What is the prevalence of cervical cytologic abnormalities and high-risk HPV in the screened population?

The prevalence of **abnormalities was 7.1%** and the prevalence of **high-risk human papillomavirus (HPV), HPV 16, and HPV 18 was 12.6%, 2.8%, and 1.0%**, respectively, in the ATHENA prospective evaluation of more than 45,000 women. Notably, the prevalence of both cytologic abnormalities and high-risk HPV positivity decreased with increasing age; high-risk HPV was detected in 31% of women 21 to 24 years old, 7.5% of women 40 to 44 years old, and 5% of women older than 70 years, for example.

FAST TRACK

The ATHENA study was designed to evaluate the cobas HPV test, which yields a pooled result for 12 high-risk HPV types, as well as individual results for HPV 16 and HPV 18

After adjustment, the prevalence of cervical intraepithelial neoplasia (CIN) 2 or greater among women 25 to 34 years old was 2.3%; it declined to 1.5% among older women.

Wright TC Jr, Stoler MH, Behrens CM, Apple R, Derion T, Wright TL. The ATHENA human papillomavirus study: design, methods, and baseline results [published online ahead of print July 22, 2011]. Am J Obstet Gynecol.

EXPERT COMMENTARY
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The Pap test wrought a sea change in the medical profession's approach to cervical cancer screening, dramatically lowering the rate of invasive cervical cancer among women who underwent the test on a regular basis. That said, the sensitivity of a single Pap test in the detection of cervical dysplasia or cancer is less than 60%.[1]

It is well established that oncogenic HPV strains, otherwise known as high-risk HPV infection, are responsible for the development of severe preinvasive dysplasia and cervical cancer. Munoz and colleagues identified subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73 as having the greatest oncogenic potential.[2] They also noted that HPV 26, 53, and 66 are probably carcinogenic.[2]

HPV DNA diagnostic tests are available to identify 14 high-risk HPV types. Current guidelines from the American Society for Colposcopy and Cervical Pathology (ASCCP) recommend both cytology and HPV testing to determine the optimal interval between screening tests and for triage to colposcopy.[3]

HPV DNA diagnostic tests have evolved one step further and can now detect HPV 16 and HPV 18 individually; these two types of HPV account for 70% of all cervical cancer cases.[4] Research is needed to determine what combination of tests will further improve outcomes in the screened population.

Details of the ATHENA study

The study was designed to evaluate the cobas HPV test (Roche), a new polymerase chain reaction–based DNA test that yields a pooled result for 12 high-risk HPV types as well as individual results for HPV 16 and 18.

ATHENA evaluates the test in three scenarios:

- as a triage test for women who have a cytologic finding of atypical squamous cells of undetermined significance (ASC-US)
- as an adjunctive test to guide clinical management in women who have cytologic findings that are negative for intraepithelial

lesions or malignancy (NILM)
- as a potential first-line test in the screening of women 25 years and older, regardless of the cytology result.

The primary endpoint in all three scenarios was to detect CIN 2 or greater.

The baseline results of this study are outlined above. Data from a 3-year follow-up of the women in the ATHENA study will be published at a future date.

Other screening studies are under way

Now that we have identified HPV as the cause of cervical cancer, researchers can investigate the best way to detect high-grade CIN. Published studies have determined that HPV testing is more sensitive and less specific than the Pap test in the detection of CIN 3 and cancer.[5]

The HPV FOCAL trial is under way to establish the efficiency of testing for high-risk HPV DNA as primary screening and as triage in three arms. In all three arms, CIN 3 is the outcome.[1]

ATHENA adds a second tier to similar studies by genotyping for HPV 16 and 18.

Unanswered questions

There is no doubt that the Pap test will be replaced as a stand-alone screening test for cervical cancer. Existing ASCCP guidelines already recommend HPV testing in patients who have normal cytology; it remains to be determined how testing specifically for HPV 16 and 18 will be incorporated into the algorithm. The ATHENA trial, and others like it, will be the basis of future cervical cancer screening guidelines.

Among the issues that need to be resolved are:
- the **age** at which testing for HPV 16 and 18 is appropriate
- the **follow-up protocol** for women who test positive for HPV 16 and 18, as well as for those who test negative
- the **cost** of adding testing for HPV 16 and 18 to screening
- the **number of women who need to be screened** to find those who are positive for HPV 16 and 18 among women infected with high-risk HPV
- the **number of extra cases** of CIN 3+ that will be identified when women who test positive for high-risk HPV are genotyped for HPV 16 and 18
- the **number of women who will undergo unnecessary colposcopy** by this approach
- the **triage protocol** that best balances sensitivity and specificity.

As guidelines become more complex and difficult to remember, compliance will no doubt be mixed. A centralized cervical cancer screening program and database are needed to reduce confusion and improve adherence to guidelines.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The findings of the ATHENA study do not alter current cervical cancer screening guidelines—yet. Until the most effective strategy of incorporating HPV 16 and 18 genotyping into screening is determined, you should follow current ASCCP guidelines. Algorithms for different abnormal cytologic findings are available at http://www.asccp.org/Portals/9/docs/pdfs/Consensus%20Guidelines/algorithms_cyto_07.pdf

››RACHEL KUPETS, MD

FAST TRACK

Continue to follow current ASCCP guidelines for different subpopulations of women

References

1. Ogilvie GS, van Niekerk DJ, Krajden M, et al. A randomized controlled trial of human papillomavirus (HPV) testing for cervical cancer screening: trial design and preliminary results (HPV FOCAL Trial). BMC Cancer. 2010;10:111.
2. Munoz N, Bosch FX, de Sanjose S, et al; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348(6):518–527. doi: 10.1056/NEJMoa021641.
3. Wright TC Jr, Schiffman M, Solomon D, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol. 2004;103(2):304–309.
4. De Sanjose S, Quint WG, Alemany L, et al; Retrospective International Survey and HPV Time Trends Study Group. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11):1048–1056.
5. Mayrand MH, Duarte-Franco E, Rodrigues I, et al; Canadian Cervical Cancer Screening Trial Study Group. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med. 2007;357(16):1579–1588.