Cytology Versus High-Risk HPV Testing for Follow-up of HPV-Positive Women Without CIN

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Abstract
Screening for cervical cancer is often considered the success story for cancer screening in the United States. However, much room for improvement still exists. For example, experts have yet to establish the best follow-up strategy for women with an abnormal Papanicolaou test and high-risk human papillomavirus (HPV) followed by a normal colposcopy or biopsy that is negative for cervical intraepithelial neoplasia. The incorporation of HPV testing has allowed the development of a more sensitive and cost-efficient strategy. This article presents a brief overview of related guidelines and current modalities, and reviews selected studies. Finally, future directions and a possible schema for clinical management of these patients are included. (JNCCN 2008;6:96–100)

Current Guidelines
Current cervical screening guidelines by the NCCN and American Society for Colposcopy and Cervical Pathology leave practitioners with 2 possible follow-up strategies once CIN has been ruled out after an LSIL or ASC-US Pap test with high-risk HPV infection. The first option involves repeating cytology at 6 and 12 months with referral to colposcopy for an ASC-US Pap test or worse. Alternatively, testing for high-risk HPV could be performed at 1 year with referral to colposcopy for positive tests. No overwhelming evidence exists for or against either strategy. Furthermore, considerable debate surrounds the appropriate screening interval for women who have HPV-positive tests.

Cervical Cytology
Although the Pap test has been heralded as one of the best cancer screening tests, it is fraught with poor sensitivity. Overall sensitivity of cervical cytology in the form of a single Pap test for CIN II or worse varies widely...
from 19% to 77% and has traditionally been quoted at approximately 50% using conventional methods. Recently, a transition has occurred to liquid-based cytology, which is touted to increase sensitivity for lesions of CIN II or worse. However, many studies supporting increased sensitivity had significant potential for bias, and a recent systematic review found little evidence supporting the putative increased sensitivity. Furthermore, a recent, well-designed, randomized evaluation using colposcopic-directed biopsy as the gold standard compared conventional versus liquid-based Pap testing and was unable to elucidate any differences. Therefore, there is room for improvement and novel cervical cancer screening strategies.

**High-Risk HPV Testing**

Experts now accept that oncogenic HPV infection almost always precedes CIN III and is a necessary condition for the presence of cervical cancer. Conversely, the absence of these high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) is largely reassuring, because women who have high-risk HPV-negative cytology have a 0.4% to 1.4% rate of CIN III or cancer. Accordingly, testing for high-risk HPV, specifically Hybrid Capture 2 (Digene Diagnostics, Gaithersburg MD), was approved by the FDA for use in conjunction with cytology in 2003. Interim guidelines concerning HPV testing in conjunction with cytologic screening were published in 2004. In an evaluation of more than 60,000 women, Cuzick et al. reported that HPV testing had considerable increased sensitivity compared with cytology for detecting CIN II or worse lesions (96.1% vs. 53.0%) but was slightly less specific (90.7% vs. 96.3%). HPV testing was found to be more uniform than cytology among different geographic populations and age groups.

Approximately 60% of women aged 18 to 21 years will be infected with HPV at some time for a mean duration of 8 months. Of those infected, 70% will clear the HPV in 1 year. Several studies have shown that a high percentage of young women will be HPV-positive within several years of becoming sexually active. As a result, HPV testing identifies many transient HPV infections and may lead to overtreatment of women with high-risk HPV-positive cytology, thus decreasing its usefulness to further triage women younger than 30 years.

Although combining cytology and HPV testing modalities has a negative predictive value approaching 100%, the linking of these tests lowers the overall sensitivity when compared with HPV testing alone and further decreases an already diminished specificity. The ASCUS-LSIL Triage Study (ALTS) trial, however, validated high-risk HPV testing as a reasonable strategy to triage high-risk HPV-positive ASC-US Pap tests to colposcopy. Conversely, reflex high-risk HPV after LSIL Pap tests was not an efficient referral strategy, because more than 80% were HPV-positive. The ALTS data showed that testing for high-risk HPV in select adult populations is useful and possibly advantageous.

**Absence of CIN**

A paucity of research is targeted at the group of women who have an ASC-US HPV-positive or LSIL Pap test but are CIN-negative. This group is clearly at lower risk than some, but is not in the lowest risk subset. Interestingly, Cox et al. report that women in the group with a normal colposcopy or normal histology were ultimately at the same risk for future high-grade lesions as those initially diagnosed with CIN I. Similarly, Guido et al. reported that the risk for subsequent CIN II or worse lesion during follow-up was essentially the same for the CIN I group and the less-than-CIN I group (10% vs. 11.3%, respectively). Furthermore, distinction between normal, HPV changes, and CIN I is not reliably histologically reproducible. Thus, reviewing studies evaluating groups with CIN I and less-than-CIN I is reasonable until more specific data exist.

**Current Data**

Guido et al. evaluated several follow-up strategies for women with low-grade or equivocal cytology who had CIN I (710 patients) or less (829 patients) at colposcopy and biopsy. Of the patients with LSIL or ASC-US HPV-positive cytology, 54% had normal colposcopy or negative biopsy. Approximately 10% of these women were diagnosed with CIN II or worse in the next 24 months. This rate was not significantly different from that for subjects with biopsy-proven CIN I.

Considered strategies included HPV viral load testing at various thresholds, cytology at various
thresholds, a combination of HPV testing and cytology, and use of the initial colposcopic impression. Initial viral load and colposcopy were found to be inadequate secondary to referral rates greater than 70% for repeat colposcopy to maintain adequate sensitivity for high-grade lesions. Individually, cytology was also found to be less than ideal, with sensitivity less than 77%. Three serial Pap tests increased sensitivity to more than 95%, but referred 70% of patients back to colposcopy. Combining HPV testing and cytology only served to increase referrals without significantly detecting more threshold lesions. With a sensitivity of 92% and referring only 55%, HPV testing at 12 months was the only single test that met current expectations of high sensitivity with limited referral to colposcopy. HPV testing at 6 months only served to refer more patients without improving sensitivity. As a result, these data suggested that the most efficient method of identifying patients with CIN II or greater after an initial diagnosis of CIN I or less is to follow-up with HPV testing only at 12 months. Alternatively, serial cytology at the ASC-US referral level could be used efficiently.

Pretorius et al. retrospectively evaluated 2490 women with abnormal cytology leading to an initial diagnosis of CIN I or less after colposcopic-directed biopsy, with 90% of women having biopsy data and 95% having endocervical curettage results. The overall follow-up rate of CIN III or cancer in this population was 1.9% (median length of follow-up 26.3 months). This cohort consisted of 2 different subgroups: those positive for high-risk HPV had a 2.3% rate of CIN III or worse, whereas those that were initially high-risk HPV-negative only had a 0.4% rate of CIN III or worse. Because the sensitivity of HPV testing for CIN III was already 97.8%, this was not significantly improved through adding cytology during follow-up. However, specificity for CIN III was significantly improved through adding cytology to HPV testing during follow-up, with an increase from 64% to 85.5%. Additionally, rates of CIN III and cancer were not associated with the initial colposcopic impression or histology. As a result, these investigators advised that HPV testing should be performed as follow-up for groups with HPV-positive cytology and that, although cytology did not add sensitivity, it was useful because most women who proceeded to develop CIN III or cancer also had abnormal cytology. The investigators also believe that the addition of follow-up cytology would safely decrease the rate of repeat colposcopy. Ultimately, the group concluded that patients with CIN I or less should be followed up with yearly cytology and HPV testing with referral to colposcopy if both HPV testing and cytology were positive, or colposcopy every 2 years if cytology remains normal but high-risk HPV persisted.

Patients that remain HPV-positive but cytology-negative presents a clinical challenge. They have a considerably lower rate of CIN II or worse disease than patients with HPV-positive cytology with an ASC-US Pap test (2.8%–4.2% vs. 5%–17%, respectively). Pretorius et al. found that the risk for CIN III in this group did not increase with increasing length of follow-up. In fact, no subject with a high-risk HPV-positive test progressed to CIN III or worse without having abnormal cytology. Because 65% of these women will clear their HPV infections within 1 year and clearly have a very low rate of severe disease, some practitioners recommend both HPV testing and cytology at 1 year with referral to colposcopy only if HPV persists or with cytology LSIL or worse. Women who have negative results for both tests can return to being tested every 3 years.

Future Directions
Approximately 5% to 8% of women older than 29 years are found to be HPV-positive. Cox et al. point out that cytology effectively triages these women into 2 groups: those that require colposcopy and those that can be followed up conservatively. Additionally, they propose 2 possible scenarios for triage: using HPV testing for routine screening and only using cytology as reflexive testing in the event of positive HPV testing. This serves as an excellent cost-saving measure, because more than 90% of women will not require cytology. Alternatively, HPV genotyping with referral to colposcopy only for the “highest risk” high-risk HPV types (16, 18, 31, 33, and 45), with all others retested again in 12 months, is a strategy that has comparable sensitivity for CIN II or worse lesions to the current guidelines, but clearly would serve to decrease the rates of follow-up visits and colposcopy. More formal trial testing is needed to support these guidelines.

Conclusions
Clearly, high-risk HPV testing, much like cervical cytology in the 1960s, will revolutionize screening for
cervical cancer. Current guidelines for CIN-negative populations allow for either cytology at 6 and 12 months or repeat high-risk HPV testing only at 12 months with referral back to colposcopy for a repeat HPV-positive test or a cytology result of ASC-US or worse.\textsuperscript{5,6} Despite these guidelines, high-risk HPV testing is inconsistently used by health care providers.\textsuperscript{23} Ongoing research in Europe and upcoming randomized trials in the United States will soon serve to increase practitioners’ confidence in HPV testing.

Ultimately, for adult patients with high-risk HPV-positive tests with less than CIN I on colposcopic-directed biopsy, some have suggested using a more conservative, cost-saving strategy. One schema that could be considered in this population is diagramed in Figure 1. This strategy suggests HPV testing only at 12 months (effectively dropping the option for cytology in 6 months) after a negative biopsy or colposcopy. A negative high-risk HPV test at 12 months warrants return to routine screening. If patients have an HPV-positive test at that time, “reflex” cytology should be sent. Patients with ASC-US or worse are referred for colposcopy. Patients with negative cytology can be followed up with repeat HPV in 12 months. If patients have a high-risk HPV-negative test at that time, they can be reverted back to routine screening. If a patient is found to be HPV-positive again, she should be referred directly to colposcopy (Figure 1).

More information may be necessary to implement such a schema, but clearly little evidence supports the continued use of cytology at 6 and 12 months, which adds additional visits and cost without additional benefit. The current recommendations are reasonable but tentative pending the support of a formal clinical trial.

References


