HPV-16, -18 Testing Outperforms Cytology

Liquid-based cytology added little to cobas HPV testing for detecting CIN 3 or worse.

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Cobas human papillomavirus testing with individual human papillomavirus types 16 and 18 detection could serve as a more sensitive and more efficient approach to cervical cancer screening than traditional liquid-based cytology methods alone, according to a subanalysis of data from the ATHENA study.

The findings of the current analysis have implications for the development of strategies – including triage to colposcopy – for managing HPV-positive women, according to Philip E. Castle, Ph.D., of the American Society for Clinical Pathology Institute, Washington, and his colleagues .

The use of HPV testing as the primary screen to rule out cervical disease, along with liquid-based cytology for triaging women to immediate colposcopy, is a rational approach.

The investigators analyzed data from 41,955 women aged 25 years and older who were part of the ATHENA (Addressing the Need for Advanced HPV Diagnostics) study, which was designed to assess the performance of HPV testing and HPV-16 and HPV-18 genotyping, compared with liquid-based cytology for cervical cancer screening. Of 40,901 women who had valid cobas HPV and liquid-based cytology test results available, 10% (4,275) tested HPV positive and 6% (2,617) had abnormal cytology; of these, 1.1 % (431) were diagnosed with cervical intraepithelial neoplasia grade 2 (CIN 2) or worse, and 0.7% (274) were diagnosed with CIN 3 or worse.

An analysis of the results of colposcopy, which was performed in 2,609 women found to have atypical squamous cells of undetermined significance (ASCUS) or worse cytology, 5,726 women with a positive HPV test by either of the first-generation HPV DNA assays used in the study (Amplicor HPV test and Linear Array HPG genotyping), and 1,041 women who were HPV negative and who had negative for intraepithelial or malignant (NILM) cervical cytology, showed that the cobas HPV test was significantly more sensitive for detecting CIN 3 or worse than was liquid-based cytology at a threshold of ASCUS or worse (92% vs. 53.3%), according to the investigators (Lancet Oncol. 2011; 12:880-90).

The addition of cytology to HPV testing increased the sensitivity for detection of CIN 3 or worse by less than 5% (from 92% to 96.7%), but increased the number of screen positives by more than 35%, Dr. Castle and his associates said.

When used as a triage test for identifying high-grade CIN (grade 3 or higher), the detection of HPV-16, HPV-18, or both alone was statistically equivalent to the detection of ASCUS or worse alone in terms of both sensitivity (59.5% and 52.8%, respectively) and positive predictive value (15.5% and 14.1%), they noted.

Sensitivity was further increased – and the positive predictive value (PPV) decreased – by use of HPV-16, HPV-18, or both as an additional or complementary triage strategy to ASCUS or worse, they said.

The authors added that "notably, testing positive for HPV-16, HPV-18, or both had a sensitivity of 53.8% … and [a] PPV of 10.2% ... for CIN 3 or worse in women aged 25 years or older who were HPV positive and had NILM cytology."

Testing and genotyping for HPV-16, HPV-18, or both – with or without liquid-based cytology – can provide potentially cost-effective and safe cervical cancer screening.

In addition, the use of a threshold of low-grade squamous intraepithelial lesion (LSIL) or worse with HPV-16, HPV-18, or both was more sensitive than detection of ASCUS or worse alone with similar PPV, and detection of high-grade squamous intraepithelial lesion (HSIL) or worse with HPV-16, HPV-18, or both had a higher sensitivity and PPV than ASCUS or worse alone.

The study findings suggest that that the use of HPV testing as the primary screening test to rule out cervical disease, along with a specific test such as liquid-based cytology to help determine which women should be sent for immediate colposcopy, is a rational approach.

The findings also support the premise that co-testing has little benefit over HPV testing alone, the investigators noted.

"However, until clinicians become comfortable with the use of HPV as a first-line test, they might initially favor co-testing, and so co-testing could have an underlying merit that is difficult to quantify," Dr. Castle and his associates wrote.

In addition, "the decision to switch from co-testing to HPV testing alone, and the intervals between screenings, will ultimately depend on clinicians' perceptions of acceptable risks," they said.

"Nevertheless, on the basis of our findings, we suggest that detection of HPV-16, HPV-18, or both combined with a raised threshold of abnormal cervical cytology (LSIL or worse) might be preferable to the existing recommendations for management of HPV-positive women," according to the investigators.

They noted that testing and genotyping for HPV-16, HPV-18, or both – with or without liquid-based cytology – can provide potentially cost-effective and safe cervical cancer screening.

"Because the HPV-16 and HPV-18 readouts for the cobas HPV test are provided concurrently with the pooled detection of other carcinogenic HPV genotypes," the use of this test to triage HPV-positive women for colposcopy could prove much more efficient than cytology, they added.

Also, a strategy of applying cytology reflexively to those who are HPV positive without HPV-16 or HPV-18 genotype, with referral to colposcopy only if they have LSIL or HSIL, or worse, would increase the sensitivity for detection of CIN 3 or worse in HPV-positive women to a level above that provided by HPV- 16 and HPV-18, or both, without sacrificing good PPV, they said. The comparative performance and cost-effectiveness of various strategies will need to be assessed in future studies to identify best practices, they noted. ■

VITALS

Major Finding: The cobas HPV test was significantly more sensitive for detecting CIN 3 or worse than was liquid-based cytology at a threshold of ASCUS or worse (92% vs. 53.3%). Adding cytology to HPV testing increased the sensitivity for detection of CIN 3 or worse by less than 5% (from 92% to 96.7%), but increased the number of screen positives by more than 35%.

Data Source: A subanalysis of the ATHENA study population to compare the screening performance of the cobas HPV test versus liquid-based cytology for cervical cancer screening.

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VIEW ON THE NEWS

Standalone HPV Testing as Primary Cervical Cancer Screening?

A cervical cancer screening strategy that allows immediate identification of all women with lesions needing treatment would be preferable to the current approach of re-screening HPV-positive women with normal cytology at 1 year, with colposcopy performed if infection is still present or if cytology has become abnormal.

"Unfortunately, all combinations of genotyping and cytology in Castle and colleagues' study had less than 80% sensitivity, leading the investigators to recommend test repetitions after 1 year," Dr. Guglielmo Ronco and his colleagues wrote in an accompanying editorial (Lancet Oncol. 2011;12:831-2).

Still, the increased sensitivity provided by the combined triage tests would allow some CIN 3 or worse lesions to be detected earlier, they noted.

Furthermore, strategies using other biomarkers to triage HPV-positive women are currently being assessed; the cross-sectional sensitivity of immunochemistry for p16INK4a overexpression for CIN 3 or worse, for example, is 91%, which suggests that short-term retesting could be avoided in those who test negative for p16INK4a. Dr. Ronco and his colleagues warned, however, that since HPV-positive women are at increased risk for developing new lesions, premature reallocation to screening intervals as long as those recommended for HPV-negative women "might not be advisable."

"Additional longitudinal data are needed to define the safest time interval before retesting in women with HPV infection who were negative for p16INK4a or any other triage test," they wrote.

They also noted that the findings of this study, though designed for developed countries, can provide useful information about triage strategies for "countries where high-quality cytology has been difficult to implement and combinations of HPV tests might eventually offer a more sustainable option."

DR. RONCO *is with the Centre of Cancer Prevention in Turin, Italy. He and his coauthors said they had no relevant financial disclosures.*