is adequate (>65 y), and the recommended interval between tests. Specifically, cotesting at a 5-y interval is either preferred or acceptable for women aged 30 to 65 y, whereas cytologic testing alone every 3 y is acceptable for women aged 21 to 65 y.

^bThe terms *preferred* and *acceptable* are not included in the USPSTF Recommendation Statement.

^cHSIL includes cervical intraepithelial neoplasia grade 3 and cases of grade 2 that stain positive for p16.⁴⁰

From Schiffman M, Solomon D. Cervical-cancer screening with human papillomavirus and cytologic cotesting. *N Engl J Med* 2013;369:2327; with permission.

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Table 2 Ranked 5-Year Risk of HSIL and Cancer and Suggested Management According to Test Results ^a			
Result on Cytologic Testing or Cotesting	Frequency of Screening Result ^b (%)	Risk of Histologic HSIL and Cancer ^c (%)	Suggested Management
SCC	0.0048	84	Immediate colposcopy
HPV+/HSIL	0.2	71	Immediate colposcopy
HSIL	0.21	69	Immediate colposcopy
HPV-/HSIL	0.013	49	Immediate colposcopy
HPV+/AGC	0.054	45	Immediate colposcopy
HPV+/ASC-H	0.12	45	Immediate colposcopy
ASC-H	0.17	35	Immediate colposcopy
HPV+/LSIL	0.81	19	Immediate colposcopy
HPV+/ASC-US	1.1	18	Immediate colposcopy
LSIL	0.97	16	Immediate colposcopy
AGC	0.21	13	Immediate colposcopy
HPV-/ASC-H	0.051	12	Immediate colposcopy
HPV+/Pap-	3.6	10	Repeat testing in 6–12 mo
ASC-US	2.8	6.9	Repeat testing in 6–12 mo
HPV-/LSIL	0.19	5.1	Repeat testing in 6–12 mo
HPV-/AGC ^d	0.16	2.2	Immediate colposcopy
HPV-/ASC-US	1.8	1.1	Repeat testing in 3 y
Pap-	96	0.68	Repeat testing in 3 y
HPV-/Pap-	92	0.27	Repeat testing in 5 y

Abbreviations: AGC, atypical glandular cells; ASC-H, atypical squamous cells (cannot rule out high-grade lesion); ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; Pap, Papanicolaou test; SCC, squamous cell carcinoma.

^aThe data are based on cytologic testing and cotesting performed by Kaiser Permanente Northern California. Under the principle of similar management of similar risks, the management guidelines for cotesting results were “benchmarked” to the current management of cytologic-testing-only results.

^bThe frequencies of cytologic-testing-only results are derived from data for all women with cytologic testing results, and the frequencies of cotesting results are derived from data for all women with cotesting results.

^cThe frequency of HSIL and cancer was estimated by the Kaiser histologic diagnoses of CIN 2, CIN 3, adenocarcinoma in situ, and cancer.

^dFor HPV-/AGC, the cancer risk remained high, justifying immediate colposcopy.

From Schiffman M, Solomon D. Cervical-cancer screening with human papillomavirus and cytologic cotesting. *N Engl J Med* 2013;369:2329 ; with permission.

follow-up is recommended. Pregnant women with CIN 3 can wait until after delivery to be treated.¹⁷ Endocervical curettage is not acceptable in pregnant women. Unless invasive cancer is detected, pregnant women should not be treated until after childbirth. A limited diagnostic excision procedure is recommended for invasive cancer in pregnant women.

Summary

In 2012, revised screening guidelines for the early detection of cervical cancer and its precursors were

developed and approved by the ACS, ASCCP, and ASCP.¹ Because these new screening guidelines were recently adopted, the ASCCP updated their guideline for managing abnormal cervical screening tests.^{1,17} NCCN endorses both of these new guidelines. In July 2013, after reviewing and validating these consensus guidelines from the ACS, ASCCP, and ASCP, the NCCN Panel decided to discontinue the NCCN Guidelines for Cervical Cancer Screening to avoid duplication of effort.

These revised screening guidelines include recommendations for special populations, such as

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(1) young women aged 21 to 24 years; (2) pregnant women; (3) postmenopausal women; and (4) women aged 65 years and older. The new recommendations involve longer screening intervals and cotesting (using liquid-based cervical cytology plus HPV testing).¹⁸ A few of the recommendations for cervical screening are as follows: (1) annual screening is not recommended for any age group; (2) HPV testing should not be used as a stand-alone test for screening; (3) cotesting every 5 years is a preferred recommendation for women aged 30 to 65 years; (4) screening with cervical cytology alone every 3 years is recommended for women aged 21 to 65 years if cotesting is not recommended or not available; (5) cotesting is not recommended for screening women aged 21 to 29 years; (6) women younger than 21 years should not be screened for cervical cancer; (7) women who have been vaccinated against HPV need to be screened using the same recommendations for unvaccinated women; and (8) screening is not recommended in women aged 65 years and older if they have had adequate prior screening with normal results.

Some of the ASCCP's recommendations for managing abnormal cervical screening tests are as follows: (1) conservative management is recommended for women age 21 to 24 years and those who are pregnant; (2) although cotesting is not recommended for screening women age 25 to 29 years, HPV testing may be recommended for management of abnormal tests in certain circumstances because the risk for cervical cancer starts to increase in this age group; (3) women older than 65 years should continue to be screened if they have ACS-US, even if they are HPV-negative; and (4) cotesting is often used for follow-up to decrease the number of return visits.

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Cervical Cancer Screening

Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at <http://education.nccn.org/node/41691>; and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-

choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet.

Posttest Questions

1. Which of the following is TRUE about management of cervical intraepithelial neoplasia (CIN) in women?
 - a. CIN 1 should not be treated in any age group unless it is persistent for 2 years
 - b. Observation is recommended for CIN 2
 - c. Young women aged 21 to 24 years with CIN 3 should be treated with a diagnostic excisional procedure but hysterectomy is not the primary treatment
 - d. All of the above
 - e. None of the above
2. Human papillomavirus (HPV) is often a transient infection and typically does not cause CIN 3 or cervical cancer; persistent infection with high-risk HPV (HPV 16 or 18) is required to cause cervical cancer.
 - a. True
 - b. False

3. Cotesting refers to assessing cervical cytology and assessing for high-risk HPV at the same time using the same sample to determine whether cervical cancer or precursors of cancer are present. Which of the following is TRUE about cotesting?



- a. Cotesting is not recommended for screening women younger than 30 years because of the high prevalence of HPV in young women and the consequent poor specificity of cotesting
- b. Cotesting every 5 years is the preferred cervical screening strategy for women aged 30 to 65 years
- c. Cotesting is more sensitive than Pap testing alone
- d. All of the above
- e. None of the above