

CORRESPONDENCE



Human Papillomavirus DNA versus Papanicolaou Screening Tests for Cervical Cancer

TO THE EDITOR: The outcome measures appear to have been chosen post hoc by Mayrand et al. (Oct. 18 issue)¹ in their screening trial comparing human papillomavirus (HPV) testing with Papanicolaou (Pap) testing.^{1,2} The “conservative” outcome definition excludes biopsy-confirmed lesions identified at colposcopy but not verified on final excision or on biopsy immediately before ablation. Such lesions are included in the “liberal” definition, along with lesions identified by random biopsy and endocervical curettage. With the conservative definition, HPV testing is clearly superior, whereas with the liberal definition, neither strategy is clearly superior. Lesions included in the liberal definition may have no potential to progress, but it is unusual to extend this rationale to lesions seen at colposcopy. The authors suggest that these visible lesions may have been squamous metaplasia histologically misinterpreted as high-grade cervical intraepithelial neoplasia (grade 2 or higher), but this hypothesis was never confirmed by pathological re-review of the targeted biopsy specimens. We propose an alternative outcome measure: the presence of histologically verified, high-grade cervical intraepithelial neoplasia in either the colposcopically targeted biopsy specimen or the final excision specimen.

Alice Lytwyn, M.D.

Laurie Elit, M.D.

McMaster University
Hamilton, ON M9B 5A2, Canada
lytwyn@hhsc.ca

John W. Sellors, M.D.

Program for Appropriate Technology in Health
Seattle, WA 98107

1. Mayrand M-H, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med* 2007;357:1579-88.

2. Mayrand MH, Duarte-Franco E, Coultée F, et al. Random-

ized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian Cervical Cancer Screening Trial (CCCaST). *Int J Cancer* 2006;119:615-23.

TO THE EDITOR: The interpretation by Mayrand et al. of cases that were negative on HPV testing, positive on biopsy, and negative on excision warrants further discussion. The authors considered these cases to represent false positive biopsy results. First of all, the criteria for grade 2 to 3 cervical intraepithelial neoplasia on biopsy are well established, and pathologists are unlikely to overdiagnose them. Second, was HPV DNA in situ hybridization performed on these specimens? Third, were deeper sections of the excision specimens examined, to detect dysplasia not seen on initial sections? The data could also be interpreted as false negative results of HPV testing. In some cases, HPV types not tested may be present or lesions may be small (sampling error). In other

THIS WEEK'S LETTERS

- 641 Human Papillomavirus DNA versus Papanicolaou Screening Tests for Cervical Cancer
- 644 Patients' Competence to Consent to Treatment
- 645 Electroconvulsive Therapy for Depression
- 647 More on Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency in a Neonate
- 647 Melanoma Complicating Treatment with Natalizumab for Multiple Sclerosis
- 649 Malignant Melanoma with Metastatic Rhabdomyosarcomatoid Transdifferentiation

cases, the lesion may have been removed by biopsies or lost to tissue inflammatory reaction. An abnormal Pap smear or HPV test result should be followed by visualization of the lesion, confirmatory biopsies, and definitive treatment with excision or ablation. The result of HPV testing should not be used as the sole criterion for rejecting the interpretation of a biopsy finding.

Bryan T. Lin, M.D., Ph.D.

Encino Tarzana Regional Medical Center
Tarzana, CA 91356
btltarzana@hotmail.com

TO THE EDITOR: The study by Mayrand and colleagues suffers from selection bias that precludes generalization to the known screening population. Exclusion of young women and pregnant women normally screened for cervical cancer introduces a bias against Pap testing and for HPV DNA testing, negating the authors' sensitivity and specificity comparisons for general screening.

Data from the Surveillance, Epidemiology, and End Results (SEER) program¹ indicate that 15.5% of cases of cervical cancer occur in women who are 20 to 34 years old, closely matching the 15.1% reported among women who are 45 to 54 years old. Exclusion of pregnant women is equally questionable. Professional and public health organizations recommend the initiation of cervical-cancer screening no later than at the age of 21 years,²⁻⁴ and colposcopy is performed in young women with screening-test indications, irrespective of pregnancy status, albeit with some procedural modification if biopsy is warranted.

The authors are straightforward in explaining why young women were excluded from their study: HPV DNA testing for cervical-cancer screening was expected to perform poorly in young women. However, since the purpose of the study was to compare the two tests for cervical-cancer screening, exclusion of women on the basis of expected test performance seems irreparably confounding.

Allan P. Frank, M.D.

5648 Cedar Crest
Dublin, CA 94568
afrankmd@msn.com

1. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) home page. (Accessed January 17, 2008, at <http://www.seer.cancer.gov>.)
2. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin* 2002;52:342-62. (Also available at <http://caonline.amcancersoc.org/cgi/content/full/52/6/342>.)
3. U.S. Preventive Services Task Force (USPSTF). Screening for

cervical cancer: recommendations and rationale. (Accessed January 17, 2008, at <http://www.ahrq.gov/clinic/3rduspstf/cervcan/cervcanrr.htm>.)

4. American College of Obstetricians and Gynecologists concurrence of cervical cancer screening initiation. (Accessed January 17, 2008, at http://www.acog.org/from_home/publications/press_releases/nr07-31-03-1.cfm.)

TO THE EDITOR: Mayrand and colleagues present 95% confidence intervals for the sensitivities of cytologic examination and HPV testing. For the HPV test, the lower bound of the interval is 84.2%. We think that this lower bound gives an overly optimistic impression of the test's sensitivity. The 95% confidence intervals were computed with the use of normal reference distributions. Such confidence intervals may have poor coverage.¹ Suppose that Mayrand and colleagues found 1 woman instead of none with grade 2+ cervical intraepithelial neoplasia in the group of 652 women with two negative screening tests and histologic verification. Then the sensitivity of the HPV test would drop below 80%, indicating that the confidence interval may be too narrow. We think that in order to make a reliable statement about the test sensitivity, the sample of women with two negative tests and histologic verification needs to be substantially larger than 652. We understand that such data are difficult to obtain because of costs and patient discomfort. We nonetheless think that the coverage of the confidence interval should have been discussed, since this information is important for health care decision makers.

Johannes Berkhof, Ph.D.

Chris J. Meijer, M.D.

VU University Medical Center
1007MB Amsterdam, the Netherlands
h.berkhof@vumc.nl

Dr. Meijer reports receiving consulting fees from Digene. No other potential conflict of interest relevant to this letter was reported.

1. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Stat Sci* 2001;16:101-17.

TO THE EDITOR: Runowicz, in the editorial accompanying the article by Mayrand et al., wonders whether widespread HPV DNA testing would result in more colposcopies, "thereby considerably increasing the use of health care resources."¹ I believe that with proper triage algorithms, rates of detection of cervical cancer would significantly improve, and systemwide expenses would go down.

Currently, many physicians recommend an annual Pap smear for all women. Yet if we now know that more than 99% of women in whom cervical cancer ultimately develops are HPV-positive,² and if we determine the HPV status of all women, why continue to perform an annual Pap smear in HPV-negative women who are not at risk for this disease?

Robert P. Fields, M.D.

18109 Prince Philip Dr.
Olney, MD 20832

1. Runowicz CD. Molecular screening for cervical cancer — time to give up Pap tests? *N Engl J Med* 2007;357:1650-3.
2. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12-9.

THE AUTHORS REPLY: Lytwyn et al. and Lin underscore the importance of outcome definition in screening trials. Despite Lin's assertion, pathologists often overinterpret grade in cervical-biopsy specimens. The literature on cervical pathology leaves no doubt about the issue of interobserver variability.¹ Likewise, there is substantial variation in colposcopic diagnoses,² a point with which Lytwyn et al. would probably agree. Mindful that variations in disease ascertainment could differ in the test groups and thus bias our results, we adopted a standardized colposcopy protocol requiring endocervical curettage and biopsies regardless of the reason for referral (blinded), whether because of a test result or random assignment. This approach to ascertaining disease is more thorough than community colposcopy practiced throughout North America. Therefore, the disease prevalence in our trial included many low-volume, incipient lesions, which required separate consideration. Although it is unlikely because of our protocol's heightened scrutiny, pathologists may have occasionally missed dysplastic tissue in excisional or ablative specimens. However, a lesion that spontaneously resolved or was "cured" by a simple biopsy does not have the same influence on the risk of subsequent cancer as a lesion whose size and grade caused it to remain detectable in the confirmatory specimen. We reported the results of the first screening round. Once the trial's second round and follow-up have been completed,³ pathological adjudication will permit an evaluation of different outcome definitions, as proposed by Lytwyn et al. Also planned is typing of all HPV-

positive specimens, which will shed light on Lin's point.

Concerning the issue raised by Frank, exclusion of young and pregnant women does not bias the results (interval validity) but does preclude extension of the findings to these groups (external validity). We excluded pregnant women on ethical grounds because of our augmented colposcopy referral criteria. Our aim was to compare tests in women who were 30 years of age or older, a restriction that maximizes both Pap and HPV performance but does not confound the results. By analogy with breast screening, mammography does not perform as well in premenopausal women as it does in postmenopausal women, but this does not preclude its broad recommendation. Optimal cervical-cancer screening in women younger than 30 years of age is still an area in need of much research.

Berkhof and Meijer allude to the issue of precision stemming from our estimates corrected for verification bias. Although we agree that cases among subjects with negative tests are very influential with respect to the estimates, the need for ascertaining disease unconditionally on the basis of test status to correct for this bias is a tradeoff between ethical concerns and external validity. Ultimately, we compared the tests on the basis of statistical significance, which provides the evidence for health technology assessment.

Eduardo L. Franco, Dr.P.H.

Marie-Hélène Mayrand, M.D.

McGill University
Montreal, QC H2W 1S6, Canada
eduardo.franco@mcgill.ca

Sam Ratnam, Ph.D.

Newfoundland Public Health Laboratory
St. John's, NF A1B 3T2, Canada

for the Canadian Cervical Cancer Screening
Trial Study Group

1. Castle PE, Stoler MH, Solomon D, Schiffman M. The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. *Am J Clin Pathol* 2007;127:805-15.

2. Jeronimo J, Massad LS, Castle PE, Wacholder S, Schiffman M, National Institutes of Health (NIH)-American Society for Colposcopy and Cervical Pathology (ASCCP) Research Group. Interobserver agreement in the evaluation of digitized cervical images. *Obstet Gynecol* 2007;110:833-40.

3. Mayrand MH, Duarte-Franco E, Coutlée F, et al. Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian Cervical Cancer Screening Trial (CCCaST). *Int J Cancer* 2006;119:615-23.

THE EDITORIALIST REPLIES: Although we may one day use HPV testing for primary screening, we are not ready to do so at this time. Before we can accept HPV testing for primary screening, we will need to develop a rapid, simple, accurate, and affordable HPV DNA test. New algorithms, including a triage for HPV DNA tests, will need to be developed and tested. The duration of protection afforded by a negative HPV DNA test will require further long-term follow-up of studies like the one reported by Mayrand and colleagues.

As noted in my editorial, the ultimate goal of cervical screening has to be to reduce the incidence of and mortality from invasive cervical cancer worldwide with the use of a cost-effective and readily available test. The optimal approach will depend on the prevalence of disease, access to screening, and available resources. We are not there yet.

Carolyn D. Runowicz, M.D.
University of Connecticut Health Center
Farmington, CT 06030

Patients' Competence to Consent to Treatment

TO THE EDITOR: In his Clinical Practice article on the assessment of patients' competence to consent to treatment (Nov. 1 issue),¹ Appelbaum invokes the ability to reason as a central criterion for capacity. I consider this ethically troublesome. The criterion that can replace reasoning, with fewer unintended consequences, is consistency over time.² Capacity has more to do with acting characteristically than with acting reasonably.

Appelbaum concludes, for the case presented, that "psychiatric consultation should be considered" because of the possible presence of early dementia or depression, despite acknowledging that neither condition rules out capacity. Capacity is presumed for all adults, like the presumption of innocence in a criminal trial. When in doubt, capacity should be assessed by those who best know the patient. Hence, the primary care physician is usually better able to assess capacity than is a psychiatric consultant. When additional input is needed, a more patient-centered alternative to psychiatric consultation is available at most teaching hospitals — namely, an ethics consultation.

Jeffrey P. Spike, Ph.D.
Florida State University College of Medicine
Tallahassee, FL 32306-4300
jeffrey.spike@med.fsu.edu

1. Appelbaum PS. Assessment of patient's competence to consent to treatment. *N Engl J Med* 2007;357:1834-40.

2. Spike JP. Assessment of decision-making capacity. In: Aronson C, Brummel-Smith K, eds. *Reichel's care of the elderly*. 6th ed. New York: Cambridge University Press (in press).

THE AUTHOR REPLIES: As I state in the article with regard to psychiatric consultation, "treating physicians may have the advantage of greater familiarity with the patient and with available treatment options. Psychiatric consultation may be helpful in particularly complex cases or when mental illness is present." That ethics committees sometimes play helpful roles offers no reason to alter that judgment.

Although Spike would favor application of a consistency standard rather than reasoning, this is not generally accepted¹ — for good reason. Consistency with past behavior is a difficult determination,² especially for unprecedented decisions (e.g., amputation); moreover, a consistency standard risks denying patients the right to choose differently today than they have in the past.

Paul S. Appelbaum, M.D.
Columbia University College of Physicians and Surgeons
New York, NY 10032
psa21@columbia.edu

1. Berg JW, Appelbaum PS, Grisso T. Constructing competence: formulating standards of legal competence to make medical decisions. *Rutgers Law Rev* 1996;48:345-71.

2. Gutheil TG, Appelbaum PS. Substituted judgment: best interests in disguise. *Hastings Cent Rep* 1983;13(3):8-11.