Cervical Screening: What is the Evidence to Support the Introduction of a National Cervical Screening Programme?

Syed Ian Nabeel Gilani

Introduction

Cervical cancer is the third most common cancer in women overall. It is an important cause of morbidity and mortality worldwide. It is estimated that at least 370,000 new cases are identified each year, with more than 80% occurring in the developing world[1]. Although the developed world only accounts for the remaining 20% of new cases, the incidence and mortality are by no means marginal. In the USA alone it is estimated that in the year 2000, there will be 12,800 cases of cervical cancer and the death of over 4,600 women[2]. Many countries have introduced mass screening programmes to tackle this problem and have been rewarded with decreases of as much as 90% in the incidence and mortality of cervical cancer[3,4,5]. The Republic of Ireland has conducted an opportunistic rather than mass screening programme. This has been proven ineffective in decreasing the overall mortality in women. Indeed, examination of data from the National Cancer Registry shows that there has been a steady *increase* in the incidence rate of cervical cancer in women since 1994, as well as an increase in the mortality/incidence ratio[6,7]. The aim of this paper is to provide evidence supporting the introduction of a national cervical screening programme, and to give consideration to the appropriate frequency of screening.

What is screening?

Screening is a means of accomplishing early detection of disease in asymptomatic people. To be successful, it has been suggested that a screening program incorporates most, if not all, of the following stipulations[8,9,10]:

1. The disease being sought should be reasonably common within the population being screened, and should cause significant morbidity and mortality which would be reduced by earlier detection.
2. There must be a test or a procedure that will detect the disease earlier than if the disease was detected as a result of development of symptoms.
3. The screening programme should be simple, cheap, reliable and acceptable to those being screened.
4. The false negative rate of the test or procedure should be low and the management of the false positive case should not result in the production of serious morbidity.
5. There must be methods and procedures for treating cases of the disease picked up upon screening.

In addition, a long natural history of the disease allows periodic screening and the identification of risk factors, in order to pinpoint a high-risk group. This allows concentration of resources when planning such a programme.

The natural history of cervical cancer

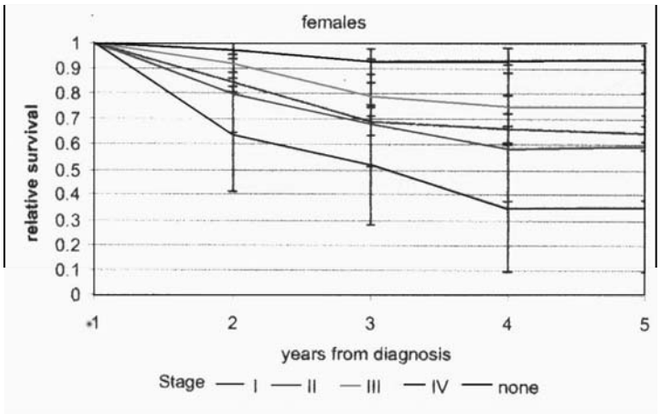
Squamous cell carcinomas account for 80-95% of cervical cancers; a small minority are adenocarcinomas. The natural history of cervical cancer remains uncertain. Sir John Williams was the first to describe the presence of non-invasive tissue resembling malignancy adjacent to the area of micro-invasive carcinoma in a hysterectomy specimen. Following the subsequent descriptions of dysplastic changes in the 1940s, it has become widely accepted that the majority of cases of invasive carcinoma of the cervix are preceded by a pre-cancerous stage. This pre-cancerous stage was originally thought to represent a continuum of change and was divided correspondingly by a variety of descriptive systems: the Bethesda System of atypical squamous cells of undetermined significence (ASCUS) and low/high grade squamous intraepithelial lesion (L/HGSIL); the Richart System of cervical intraepithelial neoplasia (CIN) grades 1 to 3 and condyloma; the Reagen (WHO) system of atypia and mild/moderate/severe dysplasia; the Papanicolaou System of grades I to III.

More recently the theory of a continuum has been challenged. The process seems to be a series of discrete events commencing with the sexual transmission of a carcinogen[11]. Epidemiological studies have suggested the Human Papilloma Virus (HPV) as the primary infectious agent[12,13] which is further corroborated by the detection of HPV DNA in the majority of cellular genomes of invasive cervical carcinomas[14]. However, this remains to be demonstrated by direct infection. It is probable that the HPV infection is merely one of a number of contributing factors. Other putative cofactors include genotype HLA DQw3 and smoking.

The pre-cancerous lesions can persist, regress or progress to an invasive malignancy. The average time for progression of CIN 3 to invasive cancer has been estimated as 10 to 15 years based on the mean age of diagnosis of these two conditions[8,15] and occurs most frequently in those above 60 yrs of age[6].

A small subset of rapidly progressive cervical cancers has been seen, which are diagnosed within three years of a confirmed negative Pap test. These tumours tend to occur in younger women of higher socio-economic status when compared to a control cervical cancer group, and one third of these cancers are adenocarcinoma of endocervical origin rather than of squamous origin.

Figure 1: Illustrating the variation in 5 year survival rates in different stages of cervical cancer (95% confidence interval)[6]



Analysis of data indicates that survival from cervical cancer appears to be directly related to the stage of disease at diagnosis[6,7], with a 5 year relative survival rate of 93-94% for stage I cancer (see Figure 1). Early detection should therefore cause a decrease in the mortality from cervical cancer.

The pap smear and national screening

The Papanicoloau (Pap) Smear is a means of examining the cervix using exfoliative epithelial cytology. It has been introduced in many countries without conclusive evidence of its effectiveness from randomised trials. Its widespread acceptance makes the possibility of testing the efficacy of cervical cytology by randomised trials remote, never mind ethically questionable. Nevertheless, there is substantial evidence from observational studies of the decrease in the incidence and mortality from cervical cancer in several large populations following the introduction of well-run screening programs,[3,4,16,17,18,19,20] the greatest of which have been in those countries that instituted national screening programmes.

The Scandinavian countries were amongst the first to institute mass organised screening programs and have shown the greatest decrease in incidence and mortality[3,16,17]. In Iceland screening was commenced in 1964 with women being screened every two or three years and, by 1977, there was a decrease in the mortality rate of 80%. In Finland, screening commenced in the early 1960s, and by the 1980s, there was a decrease in the mortality rate of 50%. The introduction of screening programmes in the USA has resulted in a fall in mortality of 50% over 23 years[14].

Screening in Canada began in 1949 with the implementation of an organised or mass-screening programme in British Columbia. From here screening programmes spread to the remainder of the country, however the majority of these were implemented in an opportunistic rather than organised fashion. By 1992 British Colombia was seen to have a lower mortality rate than the rest of Canada[21].

In Aberdeen, in the Grampian region of Scotland, systematic screening was instituted in 1960, practice by practice. It was directed at married women between the ages 25 and 60 years of age, the group that presented with the highest risk of invasive disease at that time. In 1982 a computerised call and recall system became available, where all women registered within the National Health Service were identified by regional age-sex data and were invited for their first smear and subsequent smears. By 1992, only 8% of the women aged 21 to 60 years remained unscreened. Data analysis from the Grampian region has shown a substantially greater fall in the incidence and mortality of invasive cancer compared with the rest of Scotland, where such organisation did not take place[20].

In England the number of smears taken rose continuously between the mid-1960s and the end of the 1980s. Analysis has shown that over this period of time the overall incidence of invasive disease remained relatively stable, while the mortality fell at a steady rate of 1.5% each year[22]. In 1988 a national call and recall system was introduced, which led to a doubling of the coverage of the target population by 1994. This resulted in a marked change in the incidence and mortality rates, with rates falling by 35% and 40%, respectively (see Figures 2 and 3). This was further confirmed by a similar analysis of national, age and mortality specific, cancer registration data. Interestingly, this showed that the reduction had been confined to squamous cell carcinoma, the commonest form of the disease, whereas the adenocarcinoma rates continued to rise. Four new studies have now been initiated to investigate the effectiveness of the Pap smear in the prevention of adenocarcinoma.

Is the pap test the best method of detection?

Although most countries have focussed upon cytological screening programmes there are other means of detection available, and it is prudent to compare these with the Pap smear. The various other techniques of detection are:

1. Visual inspection using a speculum and light source alone can be used. However, the disadvantage of this method is that it most easily identifies invasive cancer which, although in the early stages carries a good five-year prognosis, is a stage later than current programmes target, and is more difficult and costly to treat[1].

2. Aided Visual Inspection (AVI) involves the use of a simple magnifying lens to view cervices, which have been treated with acetic acid solution to highlight the abnormal tissue. A large prospective study of 10,934 women in Zimbabwe showed the sensitivity of AVI to be as high as 76-77%, compared to 44.3% for cytology[23]. However, AVI had a much lower specificity (64.1%) than cytology (90.6%), and therefore would be a greater cost to the system, and to the patient, in terms of false positives.

3. HPV DNA Sampling (Hybrid capture tests – HCT) identifies the presence of carcinogenic HPV based on a signal that can be generated by various HPV types, including HPV 16 and 18, which are more commonly associated with invasive dis-

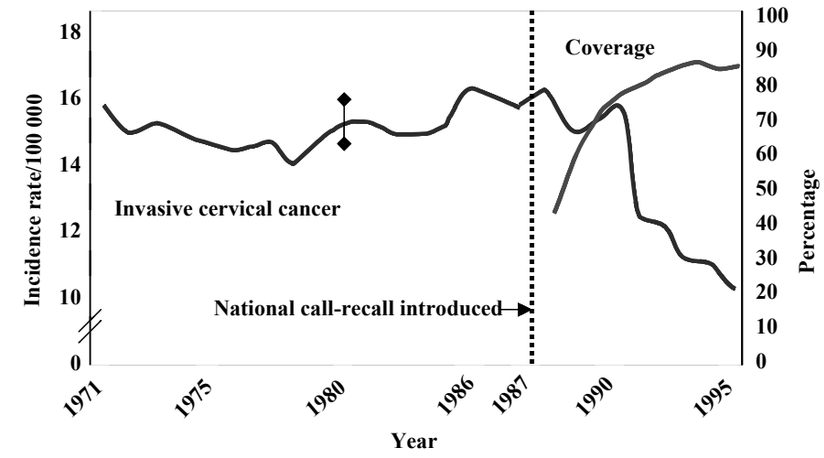
ease. A recent study found a higher sensitivity in the detection of CIN 2 and 3, with the combination of Pap and HCT when compared with Pap alone. However, the same study also found a significant decrease in specificity.

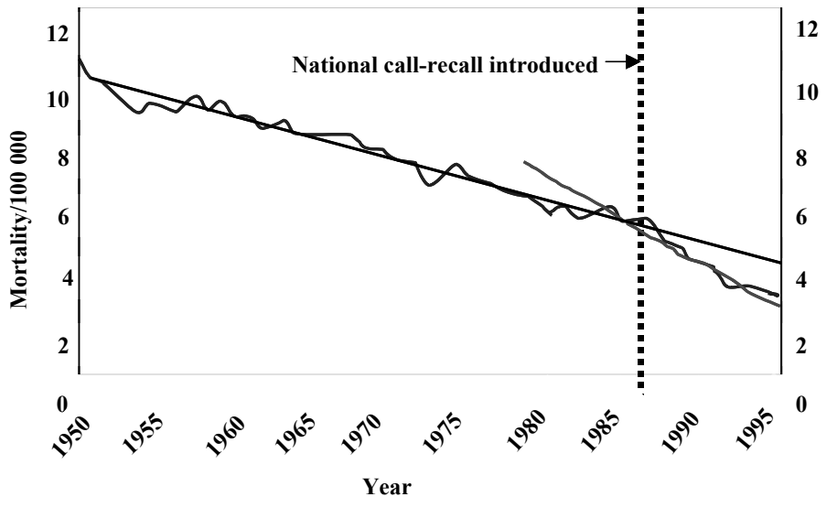
At this time, for those countries able to afford it, the Pap smear still remains the most effective means of detection, in terms of morbidity and cost-benefit. HCT sampling has much potential as a screening tool, especially as an adjunct to the Pap smear, or as a screening tool in woman with ASCUS (atypical squamous cells of undetermined significance). However, larger randomised trials and economic models must be carried out before its actual effectiveness, as a screening tool, can be determined[24].

Targeting of resources

Once it has been accepted that mass screening is worthwhile, then it is important to decide who should be screened and how often screening should be performed. There is no doubt that screening programmes are very expensive, costs in England being over £200 million per annum. At a time when rationing plays a large part in health economics, public health departments must decide the most effective way of expending resources.

The frequency of screening varies from country to country. In America, the College of Obstetricians and Gynaecologists suggest that women are screened annually, and many are screened more often. In Scandinavian countries, the policy has been more conservative, with screening recommended at three to five year intervals. In Britain, screening is organised on a regional basis for woman aged 20 yrs to 64 yrs, on a maximum of a five yearly cycle; however most regions screen three yearly. In the Grampian region, case control studies showed that the longer the time since the last negative smear, the higher the risk of invasive cancer and similarly, a higher risk of invasive cancer in those who had never been screened[20]. Screening every 2 to 3 years, however, has not been found to increase the risk of finding invasive cervical cancer significantly above the risk expected with annual screening,[25,26]as was further corroborated by a recent large multi-centre cohort study in the USA[27]. This demonstrated that, in smears performed three years after normal cytology, the incidence of HGSIL (high grade squamous intraepithelial lesion) or worse was uncommon, and that the incidence rate, when it occurred within this time frame, was unre-





Figures 2 and 3:
The changes in the age-standardised incidence and mortality in England[21]

lated to the time since the last smear.

Mathematical simulations of the presumed natural history of cervical cancer have been used to try to devise an optimal screening programme. One such study predicts a saving of resources of up to 25% for smear tests and 18% for colposcopies when withdrawal occurs at the age of 50 yrs, as compared to 64 years of age[28]. It should be noted that the risk of cervical cancer does not disappear in this older age group, however it becomes increasingly less cost effective in those who have had constantly negative smears; similarly this applies in those women under the age of 20 yrs.

Another model compared the cost effectiveness of increasing compliance in the population, compared with more frequent smears. It was estimated that, with a screening interval of three years, increasing compliance from 70 to 80% led to a reduction of cervical cancer from 2.1 to 1.6 cases per 10,000 women aged 18 and above. It required an increase of only 260 in the annual number of smears and 2.4 in the annual number of colposcopies per 10,000 adult women. On the other hand, if compliance remained fixed at 70% and the screening interval was reduced to one year, the incidence of cervical cancer only fell from 2.1 to 1.9 cases per 10,000 adult women and required an increase in 3240 in the annual number of smear tests and 9.3 in the annual number of colposcopies per 10,000 adult women[29].

In general terms, in order to make the greatest impact on cervical cancer mortality, it is prudent to target the higher risk groups of the population, e.g. the lower socio-economic groups, other minority groups and those with higher risk of HPV infection. It has been suggested that the first smear should be taken within two years of commencement of sexual activity. Once there have been two negative smears then smears should be taken every three to five years until the age of 60, after which it is no longer necessary to have a smear if all others have been negative. In a woman presenting at 35 yrs or later, the second smear should be performed within one year to pick up false negatives, and then she should have three to five-yearly smears. If abnormal smears have occurred, screening should be carried out more frequently, six monthly or annually, depending on advice from the local cytology unit. High risk women – including those with previous abnormal smears, those who commenced intercourse under the age of 17 yrs or with multiple partners, those who have had genital herpes infections and those with possible genital warts – should probably have annual smear. Further resources should being spent in maximising compliance.

Limitations of cervical screening

False negative smears can arise when a woman is deemed as being without cervical abnormality, when she actually has abnormal cells in the cervix. This can be due to the limitations of the test itself, as already discussed above (it is minimised when the sensitivity is maximal). However, it may occur in one of three stages once a woman has decided to undergo a routine smear: during the actual taking of the sample, during the preparation of the slide and in the actual reading of the smear in the laboratory. It has been shown that approximately two-thirds of false negatives occur as a result of sampling (taking the sample and preparation of the slide), and the remaining third from detection error[30].

Extensive reviews have been undertaken of the correct technique of sampling, not least the use of appropriate specula (brush tip vs. Ayre's spatula)[31]. Recent focus has centred on the detection error, perhaps in part due to the media coverage of prominent cases[32]. Most countries with mass screening programmes have methods of quality control, be it full rescreening of all smears; partial rescreening, targeted/directed rescreening or rapid rescreening.

Automated and semi-automated devices have been developed to address the screening errors related to slide preparation and detection. These include automated, liquid-based slide preparations, (Thinprep and Autocyte Prep), designed to provide more representative cell samples of evenly dispersed cells, and automated screening devices for the primary screening and quality control rescreening of women whose previous results were negative. Though much work needs to be done in assessing the cost-benefit of such devices, they may provide a further means in improving the effectiveness of cervical screening in the future.

Conclusion

Cervical screening has been shown to have a clear effect on the incidence and mortality of cervical cancer and the debate no longer remains as to whether or not to screen a population of women. However, the question remains of how to most efficiently screen that population with the resources available.

To date the Pap smear appears to be the most cost-effective method of detecting cervical precancer and although HPV testing may prove to be a useful adjunct in the future, at the moment there is insufficient data to advocate its routine use.

The greatest decreases in incidence and mortality rates from cervical cancer have been seen in those areas where mass screening programmes were established. Where opportunistic screening methods have been employed, screening has failed to produce a sustainable fall in incidence and mortality rates, while in areas where both mass screening and opportunistic screening have been employed, mass screening has been seen to be superior.

Mass screening has been shown to have the greatest impact on mortality when those of greatest risk are targeted. Economic modelling has indicated screening to be most cost-effective when there is a three-year screening interval and resources are concurrently spent to maximise compliance. Screening is only effective when there is appropriate follow-up. This can best be achieved with a call-recall sys-

tem.

Limitations in screening can be minimised with the introduction of systems of quality control, including the use of the correct sampling technique, correct preparation of slide, and in improved detection. This may be aided with the use automated and semi-automated devices in the future. Such systems of quality control are difficult to introduce in areas of opportunistic screening.

Considering the recent increase in incidence rate and mortality/incidence ratio in Ireland with the current opportunistic screening policy, it would seem prudent to recommend a change of policy to one of organised mass Pap screening. Such a screening programme should incorporate an appropriate call and recall policy of three-yearly intervals for those women with a normal smear, with resources being concentrated on maximising compliance, especially in those at highest risk.

References

1 National Cervical Cancer Coalition. Worldwide Cervical Cancer Issues, at web address: http//www.nccc-online.org/world-cancer.htm

2 Greenlee RT, Murray T, Bolden S *et al.* Cancer statistics: 2000. *Ca-A Cancer Journal for Clinicians* 2000;50(1):7-33.

3 Laara E, Day NE *et al*. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987;1(8544):1247-1249.

4 Miller A, Lindasy J. *et al*, Mortality from cancer of the uterus in Canada and its relationship to screening for cancer of the cervix, *Int J of Cancer* 1976;17(5):602-612.

5 Sigurdsson K. Effect of organised screening on the risk of cervical cancer: evaluation of screening activity in Iceland, 1964-1991. *Int J of Cancer* 1993;54(4):563-570.

6 Cancer of the Uterine Cervix, National Cancer Registry, Ireland, 1996.

7 Cancer in Ireland 1997: A Summary, National Cancer Registry, Ireland 1997.

8 McPherson A, Anderson A, Women's Problems in General Practice, Oxford University Press, 1986, 9:179-203.

9 Wilson JMG, Jungner G, Principles and practice of screening for disease, Geneva World Health Organisation, 1968; WHO public health paper 34.

10 Sackett DL, Straus SE *et al.* Evidence based medicine: How to practice and teach EBM, Churchill Livingstone, 2nd Edition, Edinburgh, 2000.

11 Brinton LA. Epidemiology of cervical cancer–overview. IARC Scientific Publication, 1992;119:3-23.

12 Ley C, Bauer HM *et al.* Determinants of genital human papillomavirus infection in young women. *Journal of the National Cancer Institute.* 1991;88(14):997-1003.

13 Schiffman MH, Bauer HM *et al.* Epidemiological evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia**,** *Journal of the National Cancer Institute* 1993;85(12):958-964.

14 Reeves WC, Rawls WE, Brinton LA. Epidemiology of genital papillomaviruses and cervical cancer. *Reviews of Infectious Diseases.* 1993;11(3):426-439.

15 Barron BA, Richart RM. Statistical model of the natural history of cervical carcinoma II: Estimates of the natural transition time from dysplasia**,** *Journal of the National Cancer Institute* 1970;45(5):1025-1030.

16 Christopherson WM, Lundin FE, Mendez WM, *et al.* Cervical cancer control: a study of morbidity and mortality trends over a twenty-one-year period. *Cancer* 1976;38(3):1357-1366.

17 Johannesson G, Geirsson G, Day N. The effect of mass screening in Iceland, 1965-1974, on the incidence and mortality of cervical carcinoma. *I J of Cancer* 1978;21(4):418-425.

18 Quinn M, Babb P, Jones J. *et al.* Effect of screening on incidence and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ* 1999;318:904-908.

19 Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. *BMJ* 1999;318:1244-1245.

20 Macgregor JE, Campbello MK *et al.* Screening for cervical intraepithelial neoplasia in north east Scotland shows fall in incidence and mortality from invasive cancer with concomitant rise in preinvasive disease. *BMJ* 1994;308:1407-1411.

21 Stuart GCE, Parboosingh J. Implementation of Comprehensive Screening for Cervical Cancer in Canada: Impediments and Facilitators, *J SOGC* 1996;18:1241-1250.

22 Deacon JM, Yoon JSL *et al.* Cervical Cancer Screening and National Trends in Incidence and Mortality, St. Bartholomew's Hospital NHST, The Epidemiology Team, CRC.

23 Gaffikin I, Blumenthal PD *et al.* Visual inspection with acetic acid for cervical cancer screening: Test qualities in primary care setting, University of Zimbabwe: JHPIEGO Cervical Cancer Project. *Lancet* 1999;353:869-873.

24 Meijer CJ, Rozendall L *et al.* Human papillomavirus and screening for cervical cancer: state of the art and prospects, *Ned Tijdschr Geneeskd* 2000;144(35):1675-1679.

25 International Agency for Research on Cancer Working Group on Evaluation of Cervical Cancer Screening Programmes**,** Screening for Squamous Cervical Cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies, *BMJ* 1986;293(6548):659-664.

26 Kleinman JC, Kopstein A. Who is being screened for cervical cancer? *American Journal of Public Health* 1981;71(1):73-76.

27 Saway GF, Kerlikiwske K *et al.* Frequency of cervical smear abnormalities within 3 years of normal cytology. *Obstetrics and Gynaecology* 2000;96(2):219-223.

28 Sherlaw-Johnson C, Gallivan S, Jenkins D. Withdrawing low risk women from cervical screening programmes: mathematical modelling study. *BMJ* 1999;318:356-361.

29 Jenkins D, Gallivan S, Sherlaw-Johnson C. Compliance in screening programmes: High compliance essential in cervical screening programme. *BMJ* 1994;308:625-653.

30 McCrory DC *et al.* Evaluation of Cervical Cytology: Evidence Report/Technology Assessment Number 5, AHCPR, 1999; Publication No. 99-E010.

31 Hirsh PM, Lilford R *et al.* Efficacy of cervical smear collection devices: a systematic review and meta-analysis. *Lancet* 1999;354:1763-1770.

32 Dyer C. Health authority loses cervical smear appeal. *BMJ* 1999;391:1391.