The American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society of Clinical Pathologists have released revised consensus recommendations for cervical cancer screening. These new recommendations integrate molecular testing and include significant changes in screening, particularly in women from 30 to 65 years of age without complications who now may be screened every 5 years by co-testing with cervical cytology and high-risk human papillomavirus testing and women 21–29 years who may be screened with cervical cytology alone every 3 years. The revised recommendations include clarification on when to start and stop screening and management of women who have undergone hysterectomy. They also clarify the management of results of co-testing. The new recommendations achieve the same degree of protection against cervical cancer as previous recommendations. They require less screening and will be much more convenient for our patients. They are a further step away from the days of annual Pap tests, and the decreased requirements for cervical cancer screening pose an exciting opportunity for focusing on many other important health issues during the well woman visit.

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The recently revised Guidelines for the Prevention and Early Detection of Cervical Cancer from the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society of Clinical Pathologists consensus conference reflects the significant effect of new technologies and research on cervical cancer screening. It is the next step in the evolution of cervical cancer prevention and the next step in the evolution of our specialty. Women worldwide have greatly benefitted from Dr. George Papanicolaou’s and Dr. Herbert Traut’s development of cervical cytology screening, the “Pap test,” which initially was met with great skepticism by the medical societies. Since its integration into the care of women in the 1960s, the incidence of cervical cancer has plummeted to 12,710 new cases and only 4,290 estimated deaths from this disease in the United States in 2010.1 Most of these women who get cervical cancer have not undergone recommended cervical cancer screening.2,3 The test was originally performed annually, an interval that was chosen completely arbitrarily. This annual screening promoted increased health care visits for women. These annual visits improved not only rates of cervical cancer screening but also women’s health in general through screening, counseling, and management of many other problems. The linkage with an “annual examination” was an effective community health message that worked to benefit women before research had established the best frequency for cervical cancer screening.

This linkage began to change in 1976, when the Canadian Walton report suggested that cervical cytology screening every 3 years was as effective as annual screening in the general population. By 2003, the rapidly increasing understanding of the behavior of cervical dysplasia, the discovery of the causal relationship of human papillomavirus (HPV) infection and cervical cancer, and the ability to detect HPV in cervical samples confirmed that women could be well-protected from cervical cancer with screening intervals less often than every year. The American College of Obstetricians and Gynecologists (the College) first recommended lengthening the screening interval in 2003. Subsequent research and the advent...
of vaccines to immunize patients against the most common and carcinogenic high-risk types of HPV (16 and 18) led the College to again revise its screening protocols in 2009, which include new guidelines for initiation, cessation, and frequency of screening (College Practice Bulletin 109). The potential harm of perinatal morbidity in subsequent pregnancies from overtreatment of low-grade lesions added to the concern.

Pap testing does have important limitations. Interpretation of the Pap test result is subjective. Reproducibility between pathologists is modest, reported in one large study to be less than 50% for diagnoses of atypical squamous cells of undetermined significance (ASC-US) or high-grade squamous intraepithelial lesions, and only 68% for low-grade squamous intraepithelial lesions. A single Pap test has a relatively low sensitivity. A recent review of studies in developed countries cited a sensitivity of 44% to 65% for cytology at the threshold of ASC-US or worse in women aged 30 or older for a diagnosis of cervical intraepithelial neoplasia (CIN) 2 or worse. Cytology is also poor at preventing adenocarcinoma. Despite these performance flaws, the Pap test has been a successful screening modality because of cervical cancer’s long latency and the practice of repeating screening at frequent intervals. The test has a low positive predictive value, which leads to overtreatment with colposcopy in a large proportion of women whose transient cytological abnormalities would resolve spontaneously. In addition to cost and discomfort, some of these unnecessary colposcopies result in unnecessary treatments with potential subsequent morbidity like cervical insufficiency or preterm delivery.

When Papanicolaou and Traut showed the potential of the Pap test to screen for cervical cancer, they had no idea as to the causative agent of the disease. Pap tests were able to show precancerous cells now known as CIN 3 and other abnormalities, of which the malignant potential was unknown. We have known for the past 20 years that more than 99% of cases of cervical cancer are caused by high-risk types of HPV. Worldwide, 68% of cases of squamous cell carcinoma and 85% of cases of adenocarcinoma are caused by HPV types 16 and 18. Another 17.8% of cases of squamous cancer are attributable to HPV types 31, 33, 45, 52, and 58. These same seven HPV types are responsible for 82% of all cases of high-grade squamous intraepithelial lesions. Since 2003, three clinically validated DNA HPV tests have been approved by the U.S. Food and Drug Administration (FDA) for co-testing in conjunction with the Pap test. DNA HPV tests each include 13 or 14 high-risk HPV types, including the seven types noted previously. These tests have a high degree of reliability and in multiple studies have been shown to be more sensitive and have a higher negative predictive value than the Pap test alone. When used together in women older than 30 years, the sensitivity and negative predictive value of the combined co-test exceed either the Pap test or HPV test when used alone. Not all HPV tests have been validated in clinical trials and approved for clinical application by the FDA. Interpretation of positive HPV results is predicated on studies using tests similar to the ones approved by the FDA.

Co-testing has a higher sensitivity and negative predictive value that allow potential precancer to be identified sooner, and women with negative cervical cytology and HPV test results can go longer between screenings. Several European studies compared co-testing with cytology alone and found more CIN 3 or cancer at the initial test in the co-testing group. In a recent report of 5 years of experience with co-testing in a large U.S. health organization, co-testing was shown to perform better than cytology alone in diagnosing CIN 3. Equally important, patients with a negative cervical cytology result and a negative HPV result remained at extremely low risk for the full 5 years of the study. The rate of CIN 3 at 5 years after co-testing with negative results was 0.16%, which was comparable with the 0.17% rate seen with Pap testing after only 3 years. This extended high negative predictive value has been seen in other studies in the United States and Europe that compared cervical cytology with HPV testing alone and as part of co-testing.

In the presence of a negative Pap test result, a positive high-risk HPV result does not predict a risk of CIN 3 or cancer high enough to justify colposcopy. Persistence of the positive HPV result at 12 months follow-up or conversion of a previously negative Pap test result to squamous intraepithelial lesions does warrant colposcopy. High-risk HPV tests approved by the FDA for co-testing do not specify which of the 13 or 14 included types may be present. However, two other tests that specifically identify genotypes 16 and 18 have been approved by the FDA. They may be used to determine if a woman with a positive co-test result for HPV has types 16 or 18. If HPV type 16 or 18 is detected, then the risk of CIN 3 approaches 10% within a few years, a risk high enough to justify colposcopy. The new recommendations may be found at http://CAonline.AmCancerSoc.org.

The new recommendations are good news for women and their health care providers. The new
options are simpler, less frequent, and offer women outcomes that are as good as or better than current screening recommendations for both rates of invasive cancer and cancer death, while avoiding harms such as unnecessary colposcopies and potential perinatal morbidity.

The revised recommendations are: screening for all women begins at age 21 years; for women 21–29 years, cytology alone every 3 years is recommended; for women 30–65 years, co-testing every 5 years is recommended, but if HPV testing is not available, then cytology alone every 3 years may be continued to age 65 years; and most women can discontinue screening at age 65 years or after hysterectomy with removal of the cervix. Guidance is provided regarding exceptions in which screening should be continued.

With co-testing, there are two test results that are interpreted together. The new guidelines give explicit recommendations for management: ASC-US, HPV-negative results are managed the same as a normal screening result; cytology-negative and HPV-positive results are evaluated by repeat co-testing in 1 year or with immediate testing for HPV types 16 or 18, if available; and all other abnormalities are managed as per existing American Society for Colposcopy and Cervical Pathology guidelines.

The new recommendations should be simpler for clinicians to implement and, with the decreased frequency of testing, much more convenient for our patients. There are many important components of the well-woman visit and far too little time to focus on them. The decreased requirements for cervical cytology screening create a tremendous opportunity for us to be more effective in our other important counseling, screening, and management responsibilities. Screening intervals that were previously inadequate with cervical cytology screening alone will now be adequate with co-testing, which may affect cervical cancer rates in underscreened women. Simplified, less frequent screening may simplify access for currently unscreened populations.

Most of the revisions are refinements of previous recommendations. The most fundamental change is the recommendation for co-testing and the lengthened screening interval for women aged 30 to 65 years. Women need to hear the message regarding co-testing that “less is truly more.” Although patients will find the lessened discomfort and increased convenience attractive, initially they will likely be concerned about the less frequent testing. They do not need to be. With co-testing, they are getting two tests instead of one. Co-testing has many attractive test characteristics; however, the bottom line is that cervical cancer screening must reduce cervical cancer, and there is high-quality evidence that co-testing does this. Two randomized controlled trials compared co-testing with cervical cytology testing alone noted lower cancer rates at the second round of testing. One randomized controlled trial demonstrated a reduction from 0.08% to 0.02% and another demonstrated a statistically significant reduction from 0.03% to 0%.

In a decision analysis performed for the U.S. Preventive Services Task Force, the authors modeled cancer cases, deaths, and harms (as measured by colposcopy). In three separate models over a wide range of assumptions, co-testing every 5 years generally had similar or fewer cancer cases (6.23–7.39 compared with 5.98–8.97 per 1,000 women over a lifetime), cancer deaths (1.01–1.35 compared with 0.95–1.65), and colposcopies (348–907 compared with 416–1,090).

Patients may ask whether co-testing should be performed even more frequently to further reduce cancer risk. Cancer risk is already quite low at 5-year co-testing intervals. Shorter testing intervals, however, lead to the detection of many more clinically insignificant transient HPV infections, which results in many more colposcopies and potential procedures, with negligible additional reduction in cancer risk.

We can now also reassure the many women with ASC-US–negative and HPV-negative results. An ASC-US result has been incorrectly treated as a diagnosis when it actually just reflects diagnostic uncertainty. A result of ASC-US represents a mix of patients who have low-grade squamous intraepithelial lesions and others who do not, and when the cytologist is unable to differentiate, HPV testing is effective triage for this group. With a negative HPV test result, the risk of a true precancerous lesion is extremely small. In a large study, risk of CIN 3 at enrollment was 0.28%, and in a longitudinal follow-up study, the risk was 0.86% at 5 years. The risk assessment provided by the negative HPV test result indicates that ASC-US–negative HPV-negative women have a CIN 3 risk comparable to women with normal screening results, and they should be managed the same way.

The largest problem will be counseling and managing the women who have positive HPV test results but have normal cervical cytology results. In a recent study, this occurred in 3.7% of women older than 30 years. The risk of significant pathology is small in this group. The revised recommendation document summarizes 11 prospective studies with 1-year to 16-year follow-up, and noted a 12-month risk of CIN 3 of 0.8% to 4.1%. Most cervical cytology-negative HPV-positive results will reflect transient HPV infections.
without cancer risk,23 and will resolve by the time the recommended co-testing is repeated 1 year later, restricting further testing to a much smaller group of women. New molecular technologies offer an additional option for women with these results. Patients with positive test results for HPV types 16 or 18 can be referred immediately to colposcopy as opposed to waiting for repeat co-testing in 1 year. Introducing co-testing will require routine discussion with patients of the sexual transmission of HPV. This is not new, and it presents an opportunity for patient education. Raising general awareness about HPV hopefully will lead to increased use of the other effective strategy against cervical cancer, HPV vaccination.

The emblem of the College includes the proud words: “Women’s Health Care Physicians.” The Pap test and cervical cancer screening have been central to the idea of an annual gynecologic evaluation and are part of that proud tradition of leading women’s health care. This has led some health care providers to continue annual screening as part of the annual well-woman visit. We have known for some time that annual cervical cytology screening has no added benefit and does have potential harms compared with less frequent screening. Performing cervical cytology screening less frequently does not in any way lessen the importance of the annual well-woman visit. In fact, it presents an opportunity to focus on and even expand the many other essential visit components. Women’s health care has many facets: obstetric, gynecologic, wellness (including depression and violence screening), family planning, menopause management, and cancer screening and treatment, to name but a few. The specialty of obstetrics and gynecology is dedicated to enabling access to and improving the quality of care of all these areas over the patient’s entire life. These new recommendations will further improve women’s health care. The College will continue to evaluate the evolution of cervical screening as well as the life-long periodic health assessment for women and revise its recommendations to guide this continuing transformation.

The specialty of obstetrics and gynecology has many strengths. An important one is to be able to provide or coordinate the care our patients need. As obstetrician–gynecologists, we have the responsibility for many aspects of obstetric and gynecologic care, as well as immunization, smoking cessation, breast disease, and wellness issues. We now have additional time to better address these responsibilities.

Long ago a nurse told one of us, “Ob-gyns are a woman’s ongoing physician.” She was right. Although these new cervical cancer screening recommendations represent a change to traditional gynecologic practice, they also provide an additional opportunity for the obstetrician–gynecologist to continue to improve the quality of women’s health.

REFERENCES


