Physicians Turn to HPV Testing In Women With AGUS Pap Results

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VANCOUVER, CANADA — When Kaiser Permanente instituted testing for human papillomavirus in 2001, physicians were instructed not to test for the virus as a way to triage patients with Pap results showing atypical glandular cells of undetermined significance.

Clinicians "paid no attention whatsoever" to this guideline, however, resulting in data on 877 women with atypical glandular cells of undetermined significance (AGUS) smears who underwent testing for the human papillomavirus (HPV) and biopsies, Walter Kinney, M.D., said at the 22nd International Papillomavirus Conference.

DR. KINNEY

National guidelines recommend HPV testing in two situations: to help manage women with Pap smears showing atypical squamous cells of undetermined significance (ASCUS), or as cotesting with Pap smears for cervical screening in women older than 30 years.

HPV tests were positive in 33% of the women with AGUS. Of these, 33% had cervical intraepithelial neoplasia grades 2/3 or higher (CIN 2/3+). Among HPV-negative women, 3% had CIN 2/3+, said Dr. Kinney of the Permanente Medical Group, Sacramento.

Of more interest to investigators were the women whose initial colposcopies produced negative biopsy results. Their HPV status at the time of AGUS diagnosis was more predictive than biopsy results of the likelihood of developing cervical abnormalities during a 12-month follow-up, he said at the conference, sponsored by the University of California, San Francisco.

Among 95 women who were initially HPV positive but had negative biopsies, 24 (25%) developed CIN 2/3+ during follow-up. None of 260 women who were HPV negative with benign biopsies at their initial evaluation developed CIN 2/3+.

The lead investigator in this study was Barbara Fetterman, Ph.D., of the Permanente Medical Group, Oakland, Calif. In a poster presentation at the meeting, she said the "current American Society for Colposcopy and Cervical Pathology recommendations for rescreening [at 4-6 month intervals for four times] in women with atypical glandular cell cytology, and a negative initial evaluation could be replaced with a single rescreen in 12 months if a woman is also HPV negative."

Kaiser clinicians also crossed the HPV guidelines to test for HPV in 161 women with Pap results showing "atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions" (ASC-H).

HPV tests were positive in 33% of the women with AGUS. Of these, 33% had CIN 2/3+.

Results showed that HPV positivity fell significantly after age 30, from a rate of 90% in women younger than 30, to 69% of women aged 30-39 years, 45% of women aged 40-49 years, and 30% of women aged 50 and older, Dr. Fetterman reported in a separate poster.

Among 125 of the women with ASC-H who also had biopsies, 38% had CIN2/3+, including one adenocarcinoma in situ. All women with CIN2/3+ were HPV positive. As time goes on, there probably will be an HPV-negative woman with ASC-H who has CIN2-3+, Dr. Kinney acknowledged, but the correlation between a negative HPV test and low risk for CIN 2/3+ in women with ASC-H is useful.

Dr. Fetterman described how the high negative predictive value of the HPV test for CIN 2/3+ and the falling HPV positivity rate with age make it useful to triage women with ASC-H. HPV triage of women with ASC-H would send 64% of women of all ages and 48% of women aged 30 and over to colposcopy. These rates are similar to the 56% of women with ASC US sent to colposcopy in the National Cancer Institute's ALTS study (ASCUS/Low-Grade Squamous Intraepithelial Lesions Triage Study), suggesting that "HPV triage of ASC-H may be useful in clinical practice, particularly in women age 30 and over," she said. ■

HMO Learns From Coscreening Initiative

VANCOUVER, B.C. — Incorporating testing for human papillomavirus into cervical screening practices for women older than 30 years may take more effort than one would think, Walter Kinney, M.D., said at the 22nd International Papillomavirus Conference.

He described the first 123,909 HPV tests performed within the Kaiser Permanente system on women over age 30 who also had satisfactory results from cytology performed at the same time. Kaiser said its "cotesting" policy of Pap smears plus HPV tests for women over age 30 in 2002.

"We told the lab to anticipate a tidal wave of specimens. That didn't happen," said Dr. Kinney of the Permanente Medical Group, Sacramento. "You can't just buy the reagent, announce the guidelines, turn on the machine, and expect this to happen."

Kaiser officials set out to get clinicians and patients to accept HPV testing. "This was a humbling process that went on for a couple of years" but led to strong acceptance rates for doctors and patients, Dr. Kinney said at the meeting held by the University of California, San Francisco.

Between May 2003 and August 2004 85%-93% of appropriate patients underwent cotesting at Kaiser facilities, with the exception of one facility that posted a 70% cotesting rate.

This compares with results of a 2005 survey of 185 ob.gyns. randomly selected from the American Medical Association database in which only 33% said they would offer cotesting, despite recommendations by the American College of Obstetricians and Gynecologists and the American Cancer Society (Am. J. Obstet. Gynecol. 2005;192:414-21).

Kaiser gained wider acceptance of cotesting by addressing issues related to staff, patients, and clinicians. For staff, training on how and why to do HPV testing is critical. "They have to think it's something they would choose for themselves," and they need to know how to talk with patients about it, Dr. Kinney said.

Kaiser created a specimen handling policy and flow charts for cotesting, posted summary sheets, obtained new color-coded order forms and color-coded specimen bins, and redesigned its "Pap books" to track results and patient responses.

Patients should be informed about cotesting before the clinician arrives in the exam room, he said. One way to do this is to have a medical assistant give the patient written materials after taking her blood pressure. Have information sheets hand. For patients with abnormal test results, have available brochures explaining their condition.

What the clinician says to the patient about cotesting is important too. A poll of 350 Kaiser patients and 37 physicians asking why the patient did or did not have cotesting found physicians believed their words and printed materials were important. Patients, on the other hand, felt that what mattered most was whether physicians said cotesting is a good idea and that they would choose testing themselves.

Give clinicians the education and tools they need to know what to say to patients about cotesting. Steps include guidelines, sample messages or scripts, and handouts on frequently asked questions.

In the Kaiser study, only 5.3% of the first 123,909 cotests were HPV positive. Of these, 3.7% had negative Pap tests.

The rate of HPV positivity dropped by half after age 39, from 9% in 30- to 39-year-olds to 5% of 40- to 49-year-olds. HPV positivity rates decreased with age to a low of 3% in women in their 60s, then crept up a bit over time, he said.

The lead investigator in studying the HPV data was Barbara Fetterman, Ph.D., of the Permanente Medical Group, Oakland, Calif. ■

HPV Testing May Help Manage LSIL

VANCOUVER, B.C. — Low-grade squamous intraepithelial lesions were likely to regress in women older than 30 years who were not infected with types of human papillomavirus associated with a high risk for cervical cancer, a longitudinal study found.

Of 412 women with untreated low-grade squamous intraepithelial lesions (LSIL), only women who tested positive for high-risk human papillomavirus (HPV) developed cervical intraepithelial neoplasia grades 2 or 3 (CIN 2/3) in 2 years of follow-up, Christine C. Clavel, Ph.D., said at the 22nd International Papillomavirus Conference.

HPV testing is approved in the United States to help triage women with Pap results showing atypical squamous cells of undetermined significance, or as an adjunct to Pap smears for screening women older than age 30.

Using HPV testing plus Pap smears to follow HPV-negative women with LSIL could significantly lower the number of women sent to colposcopy.

The study suggests that it also might be helpful by allowing a longer interval between follow-ups in women with LSIL and a negative HPV test, said Dr. Clavel of the University of Reims (France) Hospital Center.

At baseline, 87% of the 412 women and 80% of those older than 35 years tested positive for high-risk HPV types. Colposcopy and biopsies found 21 cases of CIN 2/3 at baseline and an additional 12 cases during the 2-year follow-up, all in women who initially tested positive for high-risk HPV, she said at the conference, sponsored by the University of California, San Francisco.

Half of the high-risk HPV infections cleared over a median of 9 months in the cohort as a whole and in the subset of women older than 35 years. Cytologic lesions cleared over time in 66% of the total cohort and in 68% of women older than 35.

"There was a significant correlation observed between an initial negative high-risk HPV test, the regression of cytologic lesions, and the absence of CIN 2/3 in follow-up," Dr. Clavel said.

Women with LSIL who test negative for high-risk HPV might safely be followed 12 months later by repeat cytology and HPV testing, she said. This would include approximately 13% of all women with LSIL, 20% over age 35 with LSIL, or 24% of women over age 45 with LSIL. In women older than 45 years, misclassification of LSIL increases and leads to a decrease in detection of LSIL at colposcopy, she noted.

Using HPV testing plus Pap smears to follow HPV-negative women with LSIL could significantly decrease the number of women sent to colposcopy, compared with follow-up using cytology alone, Dr. Clavel said. ■

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