New cervical Ca screening guidelines recommend less frequent assessment

Annual assessment increases the harms of cervical cancer screening, compared with longer intervals, according to updated guidelines

Janelle Yates, Senior Editor

New guidelines from multiple professional societies are in agreement: The cervical cancer screening interval should be extended in most women.[1,2]

"Today, there is little evidence to support the annual screening of women at any age by any screening test, method, or modality," say joint recommendations from the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology (ACS/ASCCP/ASCP).

The guideline emphasizes that point, going on to state: "Women at any age should *not* be screened annually by any screening method; rather, recommended screening intervals for women are based on age and clinical history."[2]

Overview of the guidelines

In March 2012, the ACS/ASCCP/ASCP and the US Preventive Services Task Force (USPSTF) updated existing recommendations on the fine points of cervical cancer screening. Both sets of guidelines note that financial cost was not considered in formulating the recommendations. They also point out that the guidelines apply only to women who have a cervix. In addition, both sets of guidelines exclude women who have been identified as having a high-grade precancerous lesion or cervical cancer, women who were exposed in utero to diethylstilbestrol, and women who are immunocompromised (e.g., HIV-positive).

The recommendations are categorized according to the age of the patient and her clinical history (or lack thereof):

- **Adolescents:** No screening. "Adolescent cervical cancer prevention programs should focus on universal HPV vaccination, which is safe, highly efficacious, and, when used in adolescents before they become sexually active, highly effective and cost-effective," notes ACS/ASCCP/ASCP.[2]
- **Women 21 to 29 years old:** Begin screening at age 21 and continue every 3 years until the age of 29 years. Routine testing for oncogenic human papillomavirus (HPV) strains is not recommended in this population.
- **Women 30 to 65 years old:** Cytology screening every 3 years or co-testing (cytology plus HPV testing) every 5 years. The 5-year co-testing interval is recommended by ACS/ASCCP/ASCP, whereas the USPSTF simply states: "Screening women ages 21 to 65 years every 3 years with cytology provides a reasonable balance between benefits and harms." The USPSTF also notes that "HPV testing combined with cytology (co-testing) every 5 years in women ages 30 to 65 years offers a comparable

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Population	USPSTF	ACS/ASCCP/ASCP
<21 years	Do not screen, regardless of the age of sexual initiation and other risk factors	
21–29 years	Screen with cytology every 3 years	
30–65 years	Screen with cytology every 3 years (preferred) or with a combination of cytology and HPV testing every 5 years	Screen with a combination of cytology and HPV testing every 5 years (preferred) or cytology alone every 3 years
>65 years	Do not screen women who have had adequate prior screening and who are not otherwise at high risk of cervical cancer	Do not screen women who have evidence of adequate prior screening and no history of CIN 2+ within the past 20 years. Do not resume screening for any reason, even if a woman reports having a new sexual partner.
After hysterectomy	Do not screen women who have undergone removal of the cervix and who have no history of CIN 2+ or cervical cancer	Do not screen for vaginal cancer in women who have undergone removal of the cervix and who have no history of CIN 2+. Evidence of adequate negative prior screening is not required. Do not resume screening for any reason, even if a woman reports having a new sexual partner.
HPV-vaccinated	Continue screening, according to age and clinical history	

USPSTF = US Preventive Services Task Force; ACS/ASCCP/ASCP = American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society of Clinical Pathology

balance of benefits and harms, and is therefore a reasonable alternative for women in this age group who would prefer to extend the screening interval."

- **Women over 65 years:** Discontinue screening, provided the woman has undergone adequate screening in preceding years with negative results (**TABLE**).

What to do about discordant co-test results

When a woman has atypical cells of undetermined significance (ASC-US) on cytology in combination with a negative HPV test, she should be managed the same way as women with normal screening results, says Andrew M. Kaunitz, MD, professor and associate chairman of obstetrics and gynecology at the University of Florida–Jacksonville. Dr. Kaunitz serves on the OBG MANAGEMENT Board of Editors.

"I anticipate that the greatest confusion over the new guidelines will center on the management of women who are found to be negative by cytology but positive on an HPV test," he says. The ACS/ASCCP/ASCP guidelines offer two options for this population:

- **Option 1: Repeat co-testing in 1 year.** Women who are still HPV positive at the time of repeat co-testing, or who have low-grade squamous intraepithelial lesions (LSIL) or more severe findings on cytology, should undergo colposcopy and be managed according to ASCCP guidelines.[3] Women who test HPV-negative and who have normal cytology or atypical squamous cells of undetermined significance (ASC-US) at the time of repeat co-testing should be returned to regular screening.
- **Option 2: Immediate testing for HPV 16 and 18.** Women who test positive for either of these viral types should undergo colposcopy. Women who test negative for both of these viral types should be co-tested in 12 months and managed according to Option 1.

"Women who have any other abnormality should be managed according to existing guidance from the ASCCP," Dr. Kaunitz advises.[3] "After spontaneous regression or appropriate treatment, women who have a history of cervical intraepithelial neoplasia

(CIN) grade 2 or higher should continue routine screening for at least 20 years, even if this extends screening past the age of 65 years."

Guidelines emphasize the harms of frequent screening

Both sets of guidelines mention the potential "harms" of screening. For example, the ACS/ASCCP/ASCP guidelines point out that most HPV infections and many cases of CIN 1 and CIN 2 are transient, unlikely to progress or develop into cancer.

"The potential harms associated with detecting these transient lesions include the anxiety associated with a 'positive' cancer screening test, potential stigmatization from the diagnosis of a sexually transmitted infection, discomfort from additional diagnostic and treatment procedures, bleeding from treatment, and, longer term, an increased risk of pregnancy complications such as preterm delivery due to treatment," according to the guidelines. "Having a positive test at any point in one's life may contribute to a perception of an increased risk of cancer, and a subsequent desire for more testing, further increasing the likelihood of another positive test."[2]

The USPSTF takes this concern for potential harms a step further and emphasizes the possibility of "overtreatment" when HPV testing is used as part of a cervical cancer screening strategy: "Positive screening results are more common with strategies that include HPV testing than with strategies that use cytology alone. Therefore, the likelihood of prolonged surveillance and overtreatment may increase with strategies that incorporate HPV testing."[1]

However, the ACS/ASCCP/ASCP noted that screening models indicate that co-testing of women 30 years and older at 5-year intervals results in fewer colposcopies (thereby reducing harms) and carries "a similar or slightly lower cancer risk, compared with cytology alone performed at 3-year intervals." That is because 5-year intervals reduce the number of screens in a woman's lifetime, thereby detecting fewer transient HPV infections and low-grade cellular changes not destined to become cancer.

Reducing the number of colposcopies

The guidelines aim to reduce the number of women referred to colposcopy for cytologic abnormalities or HPV-positive results. In formulating the ACS/ASCCP/ASCP guidelines, the panel calculated the number of colposcopies associated with different screening intervals, noting that "screening every 3 years is associated with a lifetime prediction of about 760 colposcopies per 1,000 women, screening every 2 years with about 1,080 colposcopies per 1,000 women (a 40% increase vs screening every 3 years), and screening every year with about 2,000 per 1,000 women."[2] However, the yield of high-grade CIN and cervical cancer identified during screening does not vary significantly between these intervals.

"The lifetime risk of cervical cancer in the United States in the absence of screening is projected to be approximately 31 to 33 cases in every 1,000 women," says Tom Cox, MD, past president of ASCCP. Dr. Cox is an OBG MANAGEMENT contributing editor. "Screening with cytology alone every 3 years reduces this risk to 5 to 8 incident cancers per 1,000 women, and the risk drops slightly with screening every 2 years to 4 to 6 cases per 1,000 women. Annual screening further reduces this risk to about 3 cases per 1,000 women. The predicted lifetime risk of death due to cervical cancer associated with screening with cytology every 3 years, every 2 years, and annually is even lower: 0.05, 0.05, and 0.03 death per 1,000 women, respectively."

"So there is a small reduction in the lifetime risk of cervical cancer with more frequent cytology screening," Dr. Cox notes, "but the harms of more frequent screening were determined by both the USPSTF and the ACS/ASCCP/ASCP to far outweigh the benefit. Co-testing at 5-year intervals provides similar, or even lower, cancer risk than cytology at 3-year intervals, justifying the choice of a longer screening interval when co-testing is negative."

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Rethinking the annual exam

Many women schedule an appointment with their gynecologist each year for the express

New guidelines are unlikely to lower the incidence of cervical cancer

What is the likely overall impact of new guidelines recommending less screening for cervical cancer?

We put this question—and others—to public health expert Neal M. Lonky, MD, MPH, clinical professor of obstetrics and gynecology at the University of California–Irvine and a member of the board of directors of Southern California Permanente Medical Group. Dr. Lonky serves as an OBG MANAGEMENT contributing editor. His responses offer a thoughtful commentary on the pressing issue of reducing the rate of cervical cancer in the United States.

"We have no evidence that any screening strategy will lower the cancer rate with any combination of cytology innovation or HPV test innovation," he says. "These guidelines purely focus on 'holding the gains' on the current cancer incidence in the United States."

OBG MANAGEMENT: Could you elaborate?
Dr. Lonky: The guidelines ask, "Are we wasting money?" and "Are we putting more women at risk with frequent testing?" They also go on to suggest that extra screening is prone to false-positive work-ups. They state that only CIN 3 is the true cancer precursor and that it should be the sole target of screening.

OBG MANAGEMENT: Do you think screening should be more frequent than the guidelines recommend?
Dr. Lonky: No, less screening is still safe—the extra cancer burden will be marginal, and some women who are not going to develop cervical cancer will be found to have CIN and treated unnecessarily. I think the common-sense response is: If we can prevent the same number of cancers with less use of screening resources and colposcopy, that is a good thing. We can use the savings to reach out to more women and increase the screening rate overall in the unscreened and under-screened populations.

OBG MANAGEMENT: Do you think the new guidelines fully address the issue of preventing cervical cancer?
Dr. Lonky: No, I don't. What bothers me terribly is the fact that the focus is more on the resources and not on the cancer rate. We had wanted to address that rate with vaccination, but, due to low utilization of the vaccine, that strategy is unlikely to eradicate cervical cancer.

Until we create a therapy that is effective in altering the natural history of all CIN in any grade that it is detected, we will be unable to eradicate cervical cancer. Early CIN or HPV infection should be the target. Regrettably, research on an effective therapy is only beginning, and liberal, inappropriate use of destructive therapies increases the harms of finding early disease—and, therefore, the harms far exceed the benefits. The presumption that we can detect and treat CIN 3 just before it invades is woefully inadequate as a "screening" or "secondary prevention" strategy. We need to put more effort into finding an effective topical or oral therapy that will reverse the neoplastic progression of CIN 1+. If we had that, we could target early HPV infection or CIN 1 instead of CIN 3.

OBG MANAGEMENT: What do you make of the fact that about 50% of the cervical cancers that are diagnosed in the United States occur in women who have never been screened—and another 10% occur in women who have not been screened within the past 5 years?
Dr. Lonky: That means that 40% of the cancers in this country occur in women who are regularly screened—and the new guidelines do nothing to reduce that rate overall. If the argument is that society as a whole should re-invest the extra, ineffective dollars tied to screening women who are already well screened and shift those dollars to outreach to and screening of the under-screened or unscreened, I laud that, but I think that is an idealistic—not realistic—goal. Health care delivery and health- seeking behavior are tied to so many variables, such as insurance and employment, that this public health care goal cannot be guaranteed or the money easily redistributed. With these new guidelines, the overall cost of screening for cervical cancer should decrease, with little or no loss in effectiveness to prevent cervical cancer. Our next job is to find the better screening method or strategy and migrate to it, to lower the cancer rate.

purpose of undergoing a Pap test. Now that the shortest recommended screening interval for cervical cancer is 3 years, will the annual gynecologic exam go the way of the dinosaurs?

"Absolutely," says Neal M. Lonky, MD, MPH, clinical professor of obstetrics and gynecology at the University of California–Irvine and a member of the board of directors of Southern California Permanente Medical Group. Dr. Lonky is an OBG MANAGEMENT contributing editor.

"If there is no preventive health activity tied to an annual visit, I think insurers will support fewer visits, requiring less reimbursement for services, especially in

HMO and PPO models. I envision more 'virtual' care—that is, visits that do not involve an examination, for purposes such as the dispensing of birth control pills. But I am hopeful that more education about the benefit of regular visits for other preventive measures would be possible."

Dr. Kaunitz also believes the updated guidelines could have an impact on women's health-care–seeking behavior.

"Many ObGyns may be concerned that longer screening intervals may translate into fewer patient visits. As we implement these new guidelines in our practices, our challenge as women's health clinicians will include educating our patients not only that cervical cancer screening can be performed less frequently without placing them at risk, but also that well-woman visits and pelvic examinations provide health benefits above and beyond early detection of cervical cancer," he says.

Dr. Cox sees things similarly: "We do have to keep in mind that screening in the United States is opportunistic, meaning that a majority of women do not receive reminders that it is time to schedule their next cervical screen. As a result, wider screening intervals could potentially result in less frequent screening than advised by the guidelines."

"For some women who already get screened infrequently, co-testing has the advantage of providing a longer period of safety than that provided by cytology alone following a negative test," Dr. Cox continues. "My only concern is that increasing the recommended screening interval to 3 years for cytology and 5 years for co-testing will undoubtedly result in some women getting screened even less frequently. A negative HPV test result has been shown to provide at least 6 years of prediction of low risk—and possibly longer—providing at least some buffer beyond the 5-year recommended interval for women who test negative on both cytology and an HPV test."

A nod to the successes of cervical Ca screening

Cervical cancer was once the leading cause of cancer death in women in the United States. It now ranks 14th.[4]

"The profound impact that annual Pap smears have had in reducing the incidence of and mortality from cervical cancer represents a triumph of preventive medicine," says Dr. Kaunitz. "Over time, we have learned that beginning screening at age 21 and performing cytology less often than annually will not compromise outcomes."

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