The merits of new alternatives to the Papanicolaou test

The claim by Eduardo Franco and colleagues that "nearly half of specimens [cervical smears] yield false-negative results" is misleading, as are several of their claims regarding the value of liquid-based and automated cytology.[1] Most studies quote a false-negative rate of approximately 1–5%.[2–4] Any laboratory with a 50% false-negative rate would be shut down.

Liquid-based preparations are not free of drawbacks, including the loss of necroinflammatory background that can be a clue to malignancy. Although it is true that "virtually all cellular material is made available to the laboratory," only a small proportion of this material is placed on the slide for screening. Conventional preparations contain many more cells. The newer methodologies are also very expensive and tightly controlled by a few companies, drawbacks that are not just "perceived." Their claims of improved false-negative rates are questioned by a recent meta-analysis, which concluded that most of the studies of liquid-based preparations and automation were "severely limited by design, inadequate reference standards, and incomplete verification of cytological diagnoses."[5] Finally, none of these technologies will reduce the number of false-negative cases that are due to suboptimal sampling or interval disease progression.

If the jury is still out on the statistical value of these methodologies, the societal value is even less certain. Traditional cervical smears have been successful because they are inexpensive, easy to perform and generally accurate. Because of slow progression to malignancy, yearly smears will detect almost all serious disease even if it is missed on one specimen. The greatest gain in cervical cancer control is in first-time screening, and the increase in cost associated with new techniques will reduce access by underserved populations. Increased costs will also follow the inevitable rise in false-positive tests.

There is a social cost in quoting questionable statistics about false-negative cervical smears, eroding both patients' and clinicians' confidence in a test that is fundamentally sound. Calculated from 8 representative studies,[3] the predictive value of a negative smear for significant disease is 99.96%. It's hard to improve on that.

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References

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[The authors respond:]

Erin Ellison has challenged our contention that the false-negative rate for conventional Papanicolaou (Pap) smears is much higher than it is generally perceived to be.[1] A recent meta-analysis conducted in primary screening settings indicated an average sensitivity of 51% (95% confidence interval 0.37–0.66).[2] This figure will be shocking to anyone, like Ellison, whose knowledge base includes studies that were plagued by verification bias (also known as diagnostic workup bias) or involved the triage of equivocal or minor abnormalities, which are situations with a high prevalence of lesions. Screening sensitivity in studies affected by verification bias is invariably overestimated[3] and should not be included in pooled overviews, a precaution that was taken in the aforementioned meta-analysis.[2] In fact, it has been recommended that cost-effectiveness models of cervical cancer screening should be revised to use more conservative estimates of Pap test sensitivity.[4]

Ellison's arguments about the draw-