The Detection of Precancerous Cervical Lesions Can Be Significantly Increased

Who Cares and Who Should Know?

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This issue of the *Archives of Pathology & Laboratory Medicine* contains an impressively large (around 2 million conventional Pap smears and 166 000 ThinPrep cases), statistically risk status–adjusted comparative analysis of ThinPrep and conventional Papanicolaou test results from the high-volume regional Quest facility in Teterboro, NJ.[1] This important substantial data set adds to the already large accumulating body of evidence[2] that, as the US Food and Drug Administration (FDA) initially concluded in 1996 on the basis of far more limited evidence,[3] the ThinPrep Pap test is significantly more effective than the conventional Pap test for the detection of precancerous cervical lesions. The current report by Limaye et al[1] specifically focuses on the detection of high-grade squamous intraepithelial lesions (HSIL), now generally regarded as the clinically significant precancerous target lesion for detection in cervical screening.[4] For those who make clinical and third-party payment decisions on the basis of scientific evidence, these data add to the compelling case that the ThinPrep Pap test should be preferred over the conventional Pap test. The report does not even consider other recent studies showing the additional power and value of coupling the ThinPrep method with human papillomavirus (HPV) DNA testing from residual vial fluid.[5–7] Taken together, these reports strongly suggest that new methods are now here that at long last offer the promise of approaching sensitive and effective detection of cervical precancers and cancers at levels expected by the public. Patients would clearly like to know of these developments and have access to these screening methods.

See also p 200.

Despite the success of the Pap test in decreasing cervical cancer in the United States by more than 70%, public expectations of 100% effectiveness have never been achieved in any screened population.[8,9] In essence, the potential public ''disappointment'' in cervical cancer screening reflects the gap between the realistic capability of the Pap test to prevent cervical cancer and cervical cancer deaths and the actual expectations of the public. The previously unrealistically high expectations of the public have especially been reflected in recent years in the legal system, where lay juries actually serve as the ultimate de facto arbiters of ''the standard of practice.'' For example, a trial lawyer's newsletter from 1997 opined: ''If a woman develops cervical cancer and undergoes a hysterectomy or dies, there is almost certainly a claim for medical malpractice against some health care provider, unless the woman utterly failed to get even periodic Pap smears'' (R. Perey, written communication, March 1997). The expectation expressed is that the Pap test should be the equivalent of a cervical cancer insurance policy that will pay a substantial dollar benefit if a woman having received any Pap testing, even a woman only periodically screened, develops cervical cancer or dies of cervical cancer.

Available evidence clearly indicates that the Pap test has significant limits for effectiveness. For example, all studies show that as the frequency of Pap screening decreases from annual testing to less frequent testing, the incidence of cervical cancer and cervical deaths increase.[10–12] Nevertheless, even doubling or tripling the ''relative risk'' of developing cervical cancer in less frequently screened women may still be discounted as only a ''small'' increase in ''absolute risk'' and is consistent with an ''acceptable'' (to whom?) and ''low underlying probability of disease.''

Epidemiologic model evaluations, almost always from a group rather than an individual patient's perspective, have argued that ''efficient'' and ''cost-effective'' cervical cancer screening programs can add only up to 32.4 days in average life expectancy, compared to a gain in life expectancy of 46 days with the total elimination of cervical cancer.[13] This type of model evaluation suggests that the last 30% gain in life expectancy is not ''efficient.'' Individual patients often have a different view, one that is debated within the tort system when outcomes perhaps acceptable to epidemiologists are judged unacceptable by the individual patient.[14]

The effectiveness of the cervical cancer screening system varies significantly, depending on the sensitivity of screening and the ability to minimize false-negative results in women with undetected clinically significant precancerous or treatable

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and curable early malignant lesions.[10] Historically, relatively few studies have reliably assessed the sensitivity of Pap testing by including in them a diagnostic biopsy assessment of a significant proportion of women with negative Pap test results against which to measure the true total prevalence of significant precancerous or early malignant disease.[7,15–19] This biopsy ''gold standard,'' however, has special significance, as it reflects the level of reliable clinical ''proof'' required in general practice on which to base definitive treatment of clinically significant, potentially progressive, life-threatening disease.[20] From this unique biopsy-based perspective, available studies suggest that the conventional Pap test is only around 70% sensitive for the detection of clinically significant high-grade squamous intraepithelial lesions or cancer. This detection rate increases to 93% to 94% in the only 2 available similar studies in which liquid-based ThinPrep Pap testing has been assessed for screening sensitivity against a biopsy-based reference standard.[7,19] The large reported Quest Teterboro experience in this issue of the ARCHIVES is consistent with and adds to the evidence that the ThinPrep method significantly enhances the detection of true precancer. Efforts in the future to ignore this large body of high-quality evidence of the enhanced capability for the early detection (and presumed subsequent appropriate treatment) of a substantial portion of prevalent precancerous lesions (HSIL) risk paralleling the tragic and misguided efforts decades ago by gynecologist Herbert Green at New Zealand's Auckland National Women's Hospital to disprove (without informed consent) the necessity of promptly treating cases of cervical carcinoma in situ. Judge Julia Cartwright's discussion of underlying ethical issues of informed consent in her report from the Cervical Cancer Inquiry bears rereading, even 15 years later.[21]

The addition of HPV DNA co-testing with Hybrid Capture methodology to liquid-based ThinPrep Pap screening further increases the sensitivity of cervical cancer screening in 2 overseas studies to almost 100% of high-grade lesions and early malignancies.[7,19,22] Indeed, in the one available biopsy endpoint-based study using FDA-approved Hybrid Capture II HPV DNA testing from ThinPrep vial fluid,[7] virtually 100% of 86 clinically significant high-grade lesions and cancers were detected by co-testing with liquid-based (ThinPrep) cytology. As noted by the authors, ''The presumption that CIN2+ lesions would not occur among the 1,332 women who had tested negative on ThinPrep Pap and direct HPV test proved valid. The presumption that CINII+ lesions would not occur among the 1,478 women who had negative colposcopic evaluations, however, was not proven valid, as 16 of these women had CIN2 or worse.'' Since this 100% level of effectiveness reflects actual public expectations, it will be important to see whether third-party payers and clinical groups support payment for this form of screening, which was recently proposed as the ''DNA Pap test'' to a March 8, 2002, supplemental premarket approval FDA panel.[23] It has been recently noted that ''although some cost effectiveness analyses are widely regarded as having shaped policy around the frequency of cervical cancer screening or the age to end it, any decision must take into account the standard of care, PATIENTS EXPECTATIONS OF CARE (emphasis added), providers' training, and the jurisdiction (country or region).''[24] Clearly, what patients and the legal system may expect and what payers are willing to pay for can be significantly different.

Nowhere is the dichotomy between expectations and what can be proven achievable more relevant than in the area of endocervical glandular neoplasms of the cervix, now representing 25% to 33% of cervical cancers.[25,26] Among litigated cervical cancer cases, however, endocervical glandular lesions may represent the majority of cases, up to 80% of litigated cervical cancer cases in one published estimate.[27] Few are aware that available studies do not indicate that the conventional Pap test is effective at lowering the incidence or death rate due to endocervical adenocarcinoma in screened versus unscreened populations.[28–31] For glandular cervical cancer, data on the improved cervical cancer screening efficacy of liquid-based ThinPrep Pap testing[32,33] along with HPV testing[34] should be quite significant in addressing patients' previously unachievable expectations.

Furthermore, for patients with abnormalities such as prevalent indeterminate atypical squamous cells of undetermined significance (ASCUS), available studies now suggest that reflex HPV testing from residual vial fluid may be both more sensitive and more cost-effective in detecting clinically significant undetected high-grade cervical intraepithelial neoplasia category 2 and 3 (CIN2/3) lesions and cancers than repeat cytology.[5,6] With these and other[7] data indicating that HPV DNA testing is at least as sensitive in detecting clinically significant target lesions as immediate 100% colposcopy, recommendations for HPV testing on ASCUS cases can be said to be as effective an approach for facilitating diagnostic detection of clinically significant precancerous disease as uniform recommendations of colposcopy. Recommendations on Pap reports for specific follow-up strategies have now been shown to increase the likelihood of a clinically appropriate follow-up on a statistically significant basis.[35] Published and unpublished studies presented at the March 2002 FDA hearings make proposals such as HPV DNA testing, either as a primary co-test along with the Pap test or as a recommended adjunctive follow-up test, formidable new concepts in the ongoing efforts to achieve very high levels of cervical screening sensitivity and disease detection. Near 100% cervical screening sensitivity, long unrealistically expected by the public, may actually be achievable by combining existing new technology methods. The large study reported from New Jersey supports the growing role of the ThinPrep in US cervical cancer screening. It should also be noted that documentation of consistent, statistically significant increases of HSIL detection of a magnitude similar to those reported by Limaye et al[1] and others[2] have not yet been established in published, peer-reviewed intended use direct-to-vial studies of other FDA-approved formulations of liquid-based cytology.[36–38] Available model studies and Healthy People 2000 recruitment efforts suggest that this introduction of more sensitive screening technology at existing rates of screening may be the most realistic strategy to achieve the ambitious

Healthy People 2010 cervical cancer goals.[39]

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