Do some women with CIN 3 test negative for high-risk HPV?

YES In this analysis from the atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) Triage Study (ALTS), 33 of 621 women who had a diagnosis of cervical intraepithelial neoplasia (CIN) 3 at baseline also tested negative for high-risk human papillomavirus (HPV) DNA.

Castle PE, Cox JT, Jeronimo J, et al. An analysis of high-risk human papillomavirus DNA-negative cervical precancers in the ASCUS-LSIL Triage Study (ALTS). Obstet Gynecol. 2008;111:847–856.

EXPERT COMMENTARY

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FAST TRACK

In the ALTS trial, 33 of 621 women who had a diagnosis of CIN 3 tested negative for high-risk HPV DNA

When it comes to cervical cancer prevention, screening and diagnostic tests have limits to their accuracy. Cancer-prevention strategies work because we assess patients over time and because we accept a small number of false positives as necessary to minimize the loss of sensitivity; in that way, we also minimize cancer-related morbidity.[1]

Link between high-risk HPV and cancer is a given

Cervical cancer is invariably linked to high-risk HPV. Women who are not truly infected with high-risk HPV are believed to have no risk for cervical cancer.[2] Assay-based endpoints such as HPV DNA testing have good accuracy indices, whereas cytologic and histologic endpoints are subject to greater human error.

A CIN 3 lesion should never occur in a woman who is negative for high-risk HPV DNA. When the combination is found, which is rare, one of two mechanisms is involved:

- a falsely negative HPV test
- a falsely positive diagnosis of CIN 3.

When HPV testing is falsely negative, it is usually due to **1)** the cutpoints used for HPV detection or **2)** the sampling technique. A diagnosis of CIN 3 may be falsely positive when benign atypical changes or lesser-grade CIN is overinterpreted. Other explanations include rapidly progressive CIN 3 when a new high-risk HPV infection occurs after the index HPV test, and CIN 3 that will not progress to cancer because it stems from a noncarcinogenic HPV type or an HPV type not recognized by the test.[3–5]

In ALTS, falsely positive histology was probably to blame

The CIN 3 detected in women who tested negative for high-risk HPV DNA (i.e., after borderline cytology rather than because of a high-grade squamous intraepithelial lesion [HSIL]) was probably associated with falsely positive histology rather than falsely negative HPV testing.

CIN 3 in women who tested negative for high-risk HPV DNA was **more likely** to be:

- diagnosed at exit
- from a center where CIN 3 diagnoses

WHAT THIS EVIDENCE MEANS FOR PRACTICE

HPV testing has good, though not perfect, sensitivity for CIN 3. These findings certainly do not suggest that HPV testing is insufficiently accurate for clinical use.

Counsel women who have borderline cytology and who test negative for high-risk HPV to undergo continued testing according to the guidelines of the American Society for Colposcopy and Cervical Pathology.

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were not confirmed by the Pathology Quality Control Group

and **less likely** to be:

- associated with a referral Pap test classified as LSIL than as ASCUS
- associated with an enrollment Pap test classified as HSIL
- symptomatic
- associated with high-grade Cervigrams.

These women also were **likely** to test negative for HPV DNA using Linear Array.

These findings suggest that some cases of CIN 3 were based on histologic overcall.

In reviewing cases of CIN 3 in the 33 women who tested negative for high-risk HPV DNA, investigators found only 8 cases attributable to falsely-negative HPV testing, whereas 12 were related to incident HPV infection. Eight cases were caused by histologic overcall; 5 represented non–high-risk HPV that was unlikely to progress to cancer.

References

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