Is it now time to evaluate the true accuracy of cervical cytology screening? A review of the literature

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Summary

The incidence of and mortality from cervical invasive carcinoma have decreased over the last 30 years in the developed world, a fact which has been attributed mainly to the implementation of cervical cytology screening programmes (Papanicolaou test). The accuracy of this screening has been questioned because of false negative reports, thus other technologies have been proposed. There are only 12 studies evaluating cytology screening in low prevalence populations. In these studies the specificity appears to be high (85-100%) but the sensitivity estimates are variable and generally much lower (22-99%). Sensitivity is increased if lower thresholds of disease are used. Sampling or laboratory errors are important causes of false negative reports. Cytological cervical screening does not demonstrate the characteristics of an optimal screening test since it is relatively insensitive to the presence of disease although highly specific. The true screening accuracy of cytology needs to be assessed so that we can introduce strategies to improve smear taking and interpretation.

Key words: Cytology; Pap test; Screening; Cervical cancer.

Cervical screening has been proven to be effective in decreasing the incidence of invasive disease where comprehensive programmes exist. The incidence of invasive cervical cancer in the UK has fallen markedly over the past decade, the rate in 1995 being 35% lower than that in 1990, with decreases being observed in all age groups [1]. It is estimated that the NHS Cervical Screening Programme in the UK saves around 1,300 lives a year, and prevents the disease from taking hold in another 3,900 cases. Between 1992 and 1997, deaths from cervical cancer fell by 25%. Most deaths occur in women who have never had a cervical smear, but some occur in women who have had recent negative test results.

Cervical screening can prevent 80 to 90% of cancers in women who attend for regular smear tests, but it is not 100% accurate. A recent retrospective study carried out in Leicester on women who went on to develop cervical cancer showed that in a third of these cases smear tests produced inaccurate results. The study reviewed the cases of 403 women diagnosed with cervical cancer between 1993 and 2000 at Leicester Royal Infirmary. This study found that 324 of the women had undergone at least one smear test prior to their diagnosis. Of those, discrepancies were found in the smear tests of 136 women. In 97 of the 136 (71%) women the discrepancy was classified as a false negative and the remaining 39 cases were classified as undergrades. For the 97 false negative reports, the revised assessment was moderate dyskaryosis for 15 women, severe dyskaryosis for 43 women, abnormal endocervical changes for 15 women and other less serious abnormalities for the remaining 24 women. The remaining 188 women's smears on review did not show any abnormality. These women genuinely did not have disease or had false negative smears because of other factors, which might contribute to false negative cytology results, such as sampling error. It is estimated that sampling error is responsible for up to two-thirds of false negative results. This occurs when representative cells are not collected or transferred to the cytology slide.

Precise estimates of cytological screening accuracy are important in determining policy decisions, e.g., frequency of screening, management of low grade disease or assessing new technologies such as HPV screening, or liquid-based cytology.

It is somewhat surprising that the overwhelming proportion of studies assessing the performance of screening cytology have been performed in high prevalence colposcopy clinics with variable methods of disease verification and sub-optimal methodologies which potentially lead to bias resulting in an over-estimation of performance. It appears that there are only 12 studies evaluating cytology screening in low prevalence populations, either women undergoing primary screening or women attending gynaecology clinics [2-13]. In some of these studies women with a history of abnormal smears were excluded [4, 5, 7, 9, 12, 13]. The performance (sensitivity and specificity) of the Pap test was assessed, compared to the "gold standard" diagnosis which was colposcopy and directed biopsies if indicated (Table 1). The prevalence of CIN (all grades or high-grade only lesions) was also calculated.

In the studies that assessed cytology performance in such populations the specificity appears to be high

Revised manuscript accepted for publication February 15, 2002

Table 1. — *Accuracy of cervical cytology in low prevalence populations.*

Study	Subjects and method	Study Design	Cytology report	Colposcopy ± biopsy report	Prevalence of disease	Sensitivity	Specificity
JHPIEGO project[2]	2148 consecutive women undergoing primaryscreening. Mean age 33 yrs	Cytology compared to Acetic Acid Inspection	LGSIL or HGSIL	LGSIL or HGSIL.	All grades: 487/2092 (0.23) High grade: 201/2092 (0.1)	High threshold 29% Low threshold 44%	High threshold 92% Low threshold 91%
Baldauf[5]	1539 consecutive women attending gynaecological clinics. Mean age 36.3 yrs	Cytology compared to Cervicography	≥ ASCUS	≥ CIN I	All grades: 62/1343 (0.05)	Low threshold 56%	Low threshold 98%
Coibion[14]	4095 consecutive women undergoing primary screening. Mean age 33 yrs	Cytology compared to cervicogaphy	> CIN 1	CIN 1, 2, 3	All grades: 123/4015 (0.03)	High threshold 22% Low threshold 58%	High threshold 86% Low threshold 85%
Davison[3]	200 consecutive premenopausal women undergoing primary screening.	Cytology compared to Colposcopy	≥ Mild Dyskaryosis	≥ CIN I	All grades: 30/196 (0.15)	Low threshold 53%	Low threshold 100%
Garutti[8]	200 consecutive premenopausal women undergoing primary screening.	Cytology compared to cervicography	≥ HPV	≥ HPV	All grades: 72/200 (0.36)	Low threshold 42%	Low threshold 86%
Giles[4]	200 consecutive premenopausal women undergoing primary screening.	Cytology compared to Screening colposcopy	≥ HPV	≥ CIN 1	All grades: 17/176 (0.10)	Low threshold 58%	Low threshold 95%
Gueerra[6]	3658 consecutive women attending antenatal clinic Mean age 29.3 yrs	Cytology compared to Screening colposcopy	ASCUS, Low or High Grade	Low or High grade	All grades: 72/3658 (0.02) High grade: 55/3658 (0.015)	≥ ASCUS 90% HSIL 88%	> ASCUS 97% HSIL 100%
Hockstad[7]	73 consecutive women attending gynaecological clinics.	Cytology compared to Colposcopy and HPV test	≥ ASCUS	≥ Low grade	All grades: 7/70 (0.10)	Low threshold 31%	Low threshold 96%
Kesic[10]	418 women women undergoing primary screening.	Cytology compared to Cervicogram	≥ (Class III) Low grade	CIN I, CIN II/ III	All grades: 27/395 (0.07)	Low threshold 52%	Low threshold 94%
Loiudice[9]	3342 consecutive premenopausal women undergoing primary screening. Mean age 33 yrs	Cytology compared to Speculoscopy	≥ Low grade	Low or High grade	All grades: 267/3300 (0.08) High grade: 25/3300 (0.01)	High threshold 40% Low threshold 75%	High threshold 96% Low threshold 93%
Mann[13]	243 consecutive women undergoing primary screening. Mean age 29 yrs	Cytology compared to Speculoscopy	≥ Low grade	Low (HPV/CIN I) or High grade (CIN II-III)	All grades: 29/243 (0.12) High grade: 6/243 (0.02)	High threshold 32% Low threshold 64%	High threshold 99% Low threshold 97%
Mannino[12]	3049 consecutive premenopausal women undergoing primary screening.	Cytology compared to Screening colposcopy	≥ Low grade	Low (HPV/CIN I) or High grade (CIN II-III)	All grades: 904/3049 (0.30) High grade: 60 / 3049 (0.02)	High threshold 30% Low threshold 99%	High threshold 100% Low threshold 93%

(85-100%) but the sensitivity estimates are variable and generally much lower than generally believed (22-99%). Sensitivity is increased if lower thresholds of disease are used, for example referring women with low grade and atypical squamous cells of undetermined significance (ASCUS) abnormalities [15]. Low sensitivity results from relatively high levels of false negative results in women, with invasive or pre-invasive disease being missed. An ideal screening test is characterised by a very high sensitivity and therefore a high negative predictive value for disease. As women with a positive screening test will be tested further while those with a negative test result will not be retested, specificity is a secondary consideration, and positive predictive value is sacrificed, acknowledging that those positive for disease on the screening test but who are in fact disease-free will be

identified as such on subsequent testing. Those women who have disease but are negative for disease on screening will probably be missed entirely and will remain at risk of developing cervical cancer.

The main aim of a screening programme is to decrease the incidence of and mortality from invasive carcinoma. Cytological cervical screening has been successful in this aspect, but does not demonstrate the characteristics of an optimal screening test since it is relatively insensitive to the presence of disease yet highly specific. The true screening accuracy of cytology needs to be assessed for health policy decision making and to educate women as to the true performance of screening. Only when we establish the true contribution of both sampling and laboratory error to screening accuracy can we introduce strategies to improve smear taking and interpretation. New technologies should only be introduced if proven to be superior to cytology in terms of markedly improved sensitivity in low-disease prevalence non-biased studies.

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