Indian Journal of Pathology: Research and Practice

Liquid based cytology-should it replace conventional pap smear for cervical cancer screening?

Aditi Raina

Assistant Professor, Department of Pathology, Hind Institute of Medical Sciences, Lucknow.

Accepted 18 February 2012

Abstract

Since the introduction of cervical cancer screening, there has been a reduction in both incidence and mortality of cervical cancer. With several studies claiming a higher accuracy of liquid based cytology (LBC), this new technology virtually replaced conventional pap (CP) smear in developing countries. In this review study, most articles comparing CP with LBC were found to have flaws in study design. In two large studies that fulfill the quality criteria laid down by QUADAS, no significant difference between the two methods was found.Also, CP may have a lower specimen adequacy only if clinicians ignore basic rules of sampling, like removing mucus and cellular debris from the cervical surface and using an adequate collection device. For routine cervical cancer screening purposes, putting emphasis on regular cervical cancer screening by CP seems to be a more reasonable option than substituting CP by the LBC technique. This study concludes that there is no conclusive evidence regarding the better accuracy of LBC. More randomised controlled studies are needed.

Keywords: Liquid; Cytology; Cervical; Review.

Introduction

Since the introduction of cervical cancer screening, studies in the western countries reported a reduction in both incidence and mortality of cervical cancer[1].Conventional Papanicolaou (CP) smear method is still commonly used for cervical cancer screening in India, whereas liquid-based cytology (LBC) has become a global phenomenon. CP is labor intensive, imperfectly sensitive and has inherent problems like obscuration by blood or inflammation, poor fixation, and inhomogeneous distribution of cells. This has lead to an interest in technologies like liquid based cytology (LBC) which claim to have a better specimen collection, higher accuracy and can support HPV co-testing[2].

This review study was done to assess whether the accuracy of this expensive technology is indeed better than conventional pap screening.

Comparing the accuracy of two methods of cervical screening is not simple. The prevalence of many abnormalities is so low that measurement of test performance requires the assessment of huge numbers of screening cases. Many studies do not use histology as the reference standard. Of the studies that do, many do not provide adequate data regarding

Corresponding Author:

Dr. Aditi Raina, Assistant Professor, Department of Pathology, Hind Institute of Medical Sciences, Lucknow.

E-mail: aditiraina@rediffmail.com.

the proportion of women verified by histology. The vast majority of studies do not apply LBC and CP to the same sample of women. Thus they do not directly compare results in individual patients.

In studies which do apply the two methods to the same sample of women, most use a split sample method in which women underwent a conventional smear test and the remaining material was used to prepare the LBC slide. The reason for higher detection rates by LBC in such studies may be that CPs that were made first contained mucus and debris that obscured the cytology.

The methods of assessing the quality of a study can be deduced from the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool[3]. On the basis of these criteria, a randomised controlled trial in which women are randomly assigned to either CP or LBC group and all positive slides are verified by a masked reference standard may be considered a good-quality study for comparing the two methods.

Of the 51 articles reviewed in the study, the majority had flaws in study design with no reporting of the proportion of cases that received an initial positive diagnosis that were histologically verified. Details regarding histological verification could be obtained in only eighteen studies. Of these, there were only six studies[4-9] in which the proportion of verified cases was more than 50%. Only two of these were randomised controlled trials and involved a large number of women. Neither study found a statistically significant difference between the accuracy of the two methods.

This review study concludes that there is no conclusive evidence regarding the better accuracy of LBC. More randomised controlled studies are needed.

Methods

Studies comparing CP with LBC, published between 1991 and 2011, were retrieved through PubMed/EmBase searching and completed by consultation of other sources. Only studies comparing LBC with CP by Thinprep, Surepathor theAutocyte system, the most commonly used LBC systemswere included.

Analysis

The methods of assessing the quality of a study can be deduced from the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool[3]. On the basis of these criteria, a good-quality study for comparing two cervical cancer screening methods should be a randomised controlled trial and all positive slides should be verified by a masked reference standard.Because of a low prevalence of HSIL, only studies involving a large number of women would be statistically meaningful.

In contrast with previous studies in literaturethat attribute an improved sensitivity of LBC to fewer inadequate smears and an improved sample quality, JH Obwegeser[10]et al observed that LBC improves specimen adequacy only if clinicians ignore basic rules of sampling. They demonstrated that removing mucus and cellular debris from the cervical surface with a cellulose swab before sampling cells results in the similar specimen adequacy asLBC and is far more economical than LBC. They also concluded that LBC, forces the physician to use an adequate collection device. With CP clinicians may use a cotton swab or Ayres spatula with inadequate sampling of the endocervical canal.

In this study, fifty one studies were reviewed. Out of these there were only eighteenstudies where details regarding histological verification could be found. Of these eighteen studies, the proportion of verified cases was more than 50% in only six[4-9] studies. A low proportion of verified cases is a work-up bias and if the unverified positive and negative tests are considered as true positives and negatives, this would artificially

inflate sensitivity in favour of the test with the higher rate of false positives.

Here two studies that fulfilled many of the criteria described in the QUADAS are discussed detail. Both the studies were randomised controlled trials meeting the criteria of masking and involving a large number of women.

AG Siebers et al[8] conducted a large scale (n=89,784), prospective RCT to compare LBC with conventional Pap testing in detecting histologically confirmed CIN in terms of test positivity rates, histological detection rates, and positive predictive values (PPVs). The trial involved women aged 30 to 60 years participating in the Dutch cervical screening program between April 2004 and July 1, 2006. Patients were followed up for 18 months through January 31, 2008.

A cluster randomization was chosen for practical reasons and to prevent contamination by preference of patient or physician (selection bias).

To prevent selective assessment bias, study personnel— gynecologists, pathologists, cytotechnologists, and others—involved in the follow-up and review of histology and cytology were blinded to the cytology screening system used.

This study indicates that liquid-based cytology does not perform better than conventional Pap tests in terms of relative sensitivity and PPV for detection of cervical cancer precursors.

In another, large-scale study (n=45 174), Ronco et al[9] found no statistically significant difference for detection of CIN grade 2 between liquid-based cytology and conventional Pap test. Similar to Siebers study, they reported a significant decrease in unsatisfactory rates too. Their results differed from the study by Siebers et al, in that they reported a reduced positive predictive value (PPV) for liquid based cytology. This was the result of an increased frequency of minor cytological abnormalities with liquid-based cytology without an increase in high grade CIN on histology.

Results and Conclusion

It is estimated that two-third of false negatives in cervical cancer screening are caused by sampling error and the rest by detection error. Sampling error occurs when abnormal cells are not transferred to the slide. Detection error is when abnormal cells are missed or misinterpreted[11].

As far as reducing the sampling error, JHObwegeser et al[10] observed that CP has a lower specimen adequacy only if clinicians ignore basic rules of sampling. They found that removing mucus and cellular debris from the cervical surface with a cellulose swab before sampling cells results in similar specimen adequacy as LBC and is much less expensive than LBC. LBC forces the physician to use an adequate collection device. With CV clinicians may use a cotton swab or Ayres spatula with inadequate sampling of the endocervical canal.

To reduce detection error, the Clinical lab improvement amendments of 1988 advocate , rescreening of 10% of negative reported random slides.

Most deaths due to cervical cancer occur in women who have never had a Pap test. Because cervical cancer is generally a slow growing disease, abnormalities missed in one screening should be detected on serial testing at 3-5 yrs[12,13].

LBC is an expensive technology and seems to offers no significant advantage in terms of accuracy. The advantageof concurrent testing for HPV testing if required does not seem to outweigh the high costs incurred .

For routine cervical cancer screening purposes, putting emphasis on regular cervical cancer screening by CP seems to be a more reasonable option than substituting CP by the LBC technique.

This study concludes that there is no conclusive evidence regarding the better accuracy of LBC. More randomised controlled studies are needed.

References

1. International Agency for Research on Cancer. Cervix Cancer Screening.IARC Handbook of Cancer Prevention. Lyon, France. *IARC Pr* 2005; 10.
2. Arbyn M, Antilla A, Jordan J, Ronco G, Schenck U, Segnan N et al. *European Guidelines for Quality Assurance in Cervical Cancer Screening*. 2nd ed. Luxembourg: Office for Official Publications of the European Communities, 2008.
3. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003; 3: 25. [PMID: 14606960]
4. Bai H, Sung CJ, Steinhoff MM. ThinPrep Pap test promotes detection of glandular lesions of the endocervix. *DiagnCytopathol.* 2000; 23:19–22. [PubMed]
5. Carpenter AB, Davey DD. ThinPrep Pap test: performance and biopsy follow-up in a university hospital. *Cancer* 1999; 87: 105–112. [PubMed]
6. Guidos BJ, Selvaggi SM. Detection of endometrial adenocarcinoma with the ThinPrep Pap test. *DiagnCytopathol* 2000; 23: 260–265. [PubMed]
7. Schorge JO, HosseinSaboorian M, Hynan L, Ashfaq R. ThinPrep detection of cervical and endometrial adenocarcinoma: a retrospective cohort study. *Cancer* 2002; 96: 338–343. [PubMed]
8. Siebers AG, Klinkhamer PJ, Grefte JM, Massuger LF, Vedder JE, Beijers-Broos A, et al. Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: a randomized controlled trial. *JAMA* 2009; 302: 1757-64. [PMID: 19861667]
9. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol* 2010; 11: 249-57.
10. Obwegeser JH, Brack S. Does Liquid-Based Technology Really Improve Detection of Cervical Neoplasia? *Acta Cytologica* 2001; 45: 709-714.
11. Nanda K, Douglas C, McCrory, Myers ER, Bastian LA, Hasselblad V, Hickey JD, Matchar DB. Accuracy of the PapanicolaouTest in Screening for and Follow-up of Cervical Cytologic Abnormalities: A Systemic Review. *Ann Intern Med* 2000; 132: 810-819.
12. Eddy DM. Screening for cervical cancer. *Ann intern Med* 1990; 113: 214-26.
13. Duke University. *Evaluation of Cervical Cytology*. Evidence Report/Technology Assessment No.5. Prepared by Duke University Rockville MD; Agency for Health Care Policy and Research, 1999.