New data support HPV testing beginning at age 25

By
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Recent findings from the ATHENA (Addressing the Need for Advanced HPV Diagnostics) study of cervical cancer screening revealed surprising statistics regarding women in the 25-29 age group:

- Of all the high-grade cervical disease (CIN3 or greater) found in the study, 28% was found in women 25-29.¹
- More CIN3 or greater was found in women 25-29 than in all women 40 and older over 3 years.¹

As a clinician, I see these findings as reason for concern and for rethinking how we screen for cervical cancer, particularly in women 25-29 years of age.

The background

The causative role of HPV (Human Papillomavirus) in cervical cancer has been clearly established, with studies linking the virus to approximately 99% of cases.² While approximately 80% of women in the U.S. will have HPV at some point in their lives,³ the majority will clear it without progression to cervical disease. The progression from cervical disease to cancer tends to happen slowly, and there has been an assumption in the U.S. clinical community that younger women in particular tend to clear the disease before it advances to precancerous lesions and then to invasive cancer. The expectation has been that most high-grade cervical disease will be in women 30 and older. This belief is reflected in the current screening guidelines for cervical cancer. Most U.S. guidelines recommend co-testing with a high-risk HPV test and Pap cytology for women 30-65, but do not make the same recommendation for women 25-29. The guidelines for women in this 25-29 age group recommend cytology alone every three years as primary screening.

The data from the ATHENA study—and others—bring this expectation and the appropriateness of the guidelines for women aged 25-29 into question.

The three-year ATHENA trial enrolled more than 47,000 women and was the largest U.S. registrational study ever conducted for cervical cancer screening. It confirmed that HPV DNA testing has a much greater
negative predictive value (NPV) than Pap cytology and that genotyping for HPV 16 and HPV 18, the highest-risk types, in particular plays an important role in patient risk assessment.

As noted above, the study also provided insight into the age-related incidence of cervical disease, showing more high-grade cervical disease (CIN3 or greater) in women 25-29 than in all women 40 and older. With the study methodology carefully designed to ensure that the age representation in the population accurately reflected U.S. demographics, this finding is cause for concern about the effectiveness of our current screening methods and guidelines regarding women 25-29.

The ATHENA study is not the only source that supports this finding. Corroborating data from the National Cancer Institute’s SEER Tumor Registry show a sharp rise in the incidence of invasive cervical cancer between the ages of 25 and 34 years.7
The rationale for HPV primary screening starting at 25
The findings in these studies and others about the incidence of cervical disease in the 25-29 age group and the higher sensitivity (especially better NPV) of HPV DNA testing compared to Pap were two key factors that led to the historic FDA approval in April 2014 of a DNA-based HPV test (with HPV 16/18 genotyping) for first-line primary screening for cervical cancer in women 25 and older.

Another factor influencing the FDA decision to approve 25 as the lower end of the age range for using the HPV test for primary screening was the poor sensitivity and negative predictive value of Pap cytology, especially in the 25-29 age group. In the ATHENA study, 57.3% of women 25-29 years of age with CIN3 or greater, a stage unlikely to regress, had a negative cytology (NILM).¹

Although cytology offers high specificity, its lack of sensitivity diminishes its ability to perform well for primary screening compared to HPV testing. Pap tests miss 50% of precancer at each round of screening,³,⁸ requiring frequent repeats. HPV testing offers far superior sensitivity: typically greater than 90%.⁶,⁸,⁹,¹¹ Disease screening protocols usually enlist the most sensitive test for first-line screening and a more specific test for triage of abnormal results.

The question for clinicians becomes, if cytology is not producing reliable results, how do we screen to accurately detect those who are at risk for developing high-grade cervical disease (CIN3 and greater), particularly in the 25-29 age group? In contrast to the low NPV of cytology, the ATHENA data revealed that a woman with a negative HPV test result alone has less than half the risk of developing ≥CIN3 within 3 years than a woman with a negative cytology result alone.

Addressing the concern about overcalling disease
The FDA approval for HPV-based primary screening beginning at age 25 has raised questions about the risk of referring HPV-positive women to further testing or treatment when in fact they may not need it because
they are younger and are likely to clear the virus on their own. This is where HPV genotyping and the streamlined primary screening algorithm approved by the FDA are pivotal.

Compared to the Pap test, which can be inconclusive or interpreted differently by different pathologists, HPV testing gives clear results: positive, negative or invalid. Yet not all HPV types are equal in terms of the risk associated with the development of cervical cancer. Even among the 14 genotypes commonly identified as high-risk, two have a much higher risk of advancing to cervical disease and cancer: HPV 16 and HPV 18. These two alone are responsible for nearly 70% of cervical cancer cases. So identifying HPV genotypes in a screening test—and particularly identifying HPV 16 and HPV 18 individually—enables clinicians to stratify risk, identifying someone who may be at risk for cervical dysplasia and cervical cancer before she has the disease, and better managing those who are at risk and reassuring those who are not.

A balanced algorithm
The primary screening algorithm for the HPV test approved by the FDA establishes a different triage pathway for patients depending on their specific HPV test results. If HPV negative, they return to customary follow-up (e.g., another HPV test in three years); if positive for one of 12 high-risk HPV types (provided as a pooled result), they are reflexed to cytology; if positive for HPV 16 and/or 18, they are referred to colposcopy.

This algorithm reconciles cervical cancer screening with other established screening and management protocols by placing the most sensitive test (HPV) first, followed by the most specific test (Pap). By limiting direct referral to colposcopy to only those patients who are positive for the highest-risk genotypes, the algorithm helps prevent unnecessary referrals and over-treatment of patients.
**Changing practices and outcomes**

Change in clinical practice tends to come slowly, but it does come, especially as cervical cancer screening guidelines are updated to address new data. As a clinician, I believe that HPV testing with genotyping, with reflex to cytology, should become the preferred screening method starting at age 25, which will allow us to make a difference in the current level of high-risk cancer, particularly in the 25-29 age group.

As physicians begin to adopt more effective screening protocols for cervical cancer and introduce HPV testing at age 25, we have the opportunity to more clearly identify the risk of cervical disease, stratify and modify our patient management accordingly, and contribute significantly to reducing the overall incidence of cervical cancer, changing the lives of women as we do.

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**References**

1. cobas® HPV Test [package insert]. Indianapolis, IN: Roche Diagnostics Corp; 2014.


**Sidebar**

**FDA approves first HPV test for primary screening for cervical cancer**

In April 2014, the FDA approved the Roche cobas® HPV Test for first-line primary screening for cervical cancer in women 25 and older. The test provides individual genotyping results for HPV 16 and 18 while simultaneously reporting the 12 other high-risk HPV types as a pooled result. The cobas HPV Test is now approved for primary screening, co-testing (with Pap) for women 30 and older, and reflex testing after Pap for ASC-US results in women 21 and older. ¹