

Cervical Screening in the UK and Laboratory Quality Control in the Context of the 2007 European Guidelines

Amanda Herbert

Histopathology Department, Guy's & St Thomas' NHS Foundation Trust, London, UK

ABSTRACT

The first part of this article will provide an overview of cervical cancer screening in the UK during the years before, during and after the introduction of a highly successful centrally organised cervical screening programme in 1988: since then the incidence of invasive cervical cancer has fallen by more than 40%. Screening was introduced in a background of opportunistic screening with poor quality control during a period of time when risk of disease was increasing, which will be demonstrated by national registrations of carcinoma in situ as well as invasive cancer. The programme is still facing new challenges and has recently recorded falling screening coverage in younger women, the causes of which have yet to be established. Liquid-based cytology is in the process of being rolled out nationally but high-risk human papillomavirus testing has yet to be introduced into the National Health Service (NHS) programme. Lessons from our experience may be relevant to countries introducing and maintaining organised programmes elsewhere under similar circumstances. The second part of the article will consider laboratory quality control as practiced in the UK and as recommended in the second edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening. These evidence-based guidelines provide recommendations for organising and monitoring quality control as well as for introducing new technology and standardising terminology, which are equally relevant for new and existing programmes. Invasive cancer audit may highlight areas where procedures could be improved in any programme but also can also demonstrate the effectiveness of screening.

Key words: Organised cervical screening, quality control, invasive cervical cancer incidence, carcinoma in situ, cervical intraepithelial neoplasia, new technology

Introduction

Across Europe in 2002 there were approximately 60,000 new cases and 30,000 deaths from invasive cervical cancer with a 5-fold variation in those rates¹. The lowest were in countries such as the United Kingdom (UK) with organised programmes, which can maximise the positive and minimise the adverse effects, but there are many different models of care. The aim is to reach the population at risk and provide a high quality service that takes account of specificity as well as sensitivity of the test. Demographic differences and changes of risk with time must also be considered when comparing programmes in countries as diverse as the whole of Europe.

Although rates of mortality and incidence relate to screening coverage of the population at risk, no amount of screening will be successful without good quality con-

trol. The second edition of the *European Guidelines for Quality Assurance in Cervical Cancer Screening* provides a comprehensive overview of cervical cancer control in Europe and describes methodology for all aspects of quality control¹. These guidelines are equally relevant to existing and new programmes with respect to target populations, intervals for screening, evidence-based indications for new technology, methodology for quality control, monitoring the effectiveness of screening and the importance of standardising terminology across a diverse and increasingly mobile group of nations.

Cervical screening has been successful in the UK since a centrally organised National Health Service Cervical Screening Programme (NHSCSP) was introduced

in 1988, which can be demonstrated by national registrations of invasive and *in situ* carcinoma of the uterine cervix (www.statistics.gov.uk). Registrations prior to 1992 can be obtained from the Office for National Statistics on CD ROM². The effects of changing risk of disease, screening coverage and quality control continue to influence the evolution of the programme and may provide lessons for other countries. The challenge of new technology affects new and existing programmes alike and should be introduced as and when it can be shown to improve sensitivity or specificity of the test. The experience of introducing liquid-based cytology (LBC) to the NHSCSP will be discussed as well as the role of high-risk human papillomavirus (hrHPV) testing, which is yet to be introduced nationally.

Screening in the UK Before and After Organised Screening Was Introduced

During the 1970s and 1980s general practitioners were paid a supplement to screen women aged 35–64, or earlier for women with three or more children. A relatively ineffective paper-based system of 5-yearly recall was in place but most screening was opportunistic, mainly in young women, and quality control was poor. Incidence per 100,000 total female population remained almost steady at 15.0 to 16.0 throughout the 1970s and 1980s when UK rates were the highest in Europe. However, there was a striking change in the pattern of disease during those decades³. Although overall numbers of cancers changed little during a 10-year period there was a nearly 3-fold increase in rates of deaths, invasive cancers, registrations of carcinoma *in situ* and high-grade cytological abnormalities in women born since the mid-1940s almost certainly because of the greater sexual freedom allowed by the availability of reliable contraception⁴. Screening coverage was poorly documented until 1990 but was lower in older (over age 40) than younger women. National registrations of carcinoma *in situ*, which include cervical intraepithelial neoplasia (CIN) grade 3 since 1983, provide evidence that many young women were effectively screened, albeit opportunistically: the number of registrations of carcinoma *in situ* had already overtaken those of invasive cancer as early as 1981 (Figure 1 and 2). Shortly before the introduction of organised screening in 1988 incidence of invasive cancer had started to rise, reaching a maximum 17.4 in 1988: the age distribution reflects the increased risk in younger women (Figure 3). It was recognised at the time that quality control was poor⁵.

The organised programme aimed to improve all aspects of quality control as well as setting up a centralised register to invite all eligible women aged 20–64 at least every five years. Incidence fell steadily during the 1990s to a figure fluctuating between 8.0 and 9.0 since 2001. Mortality rates declined from 1988 in all birth cohorts (from 1922) screened at least once in the new programme but declined earlier in life for women first screened when they were younger (the latest in the study were born in

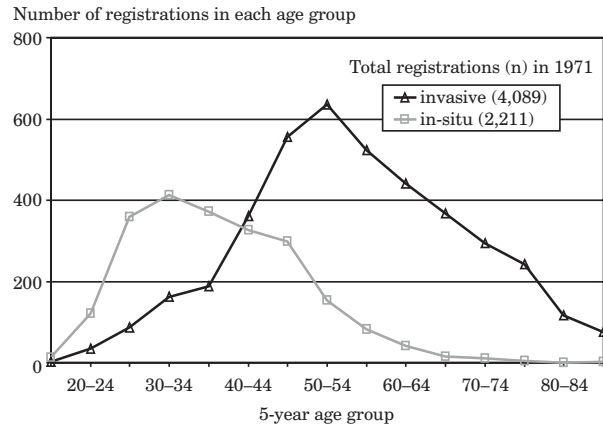


Fig. 1. Registration of invasive and *in situ* carcinoma of the uterine cervix in England & Wales (Source: Office for National Statistics, *Cancer 1971–1997*²).

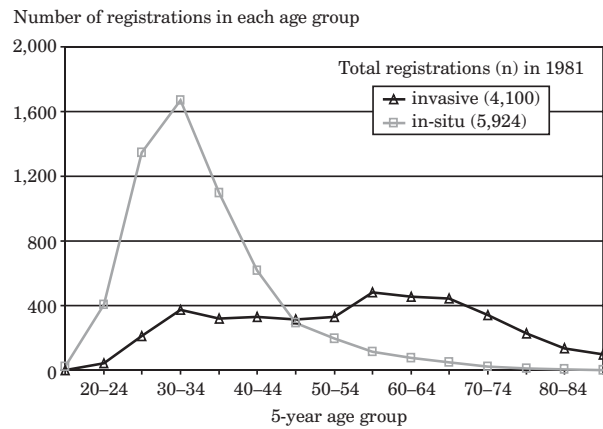


Fig. 2. Registration of invasive and *in situ* carcinoma of the uterine cervix in England & Wales in 1981 (Source: Office for National Statistics, *Cancer 1971–1997*²).

1952) in whom the death rate was substantially lower throughout life⁶. This evidence is supported by the observation that high-grade cervical intraepithelial neoplasia (CIN) is predominantly treated in young women: more than 80% of CIN3 was found in women aged less than 40 before, during and after the introduction of organised screening (Figure 4). There has been some concern about a recent decision in the UK no longer to invite women aged 20–24 for screening⁷, which was based on results of a national audit⁸ and is consistent with EU guidelines¹. However, a recent study in Iceland showed the benefit of lowering the age limit to include women aged 20–24⁹, which is in accordance with recommendations in the USA (www.ahrq.gov/clinic/3rduspstf/cervcan/cervcanrr). The NHSCSP is facing a new challenge since a fall in screening coverage has been recorded in young women, particularly those aged 25–29 in whom the highest prevalence of CIN3 is recorded. The reasons for the fall in coverage have yet to be established but the evidence suggests a need to encourage young women to be screened even though there is debate about the age of the first invitation.

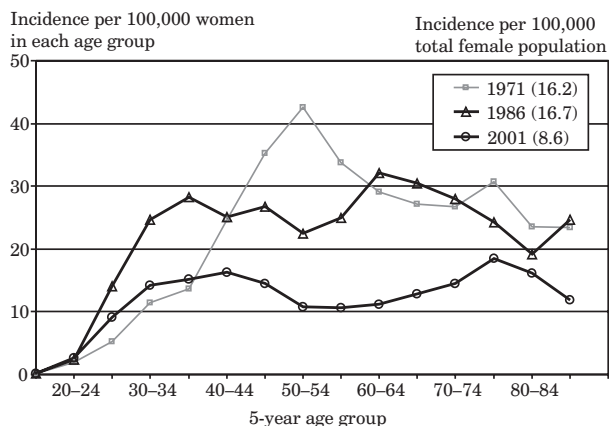


Fig 3. Incidence of invasive cervical cancer in England in 2001 (Source: www.statistics.gov.uk/statbase), and England & Wales in 1971 & 1986 (Source: Office for National Statistics, Cancer 1971–1997²).

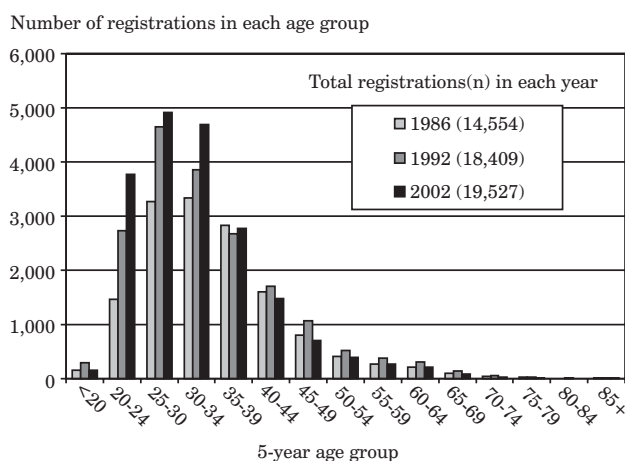


Fig. 4. Registrations of carcinoma in situ, England and Wales (1986) and England (1992 and 2002)⁷.

Quality Control of all Aspects of the Screening Programme

The European guidelines emphasise the importance of quality control of all aspects of the screening programme¹. Invitations for screening should be clear but informative, smear-takers should receive training and should be able to explain the test results to women; laboratories should have the infrastructure required for a high-quality service in terms of accommodation, equipment, adequate numbers and levels of non-medical and clerical staff, availability of training and update, information technology and medical supervision; colposcopy clinics should similarly be equipped, staffed, trained, supervised and monitored; and terminology should at least be translatable into nationally recognised systems. The NHSCSP also addresses all aspects of the programme, providing evidence-based guidelines and monitoring performance through regional quality assurance reference centres (QARCs). A centralised computer-based register

of screening records is essential and ideally should include histology and colposcopy records and should be linked to regional and national cancer incidence and mortality registries.

Quality Control in the Laboratory

The mechanisms of laboratory quality control will be considered with respect to the interlinked functions of primary screening, final cytology reports and comparison with outcome. At each level accuracy depends on the subsequent as much as the previous step and the final outcome itself depends on the accuracy of the histology report, which should not be regarded as a »gold-standard« unless it is also subjected to audit and quality control.

Quality control of primary screening

Accurate primary screening is central to the cervical screening process and its quality control is essential. One of the strengths and weaknesses of cervical cytology screening is the ease with which the glass slide may be reviewed, often with the benefit of hindsight, and methods of quality control should recognise that no test will be perfect^{10,11}. The most powerful methods of primary screening quality control involve re-screening the slides before the reports are issued, thus reducing false negative rates at the same time as monitoring individual and laboratory performance. Rapid re-screening of all negative and inadequate smears (or liquid-based slides) has been shown to be an effective method of minimising false negative results¹². Rapid pre-screening may be even more effective¹³ and both methods are recommended in the European guidelines. Both are preferable to proportional re-screening of 10% of negative slides or targeted re-screening of supposedly high-risk cases. Where rapid re-screening or pre-screening is in place, as in the UK, it may be possible to avoid targeted re-screening altogether. It should be recognised that either method may fail to detect the very abnormalities that are so easily missed: slides with small numbers of abnormal cells as well as pale and small cell dyskaryosis have been shown to be »at risk« for not being detected at primary screening of conventional smears^{14,15} and small numbers of abnormal cells may equally well be missed in liquid-based cytology¹⁶. Sensitivity of primary screening for the individual and laboratory may be calculated against the final report after the second screen has taken place and should be calculated for high-grade cytology alone and for all abnormalities. It may be helpful to calculate the »detection rates« of the final report as part of a performance profile for each screener¹⁷. Performance profiles should be monitored confidentially and sensitively, expectations should not be too high, and procedures to deal with genuine poor performance should be agreed in advance.

Pathologists' and laboratory reporting rates

Apparent sensitivity of primary screening may be influenced by the accuracy of the final report. A pathologist with an inappropriately low threshold for reporting atypical or borderline changes may spuriously reduce the sen-

sitivity of the screener. Conversely it is possible for a pathologist to override a screener’s opinion and report a genuine abnormality as reactive or benign. Pathologists and laboratory performance may be monitored by comparing reporting rates of high-grade and low-grade cytology results between observers and between laboratories, which can improve consistency¹⁸. Comparison of high-grade reporting rates is used for laboratory quality control in the NHSCSP and achievable ranges are set each year based on the 10th and 90th percentiles of national reporting rates (www.cancerscreening.nhs.uk/cervical/statistics). Rates are monitored internally by laboratory staff, externally by QARCs and are published nationally each year. While the low limit of high-grade cytology rates provides a surrogate for sensitivity, the high limit of low-grade cytology reflects specificity.

Positive predictive value

Positive predictive value (PPV) provides a convenient measure of accuracy of high-grade cytology reports and may be regarded as a surrogate for specificity. In the UK PPV is measured as the percentage of high-grade cytology results that are confirmed by at least CIN2 on biopsy (using cases with known colposcopy outcome as the denominator). Thus PPV may be influenced by the »moving target« of the histological distinction between CIN1 and CIN2 and by the sensitivity of detection of high-grade cytology: high PPVs may be seen with low detection rates of high-grade cytology. In the UK an achievable range of PPV is monitored rather than a lower limit only. Sensitivity of the test is more difficult to measure as women with negative cytology are seldom referred for colposcopy. The rate at which referrals for persistent low-grade cytology or less are found to have at least CIN3 may be used as a surrogate for sensitivity and provides a useful balance for PPV (www.cancerscreening.nhs.uk/cervical/statistics).

Quality control of histology

Because of its central role in the screening process, cytology reporting has been subjected to far more intense quality control than histology reporting although the latter forms the basis for decisions about treatment and management of CIN and invasive cancer. This is stressed

in the European guidelines as well as in the UK programme and the NHSCSP provides illustrated guidelines for reporting cervical biopsies¹⁹. It is more difficult to monitor reporting rates in histology because of the absence of a population baseline. Nevertheless, quality is greatly improved by colposcopic biopsies being reported by specialist teams and slides being reviewed and presented along with the cytology at multidisciplinary meetings. Immunohistochemistry is more readily applicable to histology than cytology and difficult distinctions between low-grade and high-grade CIN may be augmented by Ki67 and P¹⁶ink4a staining²⁰. CIN reflects a continuous spectrum of precancerous changes carrying an increasing risk of progression so there will always be inter-observer variation about the dividing lines between HPV infection and CIN1, between CIN1 and CIN2 and between CIN2 and CIN3. CIN3 has been shown to be the most robust of these diagnoses²¹ and for this reason the EU guidelines are justified in maintaining the CIN classification for histological diagnosis although decisions for treatment are usually made at the level of CIN2.

Principles of laboratory quality control

Quality control should be a continuous process involving correlation of all parameters and taking account of the nature of the spectrum of CIN. It requires good record-keeping and communication – both personal and electronic – at all stages of the process. Communication is greatly improved by standardising terminology, which is naturally more difficult with so many different languages in use across Europe. The EU guidelines have solved this problem by recognising that all terminologies should be locally agreed and should at least be translatable into the Bethesda system (Figure 5), which is widely used throughout the world²². TBS is recommended for cytology, for which it was originally developed, and the CIN system is retained for histology.

Testing and Introducing New Technology

The European guidelines are being published at a time of greatest change since the Pap smear was introduced as a screening test more than 60 years ago. Laboratories, gynaecologists, politicians and women have been

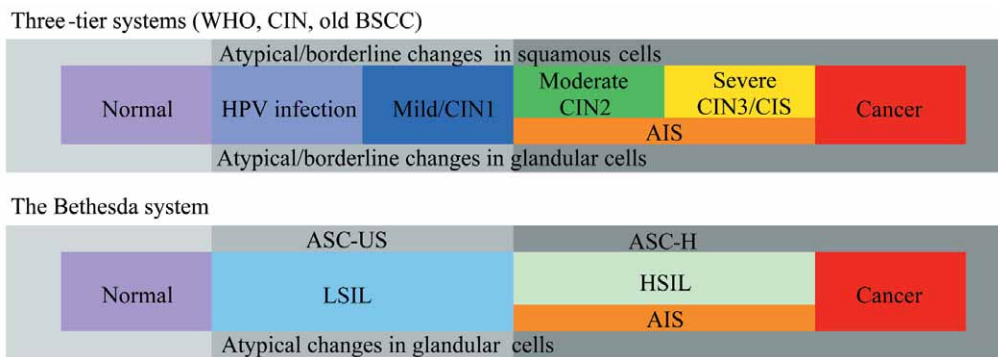


Fig. 5. Conceptual categorisation of cytological findings in a Pap smear of the uterine cervix¹.

placed under enormous pressure to introduce expensive new technology including LBC, hrHPV testing and automated screening. Technology is gradually converting a simple inexpensive test into a highly complex and much more costly multi-step process. Whether this new technology has saved any lives has yet to be determined²³. LBC was introduced throughout the UK after implementation at pilot sites in Scotland, Wales and three screening centres in England. The report recommending its implementation made the guarded statement that »overall sensitivity was at least as good as, and may be better than, the Pap smear«²⁴. The main advantage in the UK was the striking fall in the pilot sites in rates of inadequate tests, which were higher with Pap smears compared with elsewhere in the world. There are several caveats to this dramatic decline in rates of inadequate tests²⁵. Firstly, as NICE pointed out, »there is no way of verifying that a sufficient number of cervical cells have been harvested by the smear taker«²⁴. Secondly, all non-normal rates are higher in the UK, with 3–5 yearly screening than in places with annual screening because there are fewer negative tests. Thirdly, »quality indicator comments« about poor cellularity, lack of transformation zone sampling and inflammatory exudate, which are allowed with the Bethesda system²², are not allowed in the UK. Furthermore, litigation is relatively common in the UK and cytologists are aware that inadequate smears inappropriately reported as negative have been cited as reasons for »false negative« cytology preceding invasive cancer²⁶. A multi-centre study has been funded by the Health Technology Assessment programme to develop criteria for LBC adequacy appropriate for a 3–5 year programme. The European guidelines recognise that criteria may be different for organised programmes with restricted intervals and age ranges for screening and, while regarding LBC as an acceptable method of cell collection, have not recommended it in place of conventional cytology in the absence of a randomised clinical trial to demonstrate its superiority¹.

One of the main advantages of LBC is that it facilitates hrHPV testing using residual material in the vial. Some would say that hrHPV testing could replace cytology for primary screening²⁷ but this would probably only be feasible for women over 35 because of high prevalence of hrHPV in younger women. hrHPV testing is developing a firmer place in the triage of women with borderline or atypical cytology almost half of whom may not need investigation or frequent surveillance^{28,29}. Similarly it is likely to have an important role in follow-up after treatment of high-grade CIN when the minority of women with persistent hrHPV could be monitored more closely, while the majority could be returned to routine screening. Essentially, hrHPV is the one development that has the potential to increase specificity of the test by reducing the number of women investigated for borderline and ASCUS smears.

HPV vaccination is the one new development that may fundamentally change cervical cancer screening and is the subject of a supplement in the European guidelines and as a separate publication³⁰. Suffice it to say here that

vaccination will not remove the necessity to screen the current generation of women, including women who are vaccinated in adult life. Falling rates of abnormal cytology in vaccinated women coupled with a false sense of security might present additional challenges to screening programmes. There will be even more need to maintain quality control and high sensitivity of the test – to the extent that hrHPV testing might be needed as a primary investigation. There is no doubt that vaccination will radically affect screening programmes worldwide but little is yet known of its likely uptake and even the duration of protection provided.

Invasive Cancer Audit and its Role in Quality Control

The ultimate audit of cervical screening lies in monitoring invasive cancer incidence and mortality but, as indicated above, these rates should be assessed in relation to levels of high-grade CIN or CIN3 successfully detected – both as a measure of effectiveness of screening and of risk of disease. Invasive cancer rates are likely to be low in local screening centres and are therefore inappropriate as a local guide of effectiveness. However, audit of mode of presentation, stage of cancer and screening history provides a valuable method of monitoring local, regional and national screening programmes. Screening histories identify areas where screening processes may be improved – not only with respect to screening and reporting the slides. There are multiple factors that may lead to cancers not being prevented in screened women: screening may have been intermittent or infrequent, abnormalities may have been missed on slides, samples may have been inadequate, low-grade abnormalities may have been under-interpreted or not followed up, high-grade abnormalities may have been reported but not investigated and treatment of CIN may have been incomplete or not followed up³¹. Isolated reasons or combinations of those reasons may be implicated in an individual case and bear witness to the effectiveness of the screening process itself if correctly and accurately conducted. In well-screened populations such as the UK it has proved to be easier to prevent invasive cancer in older age groups⁸, presumably because there are more screening opportunities to detect a lesion that does not progress to invasion until later in life. Although cancers in young women are more difficult to prevent, and must have arisen in more aggressive lesions, they are frequently detected by positive cytology in asymptomatic women. These screen-detected cancers are almost invariably diagnosed at stage 1 (either 1A or 1B) and present a benefit of screening that provides a benefit in terms of survival that is not evident from incidence rates³².

Conclusion

Experience of introducing a highly effective national screening programme in the UK, in a partially screened population during a period of increasing risk of disease,

may provide lessons to other countries introducing national programmes in the inevitable background of opportunistic screening. Auditing screening histories of the unfortunate few women who develop invasive cancer in well-screened populations may identify processes that could be improved. The latest European guidelines for

quality assurance are being published as a time of enormous changes in technology and provide evidence-based advice to all of us, whether maintaining existing programmes or starting new ones, to help us navigate those changes in a cost-effective manner that carries cervical cancer control forward into the 21st century.

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A. Herbert

Histopathology Department, Guy's & St Thomas' NHS Foundation Trust, London, UK
e-mail: amanda.herbert@kcl.ac.uk

PROBIR RAKA VRATA MATERNICE U UJEDINJENOM KRALJEVSTVU I LABORATORIJSKA KONTROLA KVALITETE U KONTEKSTU VODIČA EU 2007

SAŽETAK

Prvi dio članka će dati osvrt na probir raka vrata maternice u UK za godine prije, za vrijeme i nakon uvođenja vrlo uspješnog organiziranog programa probira raka vrata maternice 1988. g., od kada je stopa pojavnosti invazivnog raka vrata maternice pala za više od 40%. Organizirani probir je uveden u sjeni oportunističkog probira sa lošom kvalitetom kontrole u vremenu kada je rizik za bolest rastao, na što će ukazati nacionalni registri za rak vrata maternice *in situ* te za invazivni karcinom. Program još nailazi na nove izazove, a nedavno je zabilježio pad u pokrivenosti mladih žena, uzrok čega još mora biti utvrđen. Tekućinska citologija je u procesu uspostave na nacionalnoj razini, ali testiranje na visokorizične humane papilomaviruse još mora biti uvedeno u program Nacionalnog zdravstvenog sustava (NHS – National Health Service). Lekcije iz našeg iskustva bi mogle biti od značaja zemljama koje uvode ili provode organizirane programe probira pod sličnim okolnostima. Drugi dio članka će se baviti laboratorijskom kontrolom kvalitete na način kako se provodi u UK te kako je to preporučeno u drugom izdanju »Europskog vodiča za osiguranje kvalitete u probiru raka vrata maternice«. Ovakvi vodiči pružaju preporuke za organiziranje i praćenje kontrole kvalitete, kao i za uvođenje novih metoda te standardiziranja terminologije, što je jednako važno za nove i postojeće programe. Ispitivanje invazivnog karcinoma bi moglo ukazati na područja gdje bi postupci mogli biti poboljšani bez obzira na vrstu programa, a ujedno i prikazati učinkovitost programa.