The beginning of the end of the Pap?

It seems so. Investigators reviewed extended data from a large prospectively followed cohort of women within the Kaiser Permanente Northern California cohort to quantify the relative contributions of the cytology and human papillomavirus (HPV) test components of cotesting for detecting cervical precancer and cancer to help guide whether cotesting, with its costs and potential harms, should be recommended. Although bringing an end to standard cotesting presents challenges for clinicians and laboratories alike, the researchers found that cytology had limited value.

FAST TRACK

While the addition of cytology to HPV testing can add performance, it also can add further costs and the potential for unnecessary colposcopies

Schiffman M, Kinney WK, Cheung LC, et al. Relative performance of HPV and cytology components of cotesting in cervical screening [published online ahead of print November 14, 2017]. Natl Cancer Inst. doi: 10.1093/jnci/djx225.

EXPERT COMMENTARY
Mark H. Einstein, MD, MS, is Professor and Chair, Department of Obstetrics, Gynecology, and Women's Health, Rutgers New Jersey Medical School, Newark, New Jersey.

Realistic prospective performance data are needed to quantify the additional benefit of the cytology component of cotesting on top of what is already known to be highly sensitive molecular HPV testing. While the addition of cytology to HPV testing can add performance, it also can add further costs and the potential for unnecessary colposcopies for what are merely cytomorphologic manifestations of an active HPV infection. Frequent invasive procedures such as colposcopy, which can be costly and lead to anxiety and distress in generally young women and the potential for overtreatment of likely regressive lesions, has been defined as a harm of screening by the US Preventive Services Task Force (USPSTF).

Dr. Einstein has advised, but does not receive an honorarium from any companies. In specific cases his employer has received payment for his consultation from Cynvec, Altum Pharmaceuticals, Photocure, Papivax, PDS Biotechnologies, and Natera. If travel is required for meetings with any industry, the company pays for Dr. Einstein's travel-related expenses. Also, his employers have received grant funding for research-related costs of clinical trials that Dr. Einstein has been the overall principal investigator or local principal investigator for the past 12 months from Johnson & Johnson, Pfizer, Inovio, PDS Biotechnologies, and Becton-Dickinson.

Details of the study

In a cohort from Kaiser Permanente Northern California, 1,208,710 women aged 30 years or older were screened with cotesting from 2003 to 2015. Those who cotested HPV negative and cytology negative were offered triennial screening. Positive cotest results were managed according to Kaiser protocol. Women with cytologic abnormalities were referred for colposcopy. Those with HPV positive/cytology negative results or HPV negative/cytology equivocal results underwent accelerated testing at 1 year. A total of 623 cervical cancers were identified and included in the analyses.

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Excessive cervical cancer screening, including frequent cotesting, could have minimal cancer prevention benefits while increasing the harms of screening. These data confirm guidance showing HPV testing alone is an effective cervical cancer screening strategy.

MARK H. EINSTEIN, MD, MS

Using multiple analyses, Schiffman and colleagues demonstrated the sensitivity advantage of HPV testing. They clearly showed that the cytology component to cotesting performance over many years is very limited for detecting precancers and early curable cancers. For example, prediagnostic HPV testing (76.7%) was more likely to be positive than cytology (59.1%; $P<.001$ for paired comparison); 82.6% of all prediagnostic cotests were positive by HPV and/or cytology; and only 5.9% of the cotests were positive by cytology alone (HPV negative.)

Primary HPV testing is recommended as a potential screening strategy by an interim guidance group led by the Society of Gynecologic Oncology and the American Society for Colposcopy and Cervical Pathology, and it is the primary cervical cancer screening recommendation of USPSTF draft guidelines.[1] There have been reports that reliance on primary HPV testing would encourage cervical cancer mortality; Schiffman and colleagues point out, however, that according to their study data, such reports are overstated.

Despite these data, practically speaking, shifting away from standard cotesting poses numerous challenges for clinicians and laboratories alike; however, these data clearly show the limited value of cytology and, due to the overtreatment of likely regressive cervical intraepithelial neoplasia grade 2, the possible increased risk of preterm birth and its subsequent harm as well.

Study strengths and weaknesses

The authors examined the long-term relative history of HPV testing and cytology prior to cancer diagnosis in a large, prospectively followed US cohort where hundreds of women in this cohort developed cancer. There will not be a validation study of this size and scale in the near future. Further, the authors showed that the relative value of cytology to cotesting is minimal. Multiple subsequent rounds of cotesting after negative results also can be questioned.

One weakness of the study is that the data were collected from only one health care system and therefore may not be representative of all populations. Additionally, cotesting was performed on 2 separately collected specimens, which may have reduced HPV testing performance. ●

Reference

1. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Obstet Gynecol. 2015;125(2):330–337.

FAST TRACK

HPV testing alone is an effective cervical cancer screening strategy