CERVICAL SCREENING IN ENGLAND: LIQUID-BASED CYTOLOGY IN THE CONTEXT OF MODERNIZATION OF THE NHS CERVICAL SCREENING PROGRAMME

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Summary
The article will briefly explain the processes of organized screening in the NHS Cervical Screening Programme (NHSCP). Quality control is well established and monitored by regional quality assurance reference centres. The final outcome of screening is also monitored by national cervical cancer mortality and incidence rates: data will be presented for rates of in situ and invasive cervical carcinoma before and after the introduction of organized screening. The NHSCSP is using the introduction of liquid-based cytology as a platform for modernization, which is planned to include high-risk human papillomavirus (HR HPV) testing for low-grade cytology triage as well as a test of cure after treatment. Trials of computer-assisted screening are also in progress. High standards of quality control will be needed in the era of vaccination, when prevalence of preinvasive and invasive cervical cancer will decline. The NHSCSP is well placed to take on these challenges, if necessary by introducing primary HR HPV testing so that cytology screening can be concentrated on women who are genuinely at risk.

Key words: screening, cervical cancer, liquid-based cytology, England

INTRODUCTION

Cervical screening was centrally organized in 1988 on a background of opportunistic screening, mostly in young women, at a time when there was no established programme of quality control. Since the NHS Cervical Screening Programme (NHSCSP) was launched in 1988 incidence and mortality of invasive cervical cancer have fallen by about 50% despite an increased risk of disease, which affected women across Europe in birth cohorts since 1940s (1). Peto et al. estimated that cervical screening prevents around 80% of deaths and considered that an epidemic of the disease had been prevented, particularly in women screened when they were young (2). In 2003, the National Institute for Clinical Excellence (NICE) recommended liquid-based cytology (LBC) as the method for collecting samples for cervical screening (3). After a period of negotiation about which technology should be used, and training of all medical and non-medical cytologists as well as doctors and nurses collecting the samples, LBC has been introduced in most screening centres. Implementation will be complete by the end of 2008, with centres divided fairly equally between those using ThinPrep and SurePath technology. LBC has allowed modernization of the NHSCSP to take place and will be used as a platform for both high-risk human papillomavirus (HR HPV) testing and computer-assisted screening. The integration of HR HPV testing and automation is likely to be necessary in the era of vaccination, when the lower prevalence of cervical intraepithelial neoplasia (CIN) will make accuracy of screening more difficult to maintain but perhaps even more important. Furthermore, the NHSCSP requires a screening history audit of any woman developing invasive cancer, complete with slide review of any cytology tests in the ten years preceding diagnosis (4, 5) which focuses on the imperative for accurate screening. The NHSCSP will be in an excellent position to take these developments forward because the standards of cytological screening are high and sensitivity of the test has been shown to be higher than elsewhere in two separate HR HPV trials (6–7).

ORGANIZED SCREENING IN THE NHSCSP

Invitations for screening are initiated by a central computer system managed by Primary Care Trusts (PCT). PCTs send prior notification lists of women aged 25–64 to general practitioners (GP), who send personalized invitation letters to women in their practices due for tests. Women aged 25–49 are invited 3-yearly and women aged 50–64 5-yearly. Trained nurses attached to GP surgeries collect most of the samples, while the rest are taken in community clinics. Cytology laboratories process the LBC vials, screen and report the slides and send the results to the nurses and doctors who requested the tests. They also send explanatory letters to the women. Coded results are transmitted to the PCT computer so that women can be invited for repeat tests, either early or routine, after the interval recommended by the laboratory. Laboratory "failsafe" systems, which depend on ascertaining the results of colposcopy and biopsy, ensure follow-up of women recommended for investigation. Although biopsy results are not recorded on the central computer system, changes are being made to the system to code for HR HPV results. Cancer registries record histological biopsies of CIN3 (registered as carcinoma *in situ*) and invasive cervical carcinoma, which provides a mechanism for monitoring the outcome of the programme. Regionally based quality assurance reference centres (QARC) monitor all aspects of quality control and carry out regular visits to cytology laboratories, colposcopy clinics and PCT-based screening commissioners. The programme's success has been demonstrated by the fall in incidence and mortality from rates that were highest in Europe in the 1980s to rates now among the lowest (Fig. 1) (8). The only cloud on the horizon has been declining screening coverage in younger women (age 25–39) for which there may be more than one cause, including anxiety about effects of excisional treatment on pregnancy (9), a false sense of security now that incidence and mortality have declined and delaying the first invitation from age 20 to 25 (10, 11). Since most CIN3 is detected and treated in women under the age of 40 (Fig. 2) (8), there is some concern that cancer rates may increase in younger women if this trend is not reversed.

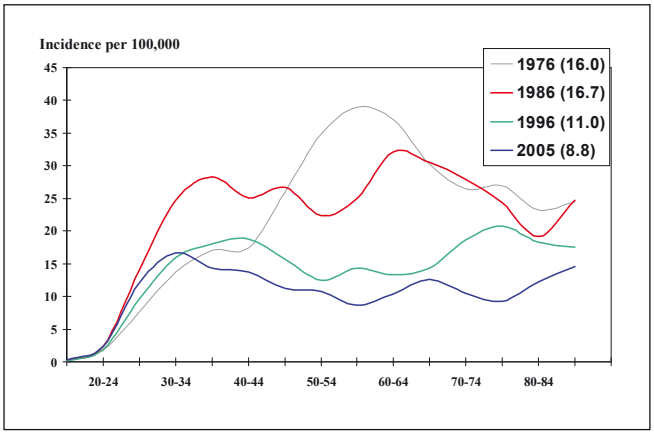

Fig. 1. *Incidence of invasive cervical cancer England & Wales 1976/86; England 1996/2005*
Data www.statistics.gov.uk/statbase8

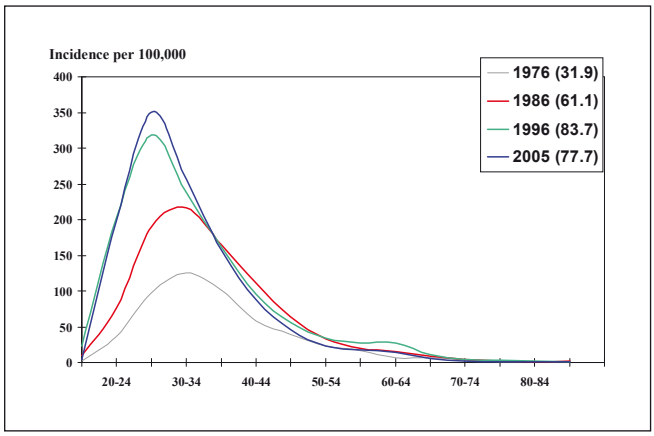

Fig. 2. *Incidence of carcinoma in situ (CIN3) England & Wales 1976/86; England 1996/2005*
Data www.statistics.gov.uk/statbase8

LIQUID-BASED CYTOLOGY

LBC is at an advanced stage of being "rolled out" nationally after the NICE recommendation in 2003 following reports of pilot site feasibility studies in Wales (12), Scotland (13) and England

(14) and a Health Technology Assessment report (15). The NICE report recognized that although numerous publications suggested that LBC would be more sensitive than conventional smears, and more specific through avoiding equivocal results, there was some skepticism among experts about the validity of many the studies (3). They concluded that "the overall sensitivity was at least as good as, and may be better than, the Pap smear", which has been born out by subsequent experience with the technology. That note of caution proved justified and subsequent meta-analyses have shown that, although high-grade reporting rates may be increased by LBC, increased detection of high-grade CIN has not been confirmed and there is no clear evidence of its greater sensitivity or specificity (14, 17).

The main advantage of LBC in the UK was the dramatic fall in rates of inadequate tests at the pilot sites for implementation – from about 10% to 1–2% (12, 13, 14). This has not been seen elsewhere in the world where inadequate rates with conventional cytology tend to be lower (16). There are several caveats to this apparent advantage for the UK. First, as NICE pointed out, with LBC "there is no way of verifying that a sufficient number of cervical cells have been harvested by the smear taker" (3); second, all non-normal cytology rates are higher in the UK because there are fewer negative tests with 3–5 yearly than with annual screening; and third, inadequate smears inappropriately reported as negative have been sited as reasons for false negative cytology preceding invasive cancer (18). In our laboratory, we count cells in ten high-power fields if a ThinPrep looks poorly cellular, using photomicrographs of known cellularity as a guide (19). We regard less than ten squamous cells per HPF, representing 13,000 in total, as inadequate. This results in an inadequate rate of about 4%, which is higher than at the pilot sites. We chose this level because an in-house study had shown that abnormal cells were less likely to be found in preparations below that cellularity (20), supporting a previous study by Bolick et al. (21) and we believe that the Bethesda system criterion of a minimum of 5,000 cells might be insufficient for a 3–5 year programme (22). A multi-centre study has been funded by the Health Technology Assessment Programme to develop criteria for LBC adequacy and the final inadequate rates may not be quite as low as at the pilot sites.

GPs and nurses prefer LBC because it relieves them of the responsibility for making and fixing direct smears. However, training remains important, partly because it is so difficult to assess sample adequacy under the microscope. Excellent guidelines for taking samples are available from the NHSCSP: the cervix should not be contaminated with gel; the cervex broom should be rotated clockwise with firm pressure no less than five times (the broom is bevelled for clockwise rotation); all the material should be rinsed into the vial (23). The EU has published guidelines on taking liquid-based as well as conventional cytology samples (24, 25).

MODERNIZATION OF THE NHS

There is no doubt that the introduction of LBC throughout the UK will be a key step in the modernization of the NHSCSP. There are two major developments that will be easier to implement now that LBC is the method of cell collection. The first is reflex HR HPV testing. Six sentinel sites have been initiated across England to test the feasibility of HR HPV triage for low-grade cytological abnormalities and as "test of cure" after treatment of high-grade CIN. Now that immediate referral of all women with mild dyskaryosis is recommended by the NHSCSP (26) (although not universally implemented), colposcopy referrals and cytological surveillance would be reduced by confining investigation to women who test positive for HR HPV. Also, long term follow-up after treatment would be reduced if HR HPV were introduced as a test of cure. Experience with other pilot site projects makes it highly likely that low-grade HR HPV triage will be launched nationally once the sentinel site projects are complete. Furthermore, the NHSCSP is fully aware that vaccination, which has been recommended in girls aged 10–14, will have a marked impact on cervical screening in the future. Primary HR HPV screening is likely to become necessary once CIN prevalence declines with vaccination so that cytology could be concentrated on the relatively small number who test positive and will be at genuine risk. Primary HPV testing would not require LBC since tests could be carried out on direct cervical brushings if material was not needed for cytological screening. Cytology triage would be carried out as a second test if HR HPV were detected. Julietta Patnick, Director of NHS Screening Programmes, has discussed the implications of vaccination in a recent statement (27) and the plans for HR HPV testing are covered in the NHSCSP 2007 Annual Report (28).

Automated computer-assisted screening is one of the attractions of LBC; but would it be needed if primary HR HPV screening and vaccination significantly reduced the volume of cytological screening? It seems doubtful that a computer-assisted mechanism such as AutoPap, which largely depends on ranking a relatively small percentage of slides to be archived without screening, would be attractive for a low-volume test (29). However, with the imperative for maintaining accuracy with low prevalence of disease and with the emphasis on cytology review of women who develop invasive cancer, computer-assisted screening would be attractive if it were shown to be more sensitive than routine screening. There is evidence that computer-assisted screening can significantly increase the detection of high-grade cytology (30) and our own experience at Guy's & St Thomas' supports those findings (unpublished observations). We have implemented the Cytyc imager as a quality control tool in place of rapid review, which does not compromise the skill of screening staff. The same biomedical scientists alternate between primary routine screening and pre-screening slides processed by the imager.

CONCLUSIONS

These are exciting times for a screening programme that has successfully moved forward from a poorly controlled opportunistic programme to one of the best organized in the world, despite increasing risk of disease in recent birth cohorts of women. There are enormous challenges to face, not least the declining screening coverage in young women, but the NHSCSP is well placed to modernize its processes to take advantages of new technology, including HR HPV testing, vaccination and computer-assisted screening. Underpinning all these developments is the need for multi-disciplinary co-operation, communication and quality control, all of which are essential for any screening programme; and are highly developed in the NHSCSP.

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