PERGAMON

European Journal of Cancer 38 (2002) 321–326

European Journal of Cancer

www.ejconline.com

Editorial Comment

The (in)efficiency of cervical screening in Europe☆

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Received 26 July 2001; received in revised form 30 September 2001; accepted 17 October 2001

In 1980, Matti Hakama electrified cancer epidemiologists attending scientific sessions on Trends in Cancer Incidence: Causes and Practical Implications, linked to the biennial meeting of the International Union Against Cancer in Oslo. There, he succinctly demonstrated the impact of the organised screening programme for cytology screening in Finland, and also in Iceland and to a lesser extent Sweden [1]. In strong contrast was the lack of a reduction in incidence in Norway, where no organised programme had been introduced, and the relatively poor impact in Denmark, where a programme had by then been initiated in only one county.

Although, somewhat to my surprise, I had recently convinced myself [2] and others [3] that the British Columbia programme in Canada had had a major impact, the extent of the impact in Finland startled me and, in practice, that demonstration largely brought discussion on whether cervical screening worked to an end. The success of the Finnish programme was even more impressive as it was based on 5-yearly screening of women aged 30–60 years, thus avoiding the trap of concentrating resources on the overscreening of young women, who have a low incidence of the disease. The Finnish investigators have continued to publish lessons from their programme, importantly demonstrating that it is the smears from the organised programme that have the greatest impact, while the spontaneous (or opportunistic) smears taken outside the programme have little impact, largely because they are taken too frequently from the same, younger age group [4]. It is important to recognise that the conclusion was based on an analysis of the impact upon invasive cancer, the correct endpoint. In contrast, an analysis in neighbouring Sweden reached the opposite conclusion [5] because they based their estimate of efficiency on cervical precursors, overlooking that detection of those not destined to progress, especially younger women, cannot be regarded as a success, but a failure of the programme.

It was somewhat disappointing to learn from the Special Issue of the *European Journal of Cancer* published towards the end of 2000 [6] that these fundamental lessons from Finland have not yet been understood by the decision-makers in many European countries. Too many countries are only now belatedly beginning to accept the European guidelines [7] and initiate organised programmes, some only as pilot projects [8]. Three countries (Austria, Germany and Luxembourg) have still not made any attempt to curtail the wasteful, inefficient tendency of gynaecologists to perform annual smears, even though the cost-ineffectiveness of this approach has been recognised for over 15 years [9]. Indeed, with annual smears, the lifetime probability of having an abnormality is substantial, whereas only approximately 1–2% of women in these countries are destined to develop invasive cervical cancer if unscreened.

Although cervical cancer used to be much more common in Europe, and still is in many developing countries, the lifetime risk of the disease, even in high-incidence countries, rarely exceeds 5%, approximately half that of breast cancer in countries with a high incidence of that disease. Now, in most of Western Europe except Denmark, the lifetime risk approximates to 1–1.5%, although it would probably be much higher in many countries if it was not for screening. Thus, it is perhaps not surprising to learn that in England, the cost-effectiveness of cervical cancer screening per life-year estimated to be saved is less that than of breast screening [10]. This is so even though both are offered in national organised programmes, and cervical cancer screening is only recommended every 3–5 years (for breast screening it is every 3 years). The reason, of course, is that in spite of the lower benefit in terms of

☆ Editorial Comment on the Special Issue "Cervical Cancer Screening in the European Union".

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PII: S0959-8049(01)00374-4

proportional mortality reduction for breast compared with cervical cancer screening, the breast screening programme is deliberately concentrated on those with maximum benefit demonstrated in trials (50–64 years), while the cervical programme also includes women aged 20–49 years. Table 1 shows the lack of correlation between the screening frequency and young women screened, with the present status of cervical cancer and all uterine cancer mortality for all ages. As Levi and colleagues [11] pointed out, because of the varying proportion of cancer of the cervix deaths that are assigned to uterus unspecified across countries, conclusions cannot be drawn from cervical cancer alone. Most of the differences in Table 1 are probably due to differences in the underlying risk of the disease, with Denmark remaining at a higher level than other countries. However, it is striking that the recommended annual screening in Germany and Austria is no more successful than the organised 5-year screening in Finland and, more recently, The Netherlands.

Planners in all European countries now need to address several issues. These include:

- How to ensure their organised programmes work most efficiently
- How to reduce opportunistic screening
- The value in changing to 5-yearly re-screening
- What age to start screening

Table 1
Average annual age standardised mortality from cervical and all uterine cancers (per 100 000), 1994–1996, related to the recommended screening policy in countries of the European Union

Country	Mortality from:		Screening policy	
	Cervical cancer	Uterine cancer	Age screened (years)	Frequency
Austria	2.7	6.8	20+	Annual
Belgium[a]	2.1	5.2	25–64	3-yearly
Denmark	3.9	7.4	23–74	3-yearly
England	3.1	5.2	20–64	5(3)-yearly
Finland	1.1	3.5	30–60	5-yearly
France	1.5	4.9	25–64	3-yearly
Germany	2.9	5.8	20+	Annual
Greece[b]	1.0	3.2	25–64	2-3 yearly
Ireland[c]	3.3	5.5	25–60	5-yearly
Italy	0.8	4.7	25–64	3-yearly
Luxembourg	1.3	4.8	15+	Annual
Netherlands	1.7	4.0	30–60	5-yearly
Portugal[d]	2.6	6.8	20–64	3-yearly
Spain[d]	1.8	4.8	25–65	3-yearly
Sweden	1.3	4.4	23–60	3-yearly[e]

[a] Mortality for 1994 only. Policy relates to the Flemish region of Belgium.
[b] Policy relates to pilot studies.
[c] Policy planned for one region of the country.
[d] Policy for one region of the country only.
[e] 5-yearly at ages 50–60 years.

- What age to stop screening
- Whether to move from cytology to one of its competitors.

I shall discuss each of these issues, drawing heavily on the understanding we now have about the natural history of the precursors identified by cytology [12–14].

1. How to ensure organised programmes work most efficiently

It is clear that very few countries have made a sufficient investment to ensure the success of their organised programmes, the exceptions being England since 1988, Finland since 1963 and The Netherlands since 1996. There are probably many reasons for this, including a lack of political will, a lack of understanding by the decision-makers as to how an investment now will reap benefits in the future and opposition to the idea by some health professionals who feel threatened. It is sometimes unfortunate that the programme is managed by professionals who stand to gain by promoting more (frequent) screening, rather than being managed by professionals who are adequately trained in public health. The epidemiologists who have already invested much time on this in other countries need to be re-enforced in their efforts and given more managerial responsibility for the programme. Hopefully, the data published in the Special Issue of the *European Journal of Cancer* [6] will do much to buttress their views.

2. How to reduce opportunistic screening

Here, in addition to the special interests of those promoting such screening, there is the problem of a lack of understanding of the screening process, and the natural history of the disease. Education of primary care practitioners and gynaecologists is also required. It is disheartening to learn that in Sweden, a country that is advanced in so many ways, there is a financial barrier to participating in the organised programme that does not exist for opportunistic screening [15]. The remedy here is obvious. There also needs to be more evaluation of the impact of organised versus opportunistic screening by epidemiologists, although using the correct endpoint, as already pointed out above.

3. The value in changing to 5-yearly re-screening

It is relevant that the countries that have the best organised programmes, and are being the most successful in achieving the desired impact, have all recommended 5-yearly screening (although in England some

areas, for reasons unexplained by Patnick [10], apparently offer 3-yearly screening). The original International Agency for Research on Cancer (IARC) model suggested that there was a benefit in moving from 5- to 3-yearly screening [9], although even then it was difficult to reconcile this with the success of the 5-yearly Finnish programme. The reason became clear when the authors of a re-evaluation of the British Columbia data [16] pointed out that, although the median duration for progression from carcinoma *in situ* to invasive cancer from the IARC study is of the order of 5–8 years, this includes within its computation screen-detected cancers whose prognosis is extremely good and who are affected by the lead time gained by screening. Correcting for such screen-detected cancers results in a computation of the median duration from their model from carcinoma *in situ* to invasive cancer of 15 years. The implication of this is that screening every 5, not 3 years, will give a 90% reduction in invasive cancer incidence and mortality in a high quality programme [17].

4. Age to start screening

There is no question that the maximum age-related benefit is derived from starting screening at the age of 35 years [18]. However, in the context of the greater perceived value of a young life than an older one, and the greater recent sexual activity of the young, this will clearly be too old for any European country to accept. The question takes on a particular poignancy when one contemplates the question of Schaffer and colleagues [19] as to whether screening women up to the age of 35 years is effective at all. At first sight, the trends in Fig. 1 of the paper of Levi and colleagues [11] would seem to provide an answer to the question, as their analysis clearly shows a decline in mortality for women age 20–44 years in several countries with organised programmes. However, that analysis is not definitive, as the numbers of deaths over the age of 35 years will vastly exceed those at ages 20–34 years. Nevertheless, the reductions in incidence at ages 25–34 years seen in Finland until recently (where organised screening commences at age 30 years) [20] must be due to a benefit in women screened under the age of 35 years.

It would not be surprising if the effect of screening was proportionally less at ages under 30 years than older. Those cases of invasive cancer that present in women in their twenties must have had a shorter natural history than those that present at older ages. Thus, they are likely to be more rapidly progressive, and more likely to slip through the screening net. Screening can not be 100% effective, even when it is designed to detect precursors as distinct from invasive cancer. It is conceivable that the resources required to detect early the few cases that could benefit from screening at younger ages may be so large that, in public health terms, the opportunity cost may be too great to justify screening at these ages. This would seem to be amenable to further evaluation. The available long-term incidence data for those countries with long running national or regional cancer registries are shown in Fig. 1(a) and (b) at ages 25–29 years and 30–34 years, respectively. There seems to be little impact of screening at ages 25–29 (Fig. 1(a)), the dominant effect, except for Finland, is an increase in incidence, presumably due to the increase in the prevalence of risk factors in young women. At ages 30–34 years (Fig. 1b), the three Nordic countries show a decline, reaching a plateau from approximately 1975–1980. However, the UK (Birmingham) shows a major increase until 1985, and then appears to plateau. The revitalised screening programme in England may be responsible for halting the rise in Birmingham, so there does seem to be an effect of screening at ages 30–34 years, but uncertainty remains regarding ages 25–29 years.

In practice, the countries that have decided to screen from the age of 25 years (a few from 23 years) have taken a pragmatic decision. Screening from the age of 15 years (as in Luxembourg) is clearly unjustified, screening from the age of 20 years needs reconsideration. It is of interest, however, that, in spite of the inference made in their 1999 paper that the age of initiating screening would not change in Finland [20], in 2000, Antilla and Nieminen [21] appear to have changed their mind. One wonders why?

5. Age to stop screening

Once again, it seems that many countries have failed to address this issue adequately. Those that have failed to introduce an upper age limit appear not to have recognised that beyond a certain age, women who have been adequately screened and always tested negative are at so low a risk of the disease that screening can be stopped. Many countries have decided that this age should be 60 years, a decision we initially took in Canada, although recognising that women who had never been screened over the age of 60 years should still be recruited into a programme, and remain in until they had had two negative smears [3]. Sufficient data from many programmes must have been accumulated to have another look at this issue. The question that should be addressed is what is the risk of subsequent development of invasive cancer in a woman who has had at least three negative smears and no positives in the last 15 years, when she has reached the ages of 45, 50, 55 and 60 years? I suspect there could be little difference, and that in each group the risk would be negligible. If I am right, we could stop screening well-screened women from the age of 50 years or even 45 years, and use these

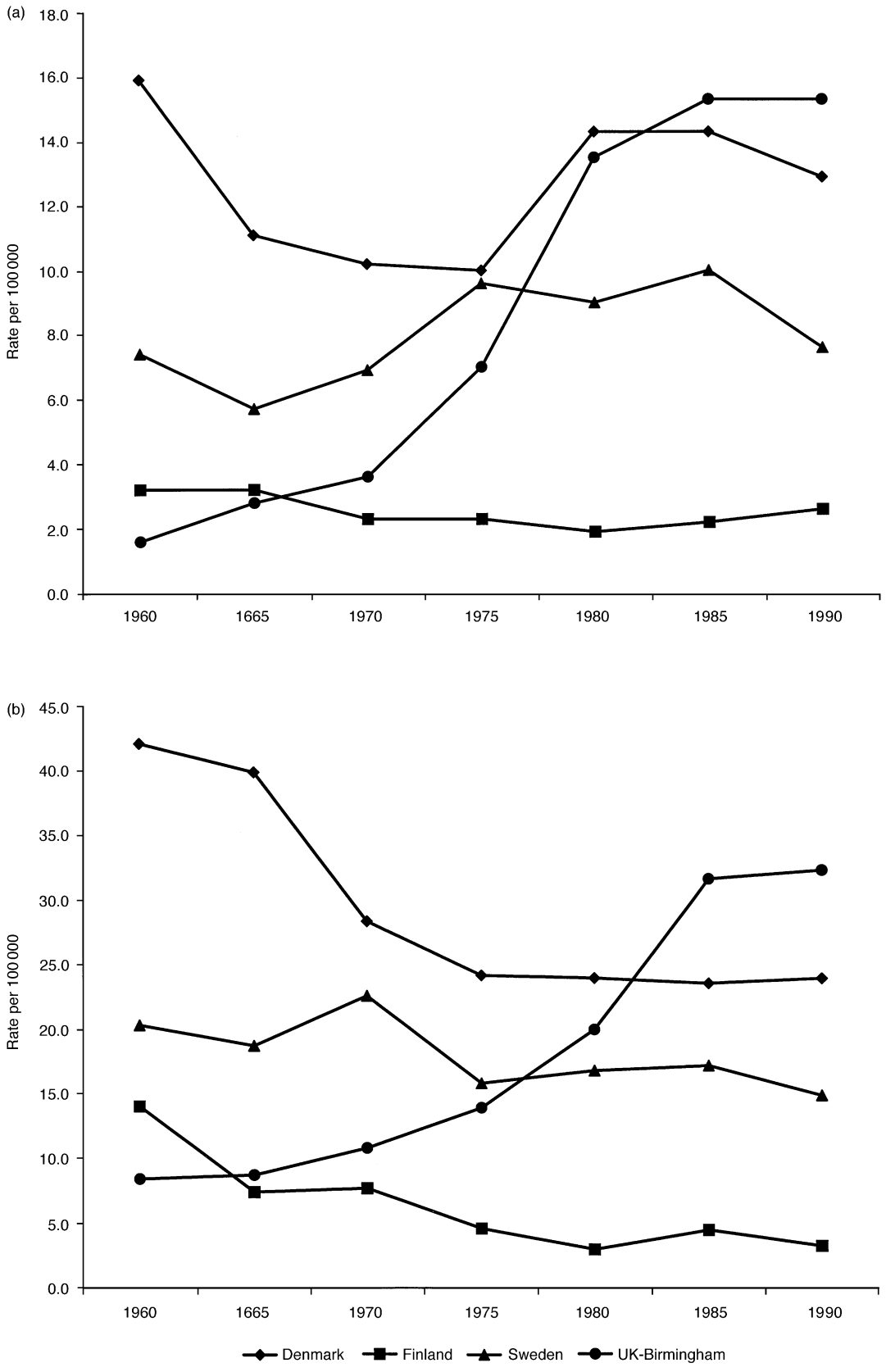

Fig. 1. (a) Trends in incidence of cancer of the cervix at ages 25–29 years in Denmark, Finland, Sweden and UK (Birmingham); (b) trends in incidence of cancer of the cervix at ages 30–34 years in Denmark, Finland, Sweden and UK (Birmingham) (source: *Cancer Incidence in Five Continents*, vols. I–VII).

resources to actively recruit those over the age of 50 years who have never been screened, or have lapsed from screening. It is among these women that the invasive cancers at older ages are occurring.

6. Whether to move from cytology to one of its competitors

This question would seem to be beyond the topics raised by the Special Issue, except for the fact that it is specifically raised by Franceschi and colleagues [22]. Visual inspection with acetic acid (VIA) has such poor specificity compared with cytology that it can be dismissed from consideration in Europe until such time that this problem is solved, as the circumstances that make it necessary to evaluate it in developing countries do not exist in Europe. Human papilloma virus (HPV) testing is another story, and it is already leading to increased costs in some laboratories, as it is being added to cytology. Although there may be value in HPV tests for triage of women with borderline lesions, in a special study in the United States (US), triage of women with low grade lesions with HPV was not valuable [23]. However, this conclusion requires confirmation in Europe because of different standards of cytological classification. Nevertheless, the major potential value for HPV testing will probably reside in identifying low risk women, who test negative to HPV over the age of 35 years, who will not need to be screened as frequently as their higher risk sisters [24]. However, we have to be cautious even among those who test HPV positive. The test has not solved one of the major problems with cytology; it has even less ability to discriminate between infections that result in the development of progressive cervical intraepithelial neoplasia (CIN) and those that do not (cytology in a good laboratory does have some discriminating power [14]). Yet far more women will experience a high risk HPV infection, mostly by their forties, than will ever develop cervical cancer. Unfortunately, even in those young women that harbour transitory infections, an abnormality is often detectable on cytology [25], thus leading to the risk of even greater over-treatment of women with lesions destined to regress than currently occurs with cervical cytology. Indeed, the detection of these lesions (often missed with cytology), has led to the impression that this test for HPV DNA is more sensitive than cytology. Yet it is likely that the apparent improved sensitivity is of little or no biological relevance, as what is being detected will have at least as great a propensity to regress, thus leading to even more functional over-diagnosis than currently occurs with cytology.

To overcome the disadvantages of both conventional cervical cytology and the HPV-DNA test, we require a test that indicates that an oncogenic HPV virus has already enhanced genetic instability and rendered infected cells susceptible to transformation, thereby facilitating the development of cancer. The ideal test in this respect should have the ability to detect those progressive cytological abnormalities that are caused by high-risk HPV infections and to discriminate them from transient low-grade lesions and those that only mimic morphological criteria of the onset of dysplasia or harbour HPV as an independent, but simultaneous, event. Such a test should have greater true biological sensitivity and specificity than cytology and could possibly solve two problems inherent to conventional cytology. It could be the solution to the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion (ASCUS/LSIL) dilemma since these categories represent mostly transient infections or in the case of ASCUS diagnostic uncertainty. The other problem that contributes to the low sensitivity of conventional cytology is overlooking and/or misinterpreting abnormal cells, a problem that also ideally should be overcome by a test that fulfills the criteria specified above. As I have recently commented elsewhere [26], to identify the minority of women with a high risk of progression we need a test for HPV that indicates the virus will exert its oncogenic potential in that woman, which probably means we should transfer our attention from the agent, to the host.

In conclusion, in most countries in Europe, a major investment is required to obtain the cost savings and major impact that an organised programme is providing in Finland, and also more recently in England. It is astonishing that countries that have accepted a responsibility of the State to provide health care are still, at the beginning of the new millennium, failing to take advantage of the knowledge gained from the research carried out on cervical cancer screening. The *European Journal of Cancer* is to be congratulated in devoting space to this important issue. I fervently hope that the next decade will see major advances everywhere in Europe.

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