



Does HPV testing lead to improved diagnosis of cervical dysplasia for patients with ASC-US cytology?

Yes, according to an analysis from the New Mexico HPV Pap Registry that looked at long-term outcomes of atypical squamous cells of undetermined significance (ASC-US) cytology with and without human papillomavirus (HPV) testing. The investigators found **increased early detection rates of cervical intraepithelial neoplasia (CIN)** but an **increased risk of additional cervical biopsies and excisional procedures**.

Cuzick J, Myers O, Lee JH, et al; New Mexico HPV Pap Registry Steering Committee. Outcomes in women with cytology showing atypical squamous cells of undetermined significance with vs without human papillomavirus testing [published online ahead of print June 22, 2017]. JAMA Oncol. doi:10.1001/jamaoncol.2017.1040.

► EXPERT COMMENTARY

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The American Society for Colposcopy and Cervical Pathology (ASCCP) has recommended HPV triage for ASC-US cytology for more than 15 years. Since the ALTS trial demonstrated improved detection of CIN2+ in women with ASC-US cytology, HPV testing has become the preferred triage strategy for women with ASC-US cytology, except

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for women under age 25.¹ However, we do not know the long-term outcomes for these women. The study by Cuzick and colleagues uniquely addresses this question.

Details of the study

The retrospective review of data from the New Mexico HPV Pap Registry examined the influence of HPV testing on outcomes in 20,677 women with ASC-US cytology between 2008 and 2012. Of those women, 80.5% had an HPV test, and the authors estimated that 80.6% of those HPV tests were for triage after ASC-US cytology as opposed to co-testing (that is, cytology and HPV testing together). Of note, the majority of these Pap tests were performed prior to the 2012 ASCCP guidelines that recommend HPV co-testing for all women aged 30 to 64 years regardless of cytology. Of the HPV tests performed, 43.1% were positive. The investigators then examined rates of CIN in the interval between ASC-US cytology and biopsy-confirmed CIN, and rates of loop electrosurgical excision procedures (LEEP) and results at 5 years.

FAST TRACK

To assess long-term outcomes of women with ASC-US cytology and HPV triage, researchers examined the interval between ASC-US cytology and biopsy-confirmed CIN, LEEP rates, and results at 5 years

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The investigators found a non-statistically significant increase in overall detection of CIN3 (relative risk [RR], 1.16; 95% confidence interval [CI], 0.92–1.45) in women who had been triaged with HPV testing, and a significant increase in overall detection of CIN2 (RR, 1.27; 95% CI, 1.06–1.53) and CIN1 (RR, 1.76; 95% CI, 1.56–2.00). CIN1, CIN2, and CIN3 were detected significantly earlier in patients with HPV testing. As expected, the majority of CIN2 and CIN3 was diagnosed in women who were HPV positive.

The proportion of women undergoing either endocervical curettage or cervical biopsy was higher in those with HPV testing (32.1% vs 20.6%, $P < .001$), as were LEEP rates (4.9% vs 4.0%, $P = .03$). LEEP rates were highest in the year after a positive HPV test and were mostly attributable to CIN1 results. However, the overall ratio of LEEP to CIN3+ diagnosis was similar in women who were tested for HPV compared with those who were not. A larger proportion of patients with HPV testing had follow-up compared with those without HPV testing (84.1% vs 78.9%, $P < .001$).

The authors concluded that HPV testing in women with ASC-US cytology leads to detecting high-grade disease earlier, but that HPV positivity results in more interventions, largely due to an overdiagnosis of CIN1. They also confirmed that the majority of high-grade lesions are found in women with positive HPV tests.

Study strengths and weaknesses

This is the first comprehensive long-term look at women with ASC-US cytology and the impact of HPV testing. The New Mexico HPV Pap Registry is the only US state-based registry with comprehensive follow-up data. This study's results build on previous data that showed sensitivity is increased with the addition of HPV testing to cervical cytology,¹ and they support current ASCCP guidelines that emphasize HPV triage or co-testing for women age 25 or older.

Potential bias. While this study has the

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The data from the study by Cuzick and colleagues support the importance of continued screening for cervical cancer and its precursors with HPV testing. However, the results also show that we need to improve our strategies for stratifying patients who actually need colposcopy. The authors assert an “enormous predictive value of HPV testing,” but this comes at the expense of many unnecessary procedures. Clinicians should continue to use cytology with HPV triage in women aged 25 years and older, but the ASCCP should reconsider guidelines to improve screening specificity. The addition of other screening modalities, such as extended genotyping, methylation testing, and p16/Ki-67 staining, are considerations for ASC-US triage.

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FAST TRACK

HPV testing in women with ASC-US cytology leads to earlier detection of high-grade disease, but HPV positivity results in more interventions, largely due to overdiagnosis of CIN1

benefit of a large cohort, it is limited by biases inherent in retrospective study design. One important potential bias is the differential utilization of HPV testing or procedures by providers. The authors acknowledge preliminary analyses that show that some clinics (rural, federally qualified health centers, public health clinics) serving underserved populations may underutilize or inappropriately utilize HPV testing.

Further, the 2008–2012 study period may make the results less generalizable to current practices since the ASCCP guidelines were adjusted to include more HPV testing in women aged 25 and older in 2012.

Finally, this study examines CIN but does not specifically look at the impact of HPV testing on the ultimate outcome of interest, cervical cancer rates. 📌

Reference

1. ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol.* 2003;188(6):1383–1392.