Pergamon

European Journal of Cancer Vol. 31A, No. 12, pp. 2040–2043, 1995
Elsevier Science Ltd
Printed in Great Britain
0959-8049/95 $9.50+0.00

0959-8049(95)00457-2

Original Paper

In Search of the Best Upper Age Limit for Breast Cancer Screening

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The aim of this study was to determine the best upper age limit for a breast cancer screening programme. We used a model-based study using optimistic and pessimistic assumptions, concerning improvement of prognosis due to screen-detection and duration of the period of mammographic detectability, resulting in upper and lower limits for favourable and unfavourable effects. Under pessimistic assumptions, the balance between positive and negative effects of screening remains favourable up to an age of around 80 years. Under optimistic assumptions, this balance never becomes clearly negative with increase of the upper age limit of a screening programme. When including the costs in the analysis, the balance between effects and costs of increasing the upper age limit from 69 to 75 years is likely to be at least as favourable as intensifying a screening programme within the age group 50–69 years. A further increase leads to a markedly less favourable balance. Competing causes of death do not lead to missing net benefit for women up to at least age 80 years, but the disproportional rise of negative effects of screening with age in older women leads to a lower cost-effectiveness ratio than intensifying screening at ages 50–69 years.

Key words: aged, breast neoplasms, cost–benefit analysis, mammography, mass screening, quality of life
Eur J Cancer, Vol. 31A, No. 12, pp. 2040–2043, 1995

INTRODUCTION

SETTING UPPER and lower age limits for a mass screening programme for breast cancer must be well justified as breast cancer is an important disease in younger as well as older women. In the U.K. screening programme, women are invited for screening every 3 years between age 50 and 65 years [1]. In the Dutch programme, women are invited for screening every other year between 50 and 70 years of age [2]. In the U.S.A., most institutions which give advice concerning breast cancer screening do not give an upper age boundary [3].

The lower boundary of age 50 years has been justified by the published results of randomised trials which show a much lower (and statistically non-significant) reduction in breast cancer mortality for those who entered the trial under the age of 50 years as compared to women who entered at higher ages [4]. This difference in effectiveness can be explained by physical changes which occur around the time of menopause (such as radiographic density of the breast and tumour growth rate) and which influence detection rates and the earliness of detection by mammography.

There is no such clear-cut justification of an upper boundary. The relevant biology for this decision is complicated. Breast cancer mortality rates are higher in older women. Therefore screening of an older population can lead to more prevented breast cancer deaths than screening of a younger population. However, the number of life-years gained by preventing a breast cancer death by screening rapidly decreases with age of detection, because life expectancy decreases with age. Nevertheless, in the Netherlands, life expectancy of a 70-year-old woman is still 15 years [5].

The increasing rates for mortality from causes other than breast cancer leads to a higher probability of women dying from other causes in the lead-time period. As a consequence, the number of extra incident cases generated by screening relative to the number of prevented breast cancer deaths increases with age at screening. This unfavourable effect of screening also increases with longer lead time, which is roughly proportional to the duration of the preclinical period of mammographic detectability.

So, on the one hand, an equal amount of screenings at higher ages will lead to more prevented breast cancer deaths, while on the other hand, there is a less favourable balance between the positive and negative effects of screening.

The latest publication on the Swedish randomised trials [4] reports a point estimate for mortality reduction in the age group 70–74 years which is much lower than for the age group 50–69 years. Since there is no biological explanation for such a difference, and the number of cases involved is very small, it seems reasonable to explain this difference by random fluctuation. However, the present lack of another explanation should not lead to neglecting the possibility that breast cancer screening

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Revised 5 May 1995; accepted 27 Jul. 1995

does lead to a smaller improvement of prognosis over the age of 70 years [6].

This paper attempts to determine the best upper age limit for breast cancer screening, once the decision to organise a programme has been taken. The balance between favourable and unfavourable effects is considered, as is the balance between costs and effects. There are not many data available about the effects of screening for breast cancer in women older than 70 years. It is, therefore, not possible to give a precise assessment of what is to be expected from mass screening in older women. However, the determinants of such an upper age limit are identified and, on basis of the existing uncertainty concerning these determinants, margins of possible outcomes are set.

MATERIALS AND METHODS

The MISCAN model for underlying natural history of breast cancer and the impact of screening, which has been used for this analysis, has been described elsewhere [7]. The disease model is based on a three-stage division of the development of invasive breast cancer in which the stage reflects tumour size. A proportion of the invasive breast cancers is preceded by a screen-detectable ductal carcinoma *in situ* (dCIS). The screen-detectable stages have an exponentially distributed sojourn time with an age-dependent mean. Most model assumptions are identical to those used for the Dutch cost-effectiveness analysis which focused on screening between the ages of 50 and 70 years. This model reflects estimates of health effects and social costs of the primary process of screening, changes in diagnostic procedures, primary therapies, follow-up after treatment, metastatic disease, terminal illness and breast cancer mortality when a 2-yearly screening programme is carried out during a period of 27 years, after which time the maximum impact of screening on mortality is reached [8]. The assumptions which are specifically relevant for screening in older women have been studied in more detail by relating them to the results of trials which included women over the age of 70 years, that is, the study in Kopparberg/Östergötland [9], the Dutch pilot project of Nijmegen (unpublished data) and the BCDDP [10].

Model variants

Two main variants were used: the 'optimistic variant' which assumes no further increase in preclinical duration after the age of 65 years and the 'pessimistic variant' assumes a futher increase in preclinical duration with age which is extrapolated from the trend in younger age groups.

The model results have been integrated in one outcome measure: 5% discounted quality adjusted life years (QALYs) gained. The number of QALYs gained by a screening programme is calculated by attributing utilities to each health state that is relevant for breast cancer screening and by multiplying these utilities with the number of life years in each of these health states. The difference between the total number of QALYs in a situation with a screening programme and the total number of QALYs in the situation without screening is the number of QALYs gained [11]. In this way, not only the effects of screening on mortality are taken into account, but also the impact of diagnostic procedures, primary therapy, follow-up after treatment, metastatic disease and terminal illness.

For demonstration purposes, an attendance rate of 100% is assumed. This gives the sharpest contrast between different variants.

For calculating cost-effectiveness ratios, an attendance pattern, as that of the Nijmegen trial (unpublished data) has been assumed. A realistic attendance pattern has been assumed because here an estimate of social costs is made, which is strongly influenced by attendance. These attendance rates decline from 75% at age 51 years, to 61% at age 71 years and 21% at age 81 years. The assumptions about social costs have been described in detail by de Koning and associates [8] using 1990 as the base year for discounting and the start of the build up of the programme. The applied exchange rate is 2.7 Dutch guilders of 1990 per pound.

RESULTS

Preclinical period

A measure of the duration of the preclinical period of mammographic detectability is the ratio between detection rates at first screening and incidence rates in the situation without screening. Table 1 shows the comparison of results from screening projects which have enrolled women over 70 years and simulated results.

It is clear that preclinical duration strongly increases between ages 50 and 70 years. Comparison of the screening results from the Kopparberg/Östergötland trial with the incidence in the control group seems to show a further increase in preclinical duration at higher ages [9]. However, a comparison with incidence from the Swedish cancer registry suggests a stabilising preclinical duration after 60 years of age. The results from the Nijmegen trial and the BCDDP show at most a slow increase of preclinical duration at ages over 70 years.

Two main variants

Table 2 shows the main positive effect of screening: life-years gained, and two important negative effects: life-years in lead time (that is time with knowledge of the disease outside the gained life-years) and extra incidence caused by screening. These are the expected results of a screening programme which starts at age 51 years and continues screening with 2-year intervals up to the upper age limits indicated. From around age 90 years further extension of the screening programme leads to so few extra life years gained, that the increase cannot be distinguished from the random fluctuation of the model. It also shows that the expected number of life-years gained is not very different in the optimistic and pessimistic variants. The important difference between the two variants is the level of negative effects.

With extension of a screening programme to higher ages, the number of extra years in lead time and the number of extra

Table 1. Ratio of detection rate at prevalence screening and incidence rate in situation without screening of different screening projects

	Kopparberg/ Östergötland				Simulated	
Age class (years)	Incidence control group	Incidence cancer registry	BCDDP	Nijmegen trial	Optimistic variant	Pessimistic variant
40–44	1.9	1.8	3.0	1.0		
45–49			3.8	2.5		
50–54	3.0	3.5	3.3	2.8	2.0	2.0
55–59			4.0	2.4	2.3	2.3
60–64	3.8	4.7	3.6	2.5	2.8	2.8
65–69			4.7	7.2	3.4	3.4
70–74	5.4	4.4		3.0	3.6	4.6
75–79	—	—	—	4.0	3.9	6.0
80–84	—	—	—	3.4	4.0	8.4

Sources [9, 10].

Table 2. Life-years gained, life-years in lead time and extra number of incidents of breast cancer to be expected from a screening programme with 100% attendance and invitations every 2 years starting at age 51 years; results for the optimistic and pessimistic variants

Upper age limit (years)	Life-years gained (*1000)		Life-years in lead time (*1000)		Extra incidence (cases)	
	opt.	pes.	opt.	pes.	opt.	pes.
69	408	395	357	377	5266	6258
71	428	416	396	433	6593	8304
73	448	436	433	495	7946	11 089
75	463	450	468	560	9406	14 633
77	475	466	495	632	10 831	19 437
79	480	476	517	703	12 205	25 142
81	486	483	538	776	13 864	32 356
83	491	489	556	848	15 582	40 647
85	494	492	570	909	17 165	49 273
87	495	495	580	973	18 547	59 816
89	494	496	586	1024	19 656	69 392
99	497	497	597	1057	22 288	77 760

opt., optimistic; pes., pessimistic

incident cases increases much more rapidly than the number of life-years gained. The pessimistic variant shows that with extending the screening programme from age 79 years to age 81 years, gaining 1 extra life-year in the population coincides with 1 extra breast cancer case (leading to 1 extra primary treatment) and leads to more than 10 extra life-years with knowledge of the disease outside the gained life-years.

Figure 1 shows the number of 5% discounted QALYs gained as a function of the upper age limit of invitation for screening of a programme with 2-year screening intervals, starting at age 51 years. There is a wide range between the optimistic and the pessimistic variant. The optimistic variant shows no clear decrease in the expected number of QALYs gained at any increase of the upper age of the screening programme. In the pessimistic variant, the balance of favourable and unfavourable effects (measured in 5% discounted QALYs) becomes negative if screening is continued beyond age 80 years. Therefore, it is very likely that when extending a mass screening project up to around age 80 years or even higher the balance between positive and negative effects remains favourable.

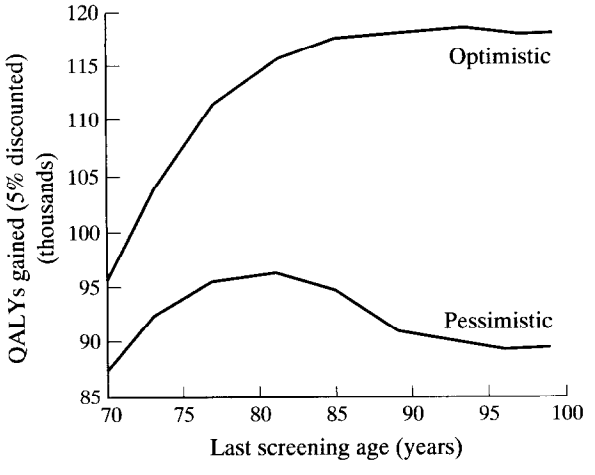

Figure 1. The number of 5% discounted QALYs gained as a function of the upper age limit of invitation for screening of a programme with 2-year screening intervals, starting at age 51 years.

Cost-effectiveness

The marginal cost-effectiveness ratio (CER) in the pessimistic variant of extending a programme from a last age of invitation of 69 years to a last invitation at 75 years is £8400 per QALY gained. This is approximately the same ratio as results from intensifying the invitation scheme in the age group of 50–70 years old. Further extension to age 79 years has a marginal CER of £36 000 per QALY gained.

No improvement of prognosis

A model which consists of the same assumptions as the pessimistic model used for cost-effectiveness analyses, but with no improvement of prognosis due to screening at ages 70+ years (therefore very close to the point estimates of the Swedish randomised trials), leads to results as shown in Table 3. As expected in such a situation, this would have detrimental effects. Screening over 70 years could lead to doubling of the years in lead time and quadrupling of the extra incidence from 0.6% to 2.4%.

DISCUSSION

The conclusion of Forrest [12, 13] concerning the upper boundary of screening is that because of the rapid fall in attendance after the age of 64 years, the invitation scheme of a screening programme should not include higher age groups. From a cost-effectiveness point of view, this seems like an overestimate of the cost of sending out invitations for screening. The cost of inviting women is relatively low as compared to the other costs, therefore a lower attendance rate should not automatically lead to an upper age limit in the invitation scheme.

Besides the upper age limit for issuing invitations, Forrest recommended encouraging older women to get screening without invitation; for which they do not mention an upper age limit. This recommendation does not acknowledge that from a certain age, the unfavourable effects of screening outweigh the favourable effects. Both recommendations together lead to underserving women just over 65 years as well as possibly harmful screening of very old women.

For an estimation with any precision of the costs and effects of a mass screening project for women over 70 years, more data on the effects of screening are needed, especially on preclinical duration of the phase of mammographic detectability. The available data leave room for a wide range of possible consequences. Nevertheless, some conclusions can be drawn.

Both main variants of the model assume an improvement of

Table 3. Life-years gained, life-years in lead time, extra number of incident cases of breast cancer and 5% discounted QALYs gained, to be expected from a screening programme with a realistic attendance and invitation starting at age 51 years; results for pessimistic variant without any improvement of prognosis due to screening

Upper age limit (years)	Life-years gained (*1000)	Life-years in lead time (*1000)	Extra incidence (cases)	QALYs gained (5% disc.)
69	292	275	4651	62 727
99	292	463	17 663	57 855

disc., discounted.

prognosis due to screen-detection of breast cancer, which is the same for women of all ages. We are aware of the fact that the results from the Swedish randomised trials show a mortality reduction which is far less for women in the age group of 70–74 years than for women in the age group of 50–69 years; i.e. 2% or 6% (depending on the way this figure is calculated) versus 29% [4]. Only a small part of this difference can be attributed to the fact that the older women were invited for screening only twice, and that older women are less likely to attend a screening. However, there is no biological explanation for this substantial difference, so for the main variants the difference was assumed to be due to random fluctuation. The estimate of mortality reduction in the age group 70–74 years is based on very small numbers of deaths, and there is no significant difference in mortality reduction between the age groups 50–69 and 70–74 years.

Although it seems reasonable to assume an equal improvement of prognosis due to screen-detection for women over 70 years as for women from 50 to 69 years old, there is no proof of a favourable effect for women over 70 years. Therefore, it is also necessary to consider a model which assumes no improvement of prognosis due to screening of women over 70 years. This assumption is very close to the point estimate from the Swedish randomised trials [4]. Such a model shows that screening women over 70 years can lead to a considerable level of unfavourable effects, which in total can cost more than 8% of the QALYs that are expected to be gained by a programme of screening women from 51 to 69 years old.

Judging only from the number of QALYs gained, it would be advisable to extend breast cancer screening at least up to age 80 years. However, because of the relatively unfavourable balance between positive and negative effects, the number of screens that is required to obtain a certain level of favourable effects is considerably higher than in younger age groups. The sharp increase of cost per QALY gained with extending a screening programme to higher ages, is only, to a small extent, caused by the cost of screening, and by far the most important cause is the strong increase in negative effects. When only the balance between favourable and unfavourable effects is considered, mass screening should be continued to at least the age of 80 years, but when efficiency is also taken into consideration, one may be hesitant to offer screening to women older than 70 years because of an increasing cost-effectiveness ratio.

Although the results leave a wide margin for the best upper age limit, not much more improvement can be expected for the near future, since of the two possible ways to improve on the estimates, one is not likely to give much better precision, the other is not likely to be attainable. The first is making existing data on screening of older women available. For instance, in the Kopparberg/Östergötland study, data on women invited at ages over 74 years have not been published [14]. However, these data are based on small numbers, so it is not to be expected that better availability of data would greatly improve the precision of the estimate. The other way is, of course, a new trial. Such a trial can give a better understanding of the natural history of breast cancer in older women. However, if it is to serve as an investigation into the possible mortality reduction of breast cancer screening, a serious problem is encountered because of the low attendance rate to be expected in older women. Even where there is a strong effect of screening, low attendance leads to a serious dilution of the contrast between the invited and not-invited group. Such a trial, therefore, would need a very large population in order to reach an acceptable power.

The risk of radiation-induced cancers is not included in this study because of the assumption that, for screening women of 50 to 70 years old, this effect is small in comparison with the other effects of screening, and even smaller when screening women over 70 years. Less readily quantifiable aspects of screening, such as a possible educational effect on women and the effect on quality of life after a negative screening result, have been omitted from the analysis, because they are assumed to be of negligible effect on the optimal upper age limit.

This paper is based on a model for the Dutch situation. This means that assumptions made about demography, epidemiology, organisation and quality of the mass screening project and on costs of health care facilities are specific for the Netherlands. This does not imply that it is not possible to generalise the conclusions of this paper to other Western countries.

The balance between favourable and unfavourable effects of screening can only be substantially influenced by large differences in life expectancy at the time of screening. These kind of differences do not occur among countries and regions where organising breast cancer screening is an issue. Cost-effectiveness considerations also depend on the effectiveness of screening at ages higher than 70 years relative to screening between 50 and 70 years which, in turn, depends on the age dependency of the risk for breast cancer. This age dependency is not very different in Western situations.

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Acknowledgements—We are grateful to Dr J.C.J.M. de Haes and B.M. van Ineveld and their collaboration.