EDITORIAL

How frequently should cervical screening be conducted – important new evidence

It is accepted that Pap smear screening has greatly reduced mortality from cervical cancer. The evidence for efficacy is based mainly on a decline in incidence of cervical cancer documented following the staggered introduction of screening in several populations together with the absence of a decline in comparable populations that remained unscreened.[1–3] But these data provide no evidence on screening frequency. How should we determine the appropriate screening interval for cervical cancer?

Case control studies provide the best evidence. Women with invasive cervical cancer (cases) will be less likely to have had a recent cervical smear than age-matched controls. From a case-control study odds ratios can be calculated that indicate the reduction in risk of invasive cancer according to the time elapsed since the last negative smear, relative to the risk in women who have never been screened. Until recently only one large study has been available - an international study conducted by the IARC based mainly on women aged 25–64 years in Scandinavian and Canadian centres.[4] This study produced the estimate that yearly screening reduces the incidence of invasive cervical cancer by 94%, three yearly screening by 91%, five yearly screening by 84%, and 10 yearly screening by 64%. It provided the basis for present policy – that yearly screening is unnecessarily frequent and three yearly or five yearly screening is best.

Two new studies, from Britain and America, have been published recently, and they provide important additional evidence on screening frequency.[5,6] The British study,[5] like the IARC study was based on about 1300 cases. But it differed from the IARC study in that the age range was wider (20–69), adenocarcinomas were included as well as squamous cell carcinomas, and microinvasive tumours (stage 1A) were excluded. Perhaps through these differences in design, the new study was able to show an important effect of age on screening frequency.

A negative smear indicated protection against invasive (stage 1B+) cervical cancer for a shorter period in younger women than older women. In women aged 20–39 risk was two thirds lower than in unscreened women two years after the last negative smear but reverted to that in unscreened women after four years. Risk was two thirds lower after four years in women aged 40–54, and after six years at age 55–69. This has important implications for screening because the incidence of invasive cancer is relatively constant across a wide age range (British data show that about a quarter of all cancers occur in each of the age groups 25–39, 40–54, 55–69 and ≥70+ years[5]).

The estimates of screening efficacy according to age are summarised in Table 1. The results allowed the authors to make the following conclusions:[5]

◆ Women ≤25 years should not be screened (less than 1% of all invasive cancers occurred in women under 25, and the false positive rate is high in this age group)

Table 1 Estimates of the percentages of invasive cervical cancers preventable by screening according to age and screening frequency[2]

Age (y)	Screening frequency		
	Yearly	3 yearly	5 yearly
20–39	76%	61%	39%
40–54	88%	84%	73%
55–69	87%	87%	83%

◆ Women aged 25–49 should be screened every three years (and there may have been some justification for recommending more frequent screening)
◆ Women aged 50–64 years should be screened every five years
◆ Women ≥ 65 years need not be screened if they have had a previous negative smear past the age of 50

The strong effect of age makes biological sense. Cervical cancer is initiated by a sexually transmitted infection, and most sexually transmitted infections occur in younger women. A rapidly growing tumour might therefore be expected to reach clinical presentation before the age of 40, and in a rapidly growing tumour the interval between a negative smear and invasive cancer would be relatively short. Cancers that grew more slowly would be characterised both by a longer interval between a negative smear and invasive cancer, and by an older age at clinical presentation.

It is interesting to note that it was variation in screening practice within a country that made these two case-control studies possible. A similar endeavour in relation to breast cancer screening would be less successful because national screening programmes invite women at fixed intervals (and rightly so); there is relatively little screening at irregular intervals, or one-off opportunistic screening.

The authors of the British study discuss some interesting methodological issues with respect to studies of this type.[5] One issue is the use of women who have never been screened as the reference group. In this group the risk of cervical cancer was statistically significantly lower than that in women who were screened occasionally. This observation could be interpreted as indicating that unscreened women may include a fair proportion of women at genuinely low risk (because of little or no sexual contact for example) who declined screening because they knew this. The authors prefer the interpretation however that the women screened occasionally are at particularly high risk (for example women who attend STD clinics and are screened only at the clinic). The authors also discuss the problems that two or more previous negative smears provide a more secure baseline than one negative smear (which may have been a false negative), and the difficulty in some circumstances of determining whether a smear was taken for screening purposes.

The new American study has reinforced the important effect of age.[6] It was based on data collected by the Center for Disease Control and Prevention (CDC), with about 500 cases of invasive cervical cancer. Set against the conservative American practice of annual cervical screening, it did not even consider the effect of five yearly screening. But projections from the data (table 4 of the paper[6]) showed that among women with at least one previous negative Pap test, annual screening had a negligible advantage over three yearly screening in preventing invasive cervical cancer in women aged 45–64, but a more pronounced advantage in younger women.

The results of both these new studies are robust. They warrant a change in national screening policy to take account of the effect of age on screening performance.

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References

1 Screening brief: Cervical cancer. *J Med Screen* 1994;**1**:255
2 Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987;**1**:1247–9
3 Austoker J. Cancer prevention in primary care. *BMJ* 1994;**309**:241–8
4 IARC 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**:659–64
5 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
6 Sawaya GF, McConnell KJ, Kulasingam SL, Lawson HW, Kerlikowske K, Melnikow J, *et al*. Risk of cervical cancer associated with extending the interval between cervical-cancer screenings. *New Engl J Med* 2003;**349**:1501–9