Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

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PROGRESS IN CERVICAL SCREENING

1. Background

Papanicolaou's seminal publication in the 1940s, which showed that exfoliated cervical cells could be reliably harvested and spread, fixed and stained on a glass slide,[1] laid the foundations of cervical screening. This technique has remained virtually unchanged to the present day and is used all over the world in the prevention of cervical cancer. During the 1960s, it became apparent that a population screening programme could reduce both the incidence and death rate from cervical cancer, as first demonstrated in British Columbia.[2]

In 1968, Junger and Wilson published a list of ten criteria against which screening strategies could be judged.[3] It was clear that the relative accessibility of the cervix, the long natural history of cervical carcinogenesis and the relatively conservative treatment for precursor lesions meant that cervical screening was indeed a feasible strategy. Cervical screening was advocated in many countries although only a few comprehensive population programmes were established, including Iceland, Finland and North East Scotland.

In the late 1970s, a large increase in the incidence of abnormal cytology coincided with the discovery that viral cytopathic effect due to infection by human papillomavirus (HPV) could be seen cytologically.[4] The last 25 years has seen immense progress in our understanding of cervical carcinogenesis and the currently accepted view is that HPV is an essential factor in the causation of the disease. If HPV infection is persistent, integration into the cellular genome may occur, which results in inactivation of tumour suppresser genes,[5] suppression of apoptosis,[6] genetic instability and the development of precancerous change. Additional genotoxic agents, such as smoking, contribute further to the process of cancer formation.

The gradual increase in the use of exfoliative cytology in the late 1960s and 1970s naturally resulted in an increase in the number of abnormal tests. This, in turn, required the means to investigate and treat cervical intraepithelial neoplasia (CIN) without the amount of damage caused by the traditional knife cone biopsy. Colposcopy therefore, became widely adopted and treatments such as laser and large-loop excision of the transformation zone (LLETZ) have been successful. The incidence of cervical cancer following treatment of CIN3 is now less than 1% and the consequent death rate less than 0.5%.[7]

Until the 1980s, cervical screening was not applied in a systematic fashion in the UK, with the result that many women at greatest risk were not screened. The death rate from cervical cancer was essentially unchanged until the national programme was instituted in 1988. This programme originally involved every woman between the ages of 20 and 64 years (20–60 years in Scotland) being called and recalled every 3–5 years for a cervical sample test. This managed programme introduced

quality standards at every step: smear takers, cytoscreeners and colposcopy, in order to assure the quality of the process.

The National Health Service Cervical Screening Programme (NHSCSP) has issued a series of guidelines governing the management of the programme, the most recent of which (NHSCSP No. 20)[8] is an evidence-based document covering all of the major aspects of screening, diagnosis, treatment and follow up. The programme has had a dramatic effect, with a falling incidence of death from cervical cancer: the death rate is now just 50% of what it was in 1988.[9,10] It is estimated that 2000 lives a year are saved, many in young women. The annual expenditure of £130 million consumed by the NHSCSP is viewed as highly cost effective. Similar falls in death rates have been seen in Finland, Iceland and the USA.

Cervical cytology, although effective, is logistically complex, requiring infrastructure in primary care, at the laboratory level and in gynaecological care to manage abnormal cytology. As such, many developing countries cannot afford cervical screening, which results in a high incidence of cervical cancer, often with limited means of treatment. For example, many countries of Sub-Saharan Africa have virtually no radiotherapy. Consequently, cervical cancer remains one of the major killers of young women worldwide.

Although cervical screening has never been subjected to a randomised trial, few now argue that it has not been a successful public health measure. In order to get the most effective use of cervical cytology screening, qualitative assurance of all stage in the process is required and this has contributed significantly to the success of the UK programme. Where new programmes are being established, building in quality assurance is crucial to a successful outcome.[11]

2. Current challenges in cervical screening

2.1 Sensitivity

It has been estimated from systematic reviews that routine primary cervical screening carries a 50–70% sensitivity to detect CIN3.[12] The majority of missed lesions are due to failure to sample the lesion. Inevitably, a few cases are thought to be due to a failure by cytoscreeners to detect cytological abnormalities (that is, false negative readings). In order to achieve maximum sensitivity it is necessary to act on the most minor abnormalities, which are associated with the lowest prevalence of high-grade CIN and borderline cytology is four times as common as severe and moderate dyskaryosis combined. This creates one of the major difficulties in cervical screening – the management of low-grade abnormalities, which carry a very low positive predictive value for the presence of CIN, yet are associated with a significant number of underlying high-grade CIN lesions.

2.2 Population coverage

A major success in the cervical screening programme has been to increase population coverage, which was 81.2% in 2003, although slightly lower, at 80.6%, in 2004. This is due in part to target payments made to general practices but computerised call/recall and improved information for women have had the biggest impact. There remain certain women who do not participate, including some ethnic minorities and some women who choose not to. A significant proportion of women who develop cancer have not been regularly screened. Additional effort is required to convince some women that screening can be life saving.

2.3 Capacity with the UKCSP

There are shortages of cytoscreeners, biomedical scientists and consultant cytopathologists; all of which contribute to lengthy turnaround times. By reducing the need for repeat smears, liquid-based cytology has improved things, as has the advanced biomedical scientist practitioner initiative.

2.4 Public education

Despite clear-cut evidence that cervical screening saves lives, it is ironic that cervical screening has had to withstand continued criticism over many years. Cases of cervical cancer in women who have undergone screening have often been publicised by the media as indicative of a poor service. The need to achieve a clearer public understanding that screening cannot prevent every case of cervical cancer is now part of a campaign to improve communication with women.

3. Current developments

The UKCSP necessitates a degree of conservatism, as any change requires to be solidly evidence based and to be implemented nationally, which therefore, involves considerable upheaval. Despite the fact that the programme is highly effective, it is responsive to robust evidence indicating the need for change and a number of developments have resulted in major changes. Complex funding systems may show the face of change implementation.

3.1 Liquid-based cytology

Liquid-based cytology involves a fluid suspension of exfoliated cells being placed into liquid medium instead of being smeared on to a glass slide. The cell suspension is aspirated through a filter and the resulting thin layer of cells is deposited on a glass slide. This technology provides cleaner preparations, which are easier to read. In order to evaluate this method of cytological preparation, large pilot studies were funded and performed in the NHS system. The conclusions of these pilots were that inadequate cytology would be cut by 80%, that laboratories could process slides more quickly and that, despite increased costs per slide, overall liquid-based cytology would be cost effective. NICE agreed that it was cost effective and its implementation across England (Scotland had previously committed to this) was announced in October 2003[13] and is now being implemented across the United Kingdom.

3.2 Screening age range and interval

The rate of incidence of cervical cancer is extremely low in women under 25 years; fewer than 40 cases occur each year. Some of these tumours are probably not detectable and to identify their antecedent CIN lesions would require screening to be extended to teenagers. This is clearly not sensible. In 2002–03, 450 000 smears were taken in women aged under 25 years, which risks doing more harm than good because of the impact of over treating low-grade cervical changes. Three thousand CIN3 lesions have been detected annually in this age group but these lesions will not progress rapidly to cancer and can be screened in women aged 25 years. A 2003 publication indicated that screening women under the age of 25 years is not cost effective in reducing deaths from cervical cancer.[14] The same paper indicated that, to be effective in younger women, screening needs to be more frequent. Therefore, the new screening intervals are to be 3-yearly until the age of 50 years, when 5-yearly screening until the age of 64 years is adequate, because most incidences of CIN will have been prevented by prior screening. The model has become a narrower age range more intensively screened.

3.3 HPV triage of borderline cytology

There has been a great deal of research over the past 5 years trying to define the role that HPV testing might play in cervical screening. The most clinically effective role defined so far is in trying to discriminate which of the large numbers of women with borderline cytology have a very low risk of high-grade CIN from those with a higher risk. A number of studies have indicated that the negative predictive value of testing HPV negative in this setting is very high, whereas the positive predictive value of testing HPV positive may merit the use of colposcopic diagnosis without lengthy periods of repeated cytology.[15] A recent systematic review has indicated that HPV triage adds sensitivity to cytology and this may be relevant in ensuring that CIN is not detected in those first screened at 25 years. The liquid-based cytology

pilots incorporated reflex HPV testing for borderline cytology and the results of these are expected to be published shortly. The potential benefits are a reduction in repeat cytology, the avoidance of default from repeat cytology and increased sensitivity to detect underlying high-grade CIN by incorporating earlier colposcopic diagnosis. Such a strategy may require more resource but would be cost effective, particularly if HPV negative borderline lesions were returned to routine screening.

4. Short- to medium-term 'hot' research areas

4.1 Automation of cytology reading

Technology has been developed to enable automated processing of cytology slides in order to present the most abnormal appearing cells to the cytoscreeners using a computer-guided microscope platform. Another development is automated reading using computerised algorithms such that the least abnormal 25% of slides can be passed negative without being seen by a cytoscreener. These technologies have received approval by the Food and Drug Administration in the USA. In order to determine their potential for use in the UKCSP, rigorous evaluation will be required. Such technology has the potential to make screening more efficient, which would be desirable, given the severe pressures faced by laboratories in achieving adequate staffing.

4.2 HPV testing

HPV testing may also have a key role in primary cervical screening, not only because women who are HPV negative are at very low risk of having high-grade CIN but also, HPV positive testing has a very high sensitivity to detect high-grade CIN. Inevitably, the specificity is relatively poor, particularly in younger women, in whom infection is common; for example, 20% of women aged 25–30 years may test HPV positive. Some advocate a model where HPV testing could be used as a primary screen with cytology being restricted to HPV positive women. One issue that needs to be addressed is the adverse psychological and psychosexual effects that HPV testing may induce in some women. The role that HPV testing may play in primary cervical screening is currently the subject of a number of large randomised trials, in several European countries, results of which will be keenly awaited over the next 3–4 years.

4.3 Cell cycle markers

Another approach being researched is that of identifying cell cycle molecular markers that could replace morphological cytology by means of immunocytochemistry. Such a marker could benefit from automation and avoid the adverse connotations of HPV testing. The challenge for such markers would be to achieve the required sensitivity while maintaining specificity at a manageable level. This will not be a simple matter. A number of candidates have emerged, such as $P16^{ink4}$a but none has been subjected to a large primary screening study, where the very low prevalence of high-grade CIN presents a tough challenge.

4.4 Prophylactic vaccines

The ultimate scenario may be to develop prophylactic vaccine programmes, which would involve vaccinating young virginal adolescents, thus preventing HPV infection and the subsequent risk of cervical pathology. Such vaccines are in development and proof of principle studies have been encouraging.[16–18] Large-scale trials are now in progress. Difficult issues remain, such as duration of protection, acceptability to society and the need to protect against many HPV types. Notwithstanding the potential benefits of these vaccines, women now aged between adolescence and 64 years who have been HPV infected will require some form of cervical screening until the means of eradicating established HPV infection is developed. In addition, women who have been vaccinated against HPV16 and 18 could become infected by other high-risk types. It may be that vaccinated women would be HPV tested at the

threshold age for screening and if HPV positive, proceed to cervical cytology. Screening will also be required for unvaccinated women. Licensing of prophylactic HPV vaccines by the European Medicines Evaluation Agency is expected late 2006 or early 2007.

5. Conclusion

The Cervical Screening Programme has made enormous strides and continues to incorporate evidence-based advances. A great deal of effort has resulted in a quality-assured programme, regarded by some as the best in the world, yet accessible to all women in this country, although a significant proportion still do not take up the invitation. It seems likely that, despite expected preventative vaccine programmes coming on stream within 10 years, cervical screening is likely to be required for several decades yet.

References

1. Papanicolaou GN, Traut HF. The diagnostic value of vaginal smears in carcinoma of the uterus. *Am J Obstet Gynecol* 1941;42:193–206.
2. Fidler HK, Boyes DA, Worth AJ. Cervical cancer detection in British Columbia – a progress report. *J Obstet Gynaecol Br Commonw* 1968;75:392–404.
3. Wilson JMG, Jungner G. *Principles and Practice of Screening for Disease*. WHO Public Paper 34. Geneva: WHO; 1968.
4. Meisels A, Fortin R. Condylomatous lesions of the cervix and vagina. I. Cytologic patterns. *Acta Cytol* 1976;20:505–9.
5. Boyer SN, Wazer DE, Band V. E7 protein of human papillomavirus-16 induces degradation of retinoblastoma protein through the ubiquitin–proteasome pathway. *Cancer Res* 1996;56:4620–4.
6. Schefner M, Werness B, Huibregtse JM, Levine AJ, Howley PM. The E6 oncoprotein encoded by HPV 16 and 18 promotes degradation of p53. *Cell* 1990;63:1129–36.
7. Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskeivaidis E, *et al*. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *Lancet* 1997;349:978–80.
8. Luesley DM, Leeson SC, editors. *Colposcopy and Programme Management: Guidelines for the NHS Cervical Screening Programme*. NHSCSP Publication No 20. Sheffield: NHS Cancer Screening Programme; 2004 [www.cancerscreening.nhs.uk/cervical/publications/nhscsp20.pdf].
9. Peto J, Gillham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. *Lancet* 2004;362:249–56.
10. Cancer Research UK website [http://info.cancerresearchuk.org/cancerstats/types/cervix/mortality/].
11. Miller AB, Sankaranaryanan R, Bosch FX, Sepulveda C. Can screening for cervical cancer be improved, especially in developing countries. *Int J Cancer* 2003;107:337–40.
12. Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselbad V, Hickey JD, *et al*. Accuracy of the Papanicolaou test in screening for and follow up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med* 2000;132:810–19.
13. National Institute of Clinical Excellence. *Guidance on the Use of Liquid-based Cytology for Cervical Screening*. Technology Appraisal 69. London: NICE; 2003 [www.nice.org.uk/page.aspx?o=TA069guidance].
14. Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *Br J Cancer* 2003;89:88–93.
15. Manos MM, Kinney WK, Hurley LB, Sherman ME, Shieh-Ngai J, Kurman RJ, *et al*. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *JAMA* 1999;281:1605–10.
16. Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, *et al*. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* 2002;347:1645–51.
17. Harper DM, Franco E, Wheeler CM, Ferris DG, Jenkins D, Schuind A, *et al*. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004;364:1757–65.

18. Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, *et al*. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial *Lancet Oncol* 2005;6:271–8.

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