Best triage for ASCUS?

TO THE EDITOR:

In "Atypical squamous cells: The case for HPV testing" (March 2004), Dr. J. Thomas Cox describes the fairly infrequent finding of cervical intraepithelial neoplasia (CIN) grade 2 or 3 (high-grade dysplasia that all experts agree are targets for detection and treatment) in women with ASCUS who test negative for high- and moderate-risk subtypes of human papillomavirus (HPV) via Hybrid Capture 1 or 2 (approximately 1% or less). As an indicator of risk (positive predictive value), a positive HPV test in the Cox, Manos, and Solomon series—all cited in the article—had at worst a 15% risk and at best an 18% risk of CIN grade 2 or greater. About 50% of those who test positive are completely disease-free.

Testing positive requires repeat visits and HPV testing in 6 months and/or 1 year. This may be more costly than a single colposcopic visit, which allows for visualization and biopsy. When it comes to patient safety, the key question is: What are we missing in the HPV-negative cohort?

Our recent study emphasized several issues that may bias the measured performance of HPV testing[1]:

1. HPV testing is not advised for ASCUS favoring premalignant changes—the category now known as ASC-H—since it may upwardly bias the HPV test as a predictor of risk, as most patients in this category are positive for high-risk HPV. In our series, 100% of 32 cases of ASCUS favoring premalignant changes tested positive via Hybrid Capture 2 (HC2).
2. If the group designated as ASCUS favoring premalignant changes is removed, the HC2 test has diminished sensitivity (75%, significantly lower than in the Manos and Solomon trials), and lower positive predictive value (16.6%, similar to the other series reported by Dr. Cox). The risk of CIN 2 or higher in a patient with undefined ASCUS or ASCUS favoring a reactive process who tested negative with HC2 was at least 4 times higher (4.3%) than in the series reported in the article.

Among the 6 patients who tested HPV-negative via HC2, tissue-based polymerase chain reaction analysis of their CIN 2 or 3 biopsy specimens showed evidence of high-risk subtypes of HPV in tissue. Perhaps the same mechanism that causes a lack of correlation between cytology when compared with underlying histology (eg, ASC Pap smear but high-grade dysplasia)—possibly altered cell exfoliation—is responsible for the lack of correlation between HC2-positive and HC2-negative cytology and histologic CIN 2 or 3. We have continued to study this phenomenon as well.

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REFERENCE

1. Lonky NM, Felix JC, Naidu YM, Wolde-Tsadik G. Triage of atypical squamous cells of undetermined significance with Hybrid Capture II: colposcopy and histologic human papillomavirus correlation. *Obstet Gynecol*. 2003;101:481–489.

DR. COX REPLIES: I disagree with Dr. Lonky's assumptions regarding the relative advantages of immediate colposcopy.

The unusually poor performance of HC2 in his study was restricted to CIN 2. Sensitivity for the more important and certain diagnosis of CIN 3 was 93.3% (14/15), consistent with the world literature.[1] The poor sensitivity that Dr. Lonky reports for the 6 cases of CIN 2 is not consistent with the multicenter findings in the ALTS trial, which had almost 20 times as many cases.[2] The 4.3% risk of CIN 2 or 3 reported by Lonky et al may be elevated by unusually poor assay performance, small numbers of the important (and well detected) CIN 3 histologic endpoint, and/or excessive emphasis on a few cases of less important, missed, or misclassified

CIN 2.[3] I propose that we de-emphasize CIN 2 for estimation of cancer risk. The risk of CIN 3 in oncogenic HPV-negative women with ASCUS in ALTS was less than 2%.

Dr. Lonky argues that even this small risk underscores the advisability of immediate colposcopy in all women with ASCUS, but is colposcopy really the best assurance against risk? As an active practitioner and teacher of colposcopy, I noted with some concern in ALTS that the strategy of sending all women with ASCUS immediately to colposcopy yielded only 53.6% sensitivity for cumulative cases of CIN 3 diagnosed over 2 years in that arm of the randomized trial.[2] The HPV triage strategy referred only slightly more than half the women to immediate colposcopy and detected 72.3% of all the cumulative cases of CIN 3 in that randomized arm. In other words, immediately referring all women with ASCUS to colposcopy, even though it included at that time those now called ASC-H, may not be the safest strategy, as proposed by Dr. Lonky.

The reasons for higher colposcopic sensitivity in the HPV triage arm are debatable, but several studies show that, when the colposcopist is aware of the Pap test interpretation, the sensitivity of colposcopy increases, particularly when a higher degree of abnormality is present. HPV-positive ASC-US is of greater concern than generic ASCUS and therefore may have generated more vigilant evaluation.

I do not recommend HPV testing for the triage of ASC-H. ■

REFERENCES

1. Arbyn M, Buntinx F, Van Ranst M, et al. Virologic versus cytologic triage of women with equivocal Pap smears: a meta-analysis of the accuracy to detect high-grade intraepithelial neoplasia. *J Natl Cancer Inst*. 2004;96:280–293.
2. 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;188:1383–1392.
3. Stoler MH, Schiffman M. Toward optimal laboratory use. Interobserver reproducibility of cervical cytology and histologic interpretations. Realistic estimates from the ASCUS-LSIL Triage Study. *JAMA*. 2001;285:1500–1505.

Correction: The letter entitled "What about repair of recurrent rectocele?" from the April 2004 issue was written by Thomas Connolly, DO, of Wausau, Wis. We apologize for the error.