

Improving the Sensitivity of Cervical Cytology: What Are the Issues?

Evan R. Myers, MD, MPH

Despite a lack of randomized trial data, the widespread consensus is that the introduction of periodic cytological examination of cells from the uterine cervix, with subsequent detection and treatment of precursor lesions and early invasive lesions, has led to a substantial decrease in morbidity and mortality from cervical cancer in the United States and other countries where screening has been introduced. However, legal action and widespread publicity about false-negative results have led investigators to seek methods that improve the sensitivity of conventional Papanicolaou (Pap) smears.

In this issue of *The American Journal of Managed Care*, Hutchinson and colleagues report the results of a cost-effectiveness analysis comparing conventional Pap smears to 3 technologies approved by the US Food and Drug Administration (FDA) for improving the sensitivity of cervical cytology.¹ The authors find that the ThinPrep Pap test (Cytoc Corporation, Boxboro, MA) is the least costly of the 3 technologies when compared to conventional Pap smears. As in every previously published model of cervical cancer, the authors show that the cost per life-year saved increases rapidly with screening frequency. At annual screening intervals, the cost is well over \$100,000 per life-year for even the preferred technology.

Given the potential legal and financial implications of false-negative Pap results and the aggressive marketing of these new technologies to physicians and patients by manufacturers, what are some of the issues that policy makers should consider as they review cost-effectiveness estimates?

Methodological Issues in Studies of Test Characteristics

Patients are ultimately managed based on the results of a colposcopic examination, usually with biopsies of cervical tissue. Studies of conventional Pap smears that used colposcopy and biopsy as the reference standard and used this reference standard on a random proportion of women with negative Pap smears have found sensitivities in the 50% to 60% range.^{2,3} The studies submitted for FDA approval, and on which the estimates of Hutchinson and colleagues are based, relied largely on consensus from an expert panel of cytopathologists. Assumptions about relative sensitivity based on cytological diagnosis can be used for modeling and estimating thresholds. However, developers of new tests cannot logically argue that the sensitivity of conventional Pap tests has been overestimated because of methodological weaknesses in study design and, at the same time, use studies with a similar lack of methodological rigor to make claims of superiority.

Clinical and Economic Significance of Increased Sensitivity

The vast majority of extra lesions detected by a test of increased sensitivity will be low grade because these will be by far the most prevalent abnormality. As many as 85% of these lesions will regress spontaneously, and few will progress to invasive cancer, so the excess costs resulting from the detection and treatment of these lesions will be substantially larger than the costs associated with preventing extra cases of cancer. Using the Duke/Agency for Healthcare Research and Quality model, we

From the Department of Obstetrics and Gynecology and The Center for Clinical Health Policy Research, Duke University Medical Center, Durham, NC.

Dr. Myers has received support from Digene Corporation (Gaithersburg, MD) for modeling studies of the use of human papillomavirus testing in cervical cancer screening and has received consultant fees from Merck & Co. (West Point, PA) for studies of a human papillomavirus vaccine.

Address correspondence to: Evan R. Myers, MD, MPH, The Center for Clinical Health Policy Research, Duke University Medical Center, DUMC 3279, Durham, NC 27710. E-mail: myers008@mc.duke.edu.

have shown that the net cost of screening with a more sensitive test will always be higher, even if the test itself adds nothing to the cost of the Pap test, unless the cost of treating these low-grade lesions is substantially reduced to levels well below the 25th percentile seen in current US practice.⁴

Quality of Life

No United States-based models incorporate validated quality-of-life measures for cervical cancer. One weakness of models that do not incorporate quality-of-life measures is that they may underestimate the benefits of cancer prevention. Early-stage cervical cancer has a high survival rate, so the “penalty” is small in terms of life expectancy in missing a high-grade preinvasive lesion that then progresses to an early-stage malignancy. However, significant differences exist in both short- and long-term morbidity between the treatment options for high-grade premalignant lesions (such as loop electrosurgical excision procedure [LEEP], cone biopsy, or simple hysterectomy) and treatment for early-stage malignant disease (radical hysterectomy, radiation, and/or chemotherapy). Using quality-adjusted life-years (QALYs) in analyses of cervical cancer screening might make improving sensitivity more efficient.

On the other hand, a large number of women undergo screening, which most women find at the least inconvenient and unpleasant, and potential psychological sequelae can result from an abnormal test result⁵ (especially one which by definition is associated with the diagnosis of a sexually transmitted disease, human papillomavirus). Relatively small decrements in quality of life associated with screening and the diagnosis of clinically insignificant lesions for a large proportion of the screened population possibly might outweigh the large gains achieved by preventing some excess cancers.

Nonmedical Costs

Similarly, nonmedical costs have not been addressed by any of the published US models. Again, relatively small costs related to time lost from work, child care, transportation, etc borne by the majority of the population may outweigh the larger costs associated with cancer.

Screening Intervals

Hutchinson and colleagues estimate cost effectiveness within screening intervals.¹ However,

because screening interval is directly related to sensitivity, as well as to specificity and efficiency (persistent lesions are more likely to progress to cancer, and undetected lesions that regress between screening intervals do not consume resources), new technologies must be compared across screening intervals. In some cases, undergoing a test with a new technology every 2 years is both more effective and less expensive than having a conventional Pap test every year. Patient compliance with screening intervals is difficult to estimate, and, if reliable data are available, using models based on these data seems reasonable. However, all models assume that patients will return for appropriate follow-up and treatment. This is clearly not the case, so the effectiveness of increased sensitivity is inevitably overestimated. Those who argue for cost effectiveness based on “real-world” patient behavior should incorporate reliable estimates of appropriate patient follow-up for abnormal results as well as for screening visits. Indeed, it seems likely that women who come least frequently for screening tests would also be least likely to have appropriate diagnosis and therapy.

Specificity

Can new technologies increase sensitivity without decreasing specificity? This is clearly an important question and one that is not often addressed. Given that the majority of women will *not* have significant cervical lesions, any decrease in specificity (and thus positive predictive value) could lead to substantially increased costs.⁴ Even if colposcopy and biopsy reveal a lesion, the ability to predict which lesions are most likely to progress to cervical cancer if untreated remains elusive. Until techniques for predicting risk of progression are perfected, technologies for increasing the sensitivity of cervical cytology are likely to lead to increased costs, primarily through detection of additional low-grade lesions.

Conclusion

New tests that improve the sensitivity of cytological screening for cervical cancer prevention may result in improved detection of cervical cancer precursor’s lesions, but they will also inevitably lead to increases in the detection and treatment of clinically significant lesions. This may have substantial impact on the costs of screening. Policy makers need to consider the complex interactions between sensitivity, specificity, the relationship between

preneoplastic lesions and the risk of cancer, and screening frequency when considering the implementation of new tests.

... REFERENCES ...

1. Hutchinson ML, Berger BM, Farber FL. Clinical and cost implications for new technologies for cervical cancer screening—the impact of test sensitivity. *Am J Manag Care* 2000;6:766-780.
2. Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. *Am J Epidemiol* 1995;141:680-689.
3. McCrory DC, Matchar DB, Bastian L, et al. *Evaluation of Cervical Cytology. Evidence Report/Technology Assessment No. 5*. Rockville, MD: Agency for Health Care Policy and Research; 1999. AHCPR publication 99-E010.
4. Myers ER, McCrory DC, Subramanian S, et al. Setting the target for a better cervical screening test: Characteristics of a cost effective test for cervical neoplasia screening. *Obstet Gynecol* (in press).
5. Paskett ED, Rimer BK. Psychosocial effects of abnormal Pap tests and mammograms: A review. *J Women's Health* 1995;4:73-82.