The Challenges of Incorporating HPV Testing in Clinical Practice

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Over the past few years, the use of human papillomavirus (HPV) testing in cervical cancer screening has continued to gain momentum with the issuance of 2012 guidelines by professional societies, the FDA’s approval of a high-risk HPV (hrHPV) test for use as a first-line screening test (HPV primary screening), and more recently the publication of interim clinical guidance on the use of HPV primary screening in cervical cancer screening. These decisions are based on compelling scientific evidence from studies around the world. In particular, the ATHENA trial, a study of more than 47,000 women, demonstrated that HPV primary screening has the highest sensitivity for the detection of grade III cervical intraepithelial neoplasia (CIN3), the highest grade of cervical pre-cancer, over three years, compared to Pap testing alone or a combination of Pap testing and cytology. The study also highlighted the superior negative predictive value of HPV primary screening—a negative result on the approved HPV primary screening test offers twice the assurance of a negative Pap test in predicting progression to CIN3.

From evidence to practice

It comes as no surprise, then, that HPV testing is increasingly part of the routine for many physicians. In practice, however, there remains a gap between ordering a test and using the test result to guide treatment and follow-up. For example, in the face of a low-grade lesion in the Pap test and a negative HPV result, a physician may still feel a gnawing discomfort about the low-grade lesion. Conversely, and perhaps even more significant, there may be overreliance on a negative Pap result that subsequently proves to have been false assurance, as illustrated in the following three cases.

A 38-year-old who had a normal Pap smear during her last pregnancy about three years earlier presented with stage IB2 cervical cancer. She was treated with surgery, chemotherapy and radiation. The cancer recurred within six months, and the patient died of the disease.

A 28-year-old who had a normal Pap smear a year earlier presented with stage IA1 cervical cancer, diagnosed on cone biopsy, with high-risk features necessitating lymph node dissection.

A 60-year-old who had had normal Pap smears all her life, most recently a year earlier, presented with stage IIB cervical cancer. She was treated with chemoradiation, which caused secondary side effects in her bones, GI and GU tract.
**The power of inertia**

The force of habit, and a physician’s natural instinct to make decisions based on what he or she has been taught, is part of the reason for the slow adoption of HPV testing in practice. Another important factor is the patient, and the physician’s desire to deliver quality care through an effective relationship with the patient. The introduction of HPV testing has created the need for the physician and staff to counsel the patient—explaining why the test is being ordered and what test results mean and minimizing the stigma associated with the fact that HPV is sexually transmitted. In this context, it is helpful to explain to patients that most HPV infections are common and resolve over time and that HPV infections are largely asymptomatic until an advanced stage.

Some physicians are concerned about the impact of new, longer intervals between Pap tests or the potential elimination of Pap tests altogether, fearing that patients will have one less reason for an office visit. In fact, the reduced need for Pap tests may free up the time to address other issues such as contraception, obesity intervention, sexual health and menopause, all of which present opportunities for proactively improving health and patient satisfaction.

**Cytology vs. HPV primary screening**

Aside from concerns about the clinical practice and patient satisfaction, physicians rely on scientific evidence to gauge the value of a diagnostic test. From this perspective, it is instructive to review recent clinical trial data. The ATHENA trial evaluated three different screening strategies for the detection of cervical disease by following 42,000 women age 25 and older over the course of three years. The chart shown here summarizes results for cytology (with HPV performed only for ASC-US) and HPV primary screening. In both groups of women (those over 25 years old and those over 30 years old), HPV primary screening detected significantly more CIN3+ cases at baseline and during follow-up. Also, HPV primary screening had a significantly higher negative predictive value than cytology.3

![Comparison of total cases of CIN3+ detected using cytology and HPV primary screening. In both age groups, HPV primary screening detected significantly more CIN3+ cases than cytology alone (p<0.05).](image)
The underlying principles for screening programs

In 1968 J.M.G. Wilson, the Principal Medical Officer for the UK Ministry of Health, and G. Jungner, the Chief of the Clinical Chemistry Department of Sahlgren’s Hospital in Gothenburg, Sweden, published a manuscript entitled *Principles and practice of screening for disease* on behalf of the World Health Organization. In this paper, they considered the benefits of bringing treatment to those with untreated disease while avoiding harm to those not needing treatment. To guide in decision making on potential screening programs, 10 principles were outlined, most of which are directly applicable to cervical cancer.4

One of the principles calls for a test that is accurate, reliable, sensitive and specific. In issuing the interim clinical guidance on the use of primary high-risk HPV testing in cervical cancer screening, the authors cited “an improved sensitivity of primary hrHPV screening for detecting cervical cancer precursor lesions [CIN2 and CIN3] compared to cytology alone” and stated that “[a] negative hrHPV test provides greater assurance of low CIN3+ risk than a negative cytology result.”3

Another underlying principle is the effectiveness of early treatment.4 Cervical cancer and its precursors have a high cure rate if detected and treated early. The 28-year-old woman described in the second case above underwent cone biopsy, with increased risks of preterm delivery or miscarriage and, although less likely, infertility, as well as lymph node dissection. The 60-year-old suffered secondary side effects in her bones, GI and GU tract during treatment. The 38-year-old patient died of the disease.

Leading the list of principles is the importance of the health problem. Cervical cancer represents 15% of the cases presented at my clinic, after endometrial cancer and ovarian cancer. According to the National Cancer Institute, there are more than 12,000 new cases of cervical cancer in the United States annually and more than 4,000 deaths due to the disease.5 While long-term data on patient outcomes and cost-effectiveness continue to accumulate, current evidence already makes a compelling case for HPV primary screening in cervical cancer screening.

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References


