

CORRESPONDENCE

Utility of Liquid-Based Cytology for Cervical Carcinoma Screening

The paper by Hutchinson et al.¹ comparing the results of conventional cervical smears with liquid-based cytology raises some important questions. The authors claim ThinPrep superiority based on the total number of patients with ASCUS or worse referred for colposcopy (1,095 vs. 579, $P < 0.001$). The screening and interpretation of the conventional smears took place in Costa Rica, whereas the ThinPrep slides were screened in Dr. Hutchinson's laboratory in Women and Infants Hospital in Providence, Rhode Island. Dr. Hutchinson is an expert in cytopathology with vast experience in the interpretation of ThinPreps, a topic on which she has published extensively. Nothing has been disclosed in this paper about the laboratory in Costa Rica, the training and experience of the cytotechnologists and cytopathologists, or the quality control measures observed there. There is evidence, however, that in some ways, the Costa Rican laboratory performed better in the assessment of cytologic abnormalities.

Based on Tables 2 and 3, it is evident that the specificity of the diagnoses on conventional smears was superior to ThinPreps. Disregarding the "equivocal" diagnoses which are poorly explained in the text, and relying only on the biopsy diagnoses of LGSIL and higher, the conventional smears led to the diagnosis of 222 lesions in 579 abnormal smears (38.3% of smears), whereas 284 such lesions were found in 1095 abnormal ThinPrep smears (25.9%). This difference is statistically significant ($P < 0.01$).

Although the conventional smears missed 28 cases of HSIL and the ThinPrep only 9, the difference pertained to 19 cases (15% of the 126 HGSIL), 10 of them diagnosed as ASCUS in ThinPreps. Thus, superior results were achieved in ThinPreps to some extent by a four-fold increase in the questionable category of ASCUS cases referred for colposcopy (650 or 7.5% vs. 159 or 1.8% in conventional smears in a cohort of 8636 women). In other words, one woman in 13 was colposcoped based on the diagnosis of ASCUS but the yield was only 27 biopsy-documented lesions (4.5%), much lower than the expected rate of intraepithelial lesions in other ASCUS studies, averaging 30% (summary in ²). These observations suggest that the ASCUS diagnosis may have been excessively used in the evaluation of the ThinPrep preparations. The disparity of results may be due as much to a major difference in diagnostic assessment of material by two laboratories with different experience and philosophies as by the techniques used. A possible explanation of this difference may be that the Costa Rican cohort of women differed significantly from the New England women who had been the subjects of prior studies by Dr. Hutchinson. It is conceivable that the rate of reactive or inflammatory changes assessed as ASCUS in ThinPreps may have been much higher

in rural Costa Rica than in New England and that the laboratory in Costa Rica was aware of it.

How many lives were saved by colposcopic examinations triggered by a four-fold increase in the non-specific diagnoses of ASCUS in ThinPreps and at what cost to the society remains to be elucidated by long-term follow-up of this cohort of women. In closing, I thank Dr. Katherine Freeman for statistical analysis.

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We thank Dr. Koss for his comments which reflect on the unique nature of this study, originally described a few years ago.¹

From the outset, the NCI sponsored a rigorously masked effort involving thousands of participants with the objective to evaluate the viability of several new cervical cancer technologies. None of the new technologies had been FDA-approved at the time the study began; now several have proven to be useful. Our publications have contributed to the literature demonstrating the possible utility of a variety of methods including the ThinPrep process,² PapNet,³ HPV DNA testing,^{4,5} and cervicography.⁶

For each technique the attempt was made to optimize the method specifically, with an expert team supporting each method. Each adapted in the earliest months of this long term prospective study with fine-tuning, due to very high rates of inflammation in the population. The adjustments in the ThinPrep process included enhancements to the processor itself, many of which were ultimately included in the FDA approved device. Importantly, however, these changes were made without knowledge of other measurements of disease (e.g. other screening techniques, colposcopy, or histology). In addition to the new techniques, we worked to optimize the conventional Pap smear as a possible

choice for cervical cancer screening programs attempting to improve on historical performance. In the Costa Rican project, an expert pathologist and cytotechnologist from the Johns Hopkins University traveled to Costa Rica to optimize the conventional Pap, working in conjunction with our collaborators on site. Our Latin American collaborators were already very experienced, and in charge of a national cytology program. Together, we improved specimen collection protocols, fixation, and staining. We worked with the collaborators on screening and interpretation using the Bethesda System. The resultant performance of the conventional Pap was exceptionally good compared to published norms.

It is true that conventional cytology was especially specific in its performance in this particular study. We did not mean to de-emphasize that fact. However, the preventive thrust of the Costa Rican research effort is to find exceptionally sensitive screening methods for the single-pass detection of high-grade lesions. The reasoning behind this approach is that very high sensitivity would mean very high negative predictive value, i.e., the reassurance that virtually no occult high-grade lesions have been missed. This reassurance could lead to safely lengthened screening intervals combined with cost effectiveness.

We concur with Dr. Koss that long-term follow-up will be the most satisfactory arbiter of which screening techniques are technically superior. Perhaps no clear superiority need be established for any one technique, as long as several techniques work well independently or in combination. Our cohort studies continue and, thus far, incident high-grade lesions have been quite rare, supporting that the overall notion of a sensitive enrollment screening has merit.

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