

## Cervical Cancer Screening: New Strategies for Finding High-Risk Women

In the United States, an estimated 50 million Papanicolaou (Pap) tests are performed each year to screen women for cervical cancer. The widespread use of this examination is largely responsible for the decrease in new cases of invasive cervical cancer and the declining number of deaths from the disease seen in recent years. However, no consensus exists about optimal screening strategies for two subgroups of women who have regular Pap tests:

- ◆ Do postmenopausal women who have had normal results on their Pap tests really benefit from annual screening examinations? Would testing at longer intervals miss high-risk lesions?
- ◆ What further evaluation is appropriate for women who receive a cervical cytologic diagnosis of atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL)? How can clinicians identify the few patients who have clinically significant disease while avoiding excessive follow-up examinations for the others who do not?

Two recent studies shed new light on such issues. Sawaya et al<sup>1</sup> evaluate the benefits of annual cervical smears in the cohort of women from the Heart and Estrogen/progestin Replacement Study (HERS). Solomon et al<sup>2</sup> compare screening strategies in the cohort from the ASCUS/LSIL Triage Study (ALTS).

### HERS COHORT

Sawaya et al<sup>1</sup> studied women from the HERS cohort who had cervical smears that were normal at baseline but abnormal at either the first or second year of follow-up. To avoid

counting more than once the women with multiple abnormal smears, the investigators “censored” women who had had an abnormal smear at year 1 from the count at year 2. Information on the follow-up for the cervical abnormalities was gathered from a questionnaire sent to clinical personnel at the study sites and from data collected during the trial. The objective was to determine the positive predictive value of cervical smears obtained within two years of a normal cytologic result.

Of the 2,561 women (mean age, 66.7 years) who had a normal cervical smear at baseline, 78 had an abnormal smear at year 1, and another 32 had an abnormal smear at year 2. Thus, the incidence of cytologic abnormalities was 110 per 4,895 person-years (or 23 per 1,000 person-years, 95% confidence interval [CI], 18 to 27 per 1,000 person-years). The most common abnormality reported was ASCUS (74 women). Atypical glandular cells of undetermined significance

**Table 1. Final diagnoses in 110 women with abnormal cervical smears**

Final diagnosis (n)	Reported cervical abnormality (n)
Normal cytology, atrophy, cervicitis, or inflammation (94)	ASCUS (66), AGCUS (20), LSIL (8)
HPV effect or CIN1 (6)	ASCUS (2), AGCUS (2), LSIL (2)
CIN2, CIN3, or vaginal intraepithelial neoplasia grade 2 or 3 (2)	ASCUS (1), HSIL (1)
Endometrial hyperplasia without atypia (1)	ASCUS (1)
Unknown (7)	ASCUS (4), AGCUS (1), LSIL (2)

HPV, human papillomavirus; CIN1, cervical intraepithelial neoplasia grade 1; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; ASCUS, atypical squamous cells of undetermined significance; AGCUS, atypical glandular cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions.

Adapted from Sawaya et al.<sup>1</sup>

(AGCUS) ranked second in frequency (23). LSIL and high-grade squamous intraepithelial lesions (HSIL) were reported less often (12 women and one woman, respectively).

A total of 231 follow-up interventions were ordered to determine the final diagnoses. Repeated cervical smears were the most common interventions undergone by women with ASCUS or AGCUS; women with HSIL or LSIL were usually evaluated with colposcopy.

**Table 2. HPV testing versus cytology for detecting CIN3+\***

Triage test threshold	Sensitivity (%)	Referral rate (%) <sup>†</sup>	Positive predictive value (%)	Negative predictive value (%)
HPV testing with HC	96.3	56.1	10.0	99.5
HSIL+ cytology	44.1	6.9	37.5	96.5
LSIL+ cytology	64.0	26.2	14.3	97.1
ASCUS+ cytology	85.3	58.6	8.5	97.9

HPV, human papillomavirus; CIN3+, cervical intraepithelial neoplasia grade 3 or worse disease; HC, Hybrid Capture™; HSIL+, high-grade squamous intraepithelial lesions or worse disease; LSIL+, low-grade squamous intraepithelial lesions or worse disease; ASCUS+, atypical squamous cells of undetermined significance or worse disease.

\* Based on the combined HPV triage and immediate colposcopy arms of the study.

† Percentage of the study population that would have been referred to colposcopy based on the use of a particular triage test threshold.

Adapted from Solomon et al.<sup>2</sup>

Other common interventions included endocervical curettage and cervical or vaginal biopsy.

Final diagnoses were determined for 103 of the women with cervical abnormalities (Table 1). The majority (94) had normal test results; one received a diagnosis of mild to moderate dysplasia. The positive predictive value for any cervical smear abnormality in the first year following a normal smear result was 0% (95% CI, 0% to 5.0%), and that in the second year following a normal smear was 0.9% (95% CI, 0% to 3.0%). Because of the high rate of false-positive results, the investigators conclude that cervical smears should not be performed in postmenopausal women within two years of normal smear results.

**ALTS COHORT**

Solomon et al<sup>2</sup> randomly assigned 3,488 women (mean age, 29 years) with ASCUS to undergo one of three screening strategies: immediate colposcopy (1,163), triage to colposcopy based on the results of testing for human papillomavirus (HPV) infection (1,161), or triage to colposcopy based on the results of repeated Pap tests (1,164). The goal was to measure the sensi-

tivity of each strategy for detecting cervical intraepithelial neoplasia grade 3 (CIN3), which carries a high risk of progression to invasive cancer. The Hybrid Capture™ test was used for HPV testing. Follow-up was scheduled at six-month intervals for two years.

Based on the results of the immediate colposcopy arm of the study, the prevalence of CIN3 among the trial population was 5.1%. (This conclusion is based on the assumption that colposcopy-directed biopsy provides virtually complete detection of disease.) A comparable prevalence of histologically confirmed CIN3 was detected in the HPV triage group, suggesting a complete capture of high-grade disease. To achieve maximal statistical power in the determinations of test sensitivities, the investigators combined both the immediate colposcopy and HPV triage arms (Table 2).

The sensitivity of HPV testing to identify women with CIN3 (or worse disease) was 96.3%, with a 56.1% colposcopy referral rate. In comparison, the sensitivity of a single repeated cytology specimen with a triage threshold of HSIL (or worse) was 44.1%,

with a referral rate of 6.9%. The sensitivity of repeated cytology at the lowest threshold (ASCUS) was 85.3%, with 58.6% of women referred.

Solomon et al<sup>2</sup> conclude that the excellent sensitivity “combined with a reasonable specificity for triage, makes HPV testing a viable option for the management of ASCUS.” In an accompanying editorial, zur Hausen<sup>3</sup> anticipates the development of tests with higher specificity and sensitivity for detecting HPV infection and progression to cervical lesions and notes that the present study “provides an excellent basis for future comparisons in randomized trials.”

**REFERENCES**

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