



Journal Review



Journal Review Highlight

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Safaeian M, Solomon D, Wacholder S, et al. Risk of Precancer and Follow-up Management Strategies for Women With Human Papillomavirus-Negative Atypical Squamous Cells of Undetermined Significance. *Obstet Gynecol.* 2007;109(6):1325-1331. Level of Evidence II.

The group from the National Cancer Institute, many of whose members reported on the pivotal ALTS (ASCUS-LSIL Triage Study) in 2001 and 2003, has looked at more follow-up data from those trials. From the study cohorts, they report now on the risk of intraepithelial neoplasia (CIN 3) or worse in women who had an ASCUS HPV-negative Pap smear after 12 months using cytology or HPV testing or both. In the groups overall, only 22 of 1,539 (1.4%) women who were ASCUS HPV-negative developed CIN 3 or worse during follow-up. The ASCUS HPV-positive group had CIN 3 in 269 of 1,767 (15.2%) women. In the low-risk group (ASCUS HPV-negative), only 7 cases of CIN 3 were diagnosed between 12 and 24 months of follow-up. The authors pointed out that this lower risk limits the power to distinguish meaningful differences in sensitivity among 12-month testing strategies. Specificity of HPV testing (84%) was significantly higher than cytology alone, using ASCUS as the threshold (71%). Using both tests resulted in even lower specificity (61%) at 12 months. Because CIN 3 cases were uncommon, the positive predictive value for subsequent CIN 3 or worse was low (under 3%) for all three modalities. Conversely, the negative predictive value for all three management strategies was very high: 99.7% for HPV testing, 99.82% for cytology, and 100% for both together.

The authors conclude that because of the very low absolute risk of subsequent detection of disease in women with ASCUS HPV-negative, they might be returned to a more routine screening interval, even longer than one year, depending on circumstances such as age and prior screening history. Their data further suggest that if a one-year follow-up is chosen, HPV testing has a higher specificity as well as a lower referral rate compared with cytology using an ASCUS threshold. There were too few cases of CIN 3 to distinguish differences in sensitivity among the various testing strategies. Furthermore, combining both HPV testing and cytology at 12 months results in extremely high sensitivity of detection of CIN 3 or worse, but with unacceptably low specificity, high referral rates, and low positive predictive value. They also point out that both Hybrid Capture 2 and PCR results were compared, and several false-negative HC2 tests were found. This would explain the low, but not zero, incidence of CIN 3 in women who were ASCUS HPV-negative. This information adds to our ability to tailor our management of patients with ASCUS HPV-negative Pap smears according to physician assessment of patient history, risk, and reliability for follow-up.

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