VIEWPOINT

Human Papillomavirus Testing for Primary Cervical Cancer Screening
Is It Time to Abandon Papanicolaou Testing?

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In the 1920s, when George Papanicolaou began to develop the screening test that now bears his name, the cause of cervical cancer was not known, and the cancer was a common cause of death among women. Since Papanicolaou testing entered clinical practice in the 1950s, however, cervical cancer incidence and mortality have markedly decreased in the United States. In 2014, there will be an estimated 12 360 new cases of cervical cancer and 4020 deaths attributable to the disease.[1]

Papanicolaou testing is the cytologic examination of cervical cells to detect abnormal cells that may harbor cancer or precancerous changes. Historically, Papanicolaou testing was conducted annually, starting in adolescence and continuing indefinitely. In general, all abnormal results were evaluated by colposcopy and diagnostic biopsy; most abnormalities were treated aggressively by means of either excision or ablation, and then annual Papanicolaou testing was resumed. This combination of screening, evaluation, and treatment of precancerous changes led to successful cancer prevention.

Over the past 20 years, however, we have learned many things about cervical cancer. For example, we now know that cervical cancer is caused by persistent infection with one of the "high-risk" types of human papillomavirus (HPV). But HPV infection is prevalent in women who are sexually active, and most of these infections resolve spontaneously and do not lead to precancerous abnormalities. Moreover, there are risks of overevaluation and treatment to prevent cervical cancer, such as pain, increased anxiety, the cost of the additional medical services, and a possible increase in the rate of preterm delivery.

In April 2014, the US Food and Drug Administration (FDA) approved 1 HPV test for use alone (that is independent of Papanicolaou testing) for primary cervical cancer screening.[2] Manufactured by Roche, the cobas HPV test was approved for use in women 25 years and older. Immediately, some in the news media were proclaiming Papanicolaou testing a thing of the past.[3] However, FDA approval merely indicates that this test is safe and effective as an alternative to existing methods for primary cervical cancer screening, that is, Papanicolaou testing or cotesting (HPV testing at the same time as Papanicolaou testing). Approval did not establish this HPV test as the preferred screening method.

The FDA first approved the cobas HPV test in 2011 for use in conjunction with or as follow-up to Papanicolaou testing for cervical cancer screening in women 30 years and older. In total, the FDA has approved 4 HPV tests for cotesting or for follow-up of an abnormal Papanicolaou test result. At present, the other 3 HPV tests are not approved for use independent of Papanicolaou testing.

What is known about primary HPV screening? Several prospective randomized clinical trials in Europe have shown the improved sensitivity of HPV testing compared with Papanicolaou testing in early detection of high-grade dysplasia when used for primary screening, with improved long-term detection of cancer, although with increased rates of colposcopy.[4] These studies, conducted in Sweden, the Netherlands, England, and Italy, collectively studied 176 464 women over a median follow-up of 6.5 years; they showed that primary HPV testing afforded 60% to 70% greater protection against invasive cervical cancer than primary cytologic examination (that is, Papanicolaou testing) especially after the first 2.5 years. In these studies, the cumulative rates of invasive cervical cancer were 8.7 per 100 000 at 5.5 years for women screened with primary HPV and 36 per 100 000 for women screened with cytologic examination alone. Furthermore, the negative predictive value of a negative HPV test result was greater 5 years after the test than the negative predictive value of a normal cytologic examination result 3 years after the test. However, this article,[4] which combined studies performed in different countries and, according to different evaluation and management strategies, reported markedly different costs for screening, depending on the strategies used in primary screening and for the follow-up of abnormal results.

The FDA approved the cobas HPV test based on a large multicenter prospective study, known as the ATHENA (Addressing the Need for Advanced HPV Diagnostics hrHPV: high-risk Human Papilloma Virus) trial, funded by Roche and conducted in the United States.[5] Although the study had not been published as of June 2014, the main results and other data are available from the FDA review.[2] The ATHENA trial compared the cobas HPV test with several well-defined approaches to cervical cancer screening (**Box**). Patients were then managed according to study algorithms. Specifically, patients in the study who had primary HPV testing and had an abnormal result were triaged to Papanicolaou testing, and if the Papanicolaou test result was abnormal, then to colposcopy. In routine clinical practice, this sequential approach would require many patients to have multiple visits for screening—the first for HPV testing, the second for Papanicolaou testing, and the third for colposcopy, if necessary. In many practices, however, this sequential approach to screening, although an essential aspect of the ATHENA trial, might not be used. For example, colposcopy might be recommended for all patients with abnormal HPV test results, regardless of the result of Papanicolaou testing.

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Box. Cervical Cancer Screening Strategies Compared in the ATHENA Trial[5] for Women Age 25 Years and Older[a]

1. Cytologic examination: Papanicolaou testing with human papillomavirus (HPV) test performed only for atypical squamous cells of underdetermined significance (ASCUS) result.

2. Cotesting: Women receive both Papanicolaou and human papillomavirus testing.

3. Hybrid: Women aged 25 to 29 years have Papanicolaou testing alone and women 30 years and older have cotesting (meant to mimic American Society for Colposcopy and Cervical Pathology, American College of Obstetricians and Gynecologists, American Cancer Society, and US Preventive Services Task Force screening guidelines from 2012).

4. Primary HPV testing, with 16 of 18 subtype analysis.

[a] After the initial screening was completed, patients were followed up based on specific study algorithms.

This method would markedly increase the number of women receiving colposcopies, an invasive and expensive procedure, without a corresponding improvement in their outcomes.

Despite the merits of the ATHENA trial, it is uncertain if this new indication will perform as well in routine practice as it did in the trial because the test has yet to be studied in routine practice. Nor has the efficacy of 3 other HPV tests been compared with the efficacy of the cobas test for primary screening. Nonetheless, practices that routinely use the other HPV tests may start to use them for primary screening, despite the lack of either FDA approval or of evidence to support this approach.

Professional societies are developing guidelines for the appropriate use of primary HPV testing. Unfortunately, the first guidelines will inevitably be based on insufficient data and may not provide the clarity that is needed for them to be clinically useful.[6] Screening for cervical cancer is already complex and expensive; the availability of screening tests, laboratory resources, such as for adjuvant testing of cytologic specimens with additional stains, and colposcopy vary markedly between practice settings. One approach to primary screening may not meet the needs of all patients and all practices.

The World Health Organization's 2013 guidelines for preventing cervical cancer include the statement that "a screening test with the highest diagnostic accuracy is not necessarily the test of choice in clinical practice."[7(p6)] The statement may seem counterintuitive—how can the most accurate diagnostic test not be the test of choice? These guidelines, however, reflect the fact that the system for screening for cervical cancer with both Papanicolaou testing and HPV testing is already working in many practices, and there is no reason to disrupt the systems that are working without adequate evidence of additional benefit from primary HPV screening. In some practices, however, such as those where access to cytologic examination is limited, primary HPV screening may allow patients to be offered screening, which had not previously been possible.

In conclusion, the approval of this new indication is an important step toward improving primary screening for cervical cancer in the United States. However, further data are needed about the actual benefits and costs and the impact on the use of colposcopy and other diagnostic tests. Until compelling evidence establishes the advantages of primary HPV screening, it is not time to abandon Papanicolaou testing.

ARTICLE INFORMATION

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