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RESEARCH

Breast cancer mortality in organised mammography screening in Denmark: comparative study

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ABSTRACT

Objective To determine whether the previously observed 25% reduction in breast cancer mortality in Copenhagen following the introduction of mammography screening was indeed due to screening, by using an additional screening region and five years additional follow-up.

Design We used Poisson regression analyses adjusted for changes in age distribution to compare the annual percentage change in breast cancer mortality in areas where screening was used with the change in areas where it was not used during 10 years before screening was introduced and for 10 years after screening was in practice (starting five years after introduction of screening).

Setting Copenhagen, where mammography screening started in 1991, and Funen county, where screening was introduced in 1993. The rest of Denmark (about 80% of the population) served as an unscreened control group.

Participants All Danish women recorded in the Cause of Death Register and Statistics Denmark for 1971-2006.

Main outcome measure Annual percentage change in breast cancer mortality in regions offering mammography screening and those not offering screening.

Results In women who could benefit from screening (ages 55-74 years), we found a mortality decline of 1% per year in the screening areas (relative risk (RR) 0.99, 95% confidence interval (CI) 0.96 to 1.01) during the 10 year period when screening could have had an effect (1997-2006). In women of the same age in the non-screening areas, there was a decline of 2% in mortality per year (RR 0.98, 95% CI 0.97 to 0.99) in the same 10 year period. In women who were too young to benefit from screening (ages 35-55 years), breast cancer mortality during 1997-2006 declined 5% per year (RR 0.95, CI 0.92 to 0.98) in the screened areas and 6% per year (RR 0.94, CI 0.92 to 0.95) in the non-screened areas. For the older age groups (75-84 years), there was little change in breast cancer mortality over time in both screened and non-screened areas. Trends were less clear during the 10 year period before screening was introduced, with a possible increase in mortality in women aged less than 75 years in the non-screened regions.

Conclusions We were unable to find an effect of the Danish screening programme on breast cancer mortality. The reductions in breast cancer mortality we observed in screening regions were similar or less than those in non-screened areas and in age groups too young to benefit from screening, and are more likely explained by changes in risk factors and improved treatment than by screening mammography.

INTRODUCTION

Comprehensive systematic reviews of randomised trials of mammography screening have estimated that mammography reduces breast cancer mortality by 15-16%.[1 2] The trials in these reviews were carried out decades ago, however, and publicly available screening programmes could yield a different effect from that in the trials because of differences in the qualifications of the staff, type of equipment, and uptake rates. Furthermore, there have been advances in treatment since the trials were completed and "breast awareness" has increased. It is therefore important to evaluate continuously the effect of public mammography screening programmes to ensure that they live up to expectations.

Denmark is uniquely suited for observational studies of mammography screening because the country has had a period of 17 years where only about 20% of the population has been offered screening; that is, there is a concomitant non-screened control group. There are, however, substantial problems in using observational studies to estimate the effect of screening.[3] For example, a decline in breast cancer mortality following the introduction of screening would not necessarily be caused by screening.

A cohort study from 2005 by Olsen et al compared Copenhagen, where screening was introduced in 1991, with non-screened areas in Denmark and reported a 25% reduction in breast cancer mortality that was attributed to screening.[4] However, there are three important concerns about this result.[5-7] Firstly, the full mortality reduction appeared three years after screening started and did not increase in the remaining observation period.[4] The mechanism of screening is to advance the time of diagnosis; therefore, an effect is not expected to appear in the first few years after its introduction but is expected to emerge after about five years and increase with further follow-up.[3] That the full effect appeared after only three years suggests that factors other than screening are the cause of the mortality reduction observed.

Secondly, the study included only Copenhagen, although the county of Funen introduced screening in 1993, has a population of a similar size, and has a higher proportion of women who repeatedly attend screening rounds (76% *v* 53%).[8] One of the authors of the paper by Olsen et al heads the Funen screening programme and should have had access to detailed data.

Thirdly, the study did not describe breast cancer mortality rates in women who were too young or too old to have benefited from screening. An absence of similar reductions in breast cancer mortality among these women would have strengthened the study's conclusions.

We hypothesised that if the reduction in breast cancer mortality that Olsen et al observed in Copenhagen was due to screening, a similar reduction should have occurred in Funen but not in the non-screened areas or in age groups outside those that could potentially have benefited.

METHODS

We retrieved data on female breast cancer mortality during 1971-2006 from the Cause of Death Register through the National Board of Health. Compared with Olsen et al,[4] we had access to data from five additional years. The numbers of breast cancer deaths were listed for each year, administrative region, and five year age group. The corresponding female population statistics were obtained from Statistics Denmark.[9]

Organised mammography screening of women aged 50-69 years began on 1 April 1991 in Copenhagen municipality, 1 November 1993 in Funen county, and 1 June 1994 in Frederiksberg municipality.[10] The Frederiksberg programme, which comprised only about 10 000 women, was incorporated into the Copenhagen programme on 1 January 1997.[10] The Copenhagen and Funen programmes both include about 50 000 women.

We divided the data into two regions. Copenhagen (including Frederiksberg municipality) and Funen county were considered together as "screening areas" to reduce the effect of random fluctuations. These screening areas were compared with the "non-screened areas," comprising the rest of Denmark (about 80% of the population).

The mortality data for both screening and non-screening areas were divided into three age bands. The 55-74 years band was composed of the women most likely to have benefited from a programme targeted at women aged 50-69 years, such as that in Denmark. Most women who die aged 50-55 years would have had their breast cancers detected before they were invited to screening. On the other hand, the majority of women aged 70-74 years when they died would have been diagnosed and offered screening when they were younger, and by six years after organised screening began, all women aged 70-74 years would have been previously offered screening.

In contrast, breast cancer mortality in women aged 35-54 years and 75-84 years would largely be unaffected by screening, although by the end of the observation period some women aged 75-84 years could have benefited through detection of slow growing cancers. These age groups also serve as control groups.

We first defined the period when screening could have had an effect. In randomised trials of mammography screening, an effect began to emerge about five years after screening was introduced,[3] which is 1996 in Copenhagen and 1998 in Funen. We used 1997 as a compromise start date in our combined analysis of the two regions. This provided a 10 year observation period (1997-2006) when screening could have had an effect.

For comparison, we used a 10 year period that ended when screening was introduced (1982-1991), but we provide mortality graphs back to 1971 for completeness. The last year before organised screening was introduced was 1990 in Copenhagen and 1992 in Funen, so we used 1991 as a compromise.

We used Poisson regression analyses to quantify changes in mortality trends, comparing regions and age groups with and without organised mammography

Table 1 | Woman years of observation, number of breast cancer deaths, and average rates per 100 000 women in screened and non-screened areas

	Screened areas			Non-screened areas		
	1982-91	1992-96	1997-2006	1982-91	1992-96	1997-2006
Number of woman years						
35-54 years	1 174 997	640 700	1 338 266	5 509 889	3 005 488	6 233 027
55-74 years	1 218 157	492 081	957 797	3 925 135	2 002 687	4 471 369
75-84 years	478 800	223 441	370 101	1 142 623	625 693	1 312 095
Number of breast cancer deaths						
35-54 years	457	257	390	1961	1055	1657
55-74 years	1478	658	980	4281	2326	4739
75-84 years	937	429	722	2003	1152	2352
Average number of breast cancer deaths per 100 000 women						
35-54 years	39	40	29	36	35	27
55-74 years	121	134	102	109	116	106
75-84 years	196	192	195	175	184	179

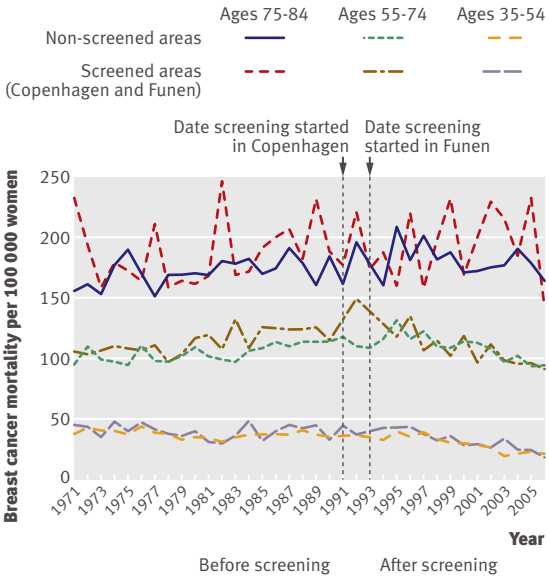

Fig 1 | Unadjusted breast cancer mortality rates for screened and non-screened areas in Denmark

screening and correcting for changes in age distribution. Statistical analyses were made using Egret version 2.0.3 (Cytel, Inc, Cambridge, MA) and graphs were made in Microsoft Excel 2000.

RESULTS

The number of woman years and the number of deaths attributed to breast cancer in the 36 year observation period in the screened areas and in the non-screened areas are presented in table 1.

Breast cancer mortality among women who could benefit from screening (ages 55-74 years)

In the 10 year period when screening could have had an effect, breast cancer mortality among women who could benefit from screening (ages 55-74 years) declined by 1% a year in the screened areas (relative risk (RR) 0.99; 95% confidence interval (CI) 0.96 to 1.01) and by 2% in the non-screened areas (RR 0.98, 95% CI 0.97 to 0.99; fig 1; table 2). Before screening was introduced, breast cancer mortality rates increased by 1% a year in the screened areas (RR 1.01, 95% CI 0.99 to 1.03) and by 2% a year in the non-screened areas (RR 1.02, 95% CI 1.01 to 1.03).

Breast cancer mortality among women too young to benefit from screening (ages 35-54 years)

In the most recent 10 year period, breast cancer mortality among women too young to benefit from screening (ages 35-54 years) declined by 5% a year in the screened areas (RR 0.95, 95% CI 0.92 to 0.98) and by 6% in the non-screened areas (RR 0.94, 95% CI 0.92 to 0.95; fig 1). Before screening was introduced, breast cancer mortality rates increased by 2% a year in the screened areas (RR 1.02, 95% CI 0.99 to 1.06) and were stable in the non-screened areas (RR 1.00, 95% CI 0.99 to 1.02; table 2).

Breast cancer mortality among women too old to benefit from screening (ages 75-84 years)

There were no significant changes in the breast cancer mortality trends among women too old to benefit from screening (ages 75-84 years), both in the screened areas and in the non-screened areas (fig 1; table 2).

DISCUSSION

Our findings contradict the conclusions of a recent observational study that reported a 25% reduction in breast cancer mortality in screening areas of Denmark (Copenhagen) compared with non-screened areas and attributed this drop to the effect of screening.[4] Our study included three screening areas in Denmark, non-screened age groups, and an additional five years of follow-up, yet we were not able to find an effect of the Danish screening programme on breast cancer mortality. We also note that in the age group too young to have benefited from screening, women experienced proportionately larger reductions in breast cancer mortality after screening was introduced than did those that could have benefited from screening.

The reduction in breast cancer mortality in Copenhagen started too early after screening was introduced for screening to be a plausible cause, although a decline within the first three years of screening formed the basis for the conclusion in the previous study,[4] and the reduction in breast cancer mortality in the second screened region, Funen, began before organised screening (see web extra). This suggests that causes other than screening were responsible for the changes in breast cancer mortality—for example, changes in risk factors and improvements in treatment may have occurred sooner in some areas than in others.

Strengths and weaknesses of our study

Opportunistic screening is rare in Denmark so could not be the reason for the reduction in breast cancer mortality in the non-screened areas. Only 2% of women aged 20-99 years and 3% of women aged 50-69 years had a mammogram outside organised screening in 2000, and some of the mammograms were diagnostic

Table 2 | Annual change in the relative risk of breast cancer death (with 95% confidence intervals) 10 years before screening was introduced and 10 years during which screening could have had an effect on breast cancer mortality

	Before screening (1982-91)	After screening (1997-2006)
Ages 35-54 years		
Screened areas	1.02 (0.99 to 1.06)	0.95 (0.92 to 0.98)
Non-screened areas	1.00 (0.99 to 1.02)	0.94 (0.92 to 0.95)
Ages 55-74 years		
Screened areas	1.01 (0.99 to 1.03)	0.99 (0.96 to 1.01)
Non-screened areas	1.02 (1.01 to 1.03)	0.98 (0.97 to 0.99)
Ages 75-84 years		
Screened areas	0.99 (0.97 to 1.02)	1.00 (0.98 to 1.03)
Non-screened areas	0.99 (0.98 to 1.02)	0.99 (0.98 to 1.02)

rather than screening mammograms.[11] Carcinoma in situ, which is detected almost entirely through screening, had a fairly constant incidence rate throughout the observation period in the non-screened areas, but the rates doubled in the screened regions when screening was introduced and have remained at that level.[12]

In the study by Olsen et al, deaths from breast cancers diagnosed before 1991, when screening was introduced in Copenhagen, were excluded from the analysis.[4] It may be reasonable to exclude breast cancers detected before screening was introduced because screening cannot affect their prognosis. Excluding such cancers is unlikely to have had an effect on our results, however, because the effect diminishes with time. Therefore, a difference in breast cancer mortality of 25% between screened and non-screened areas, if true, would be expected to be clearly apparent after 14-16 years with organised screening.

Furthermore, in 1986, before screening was introduced in the United Kingdom, the Forrest report on screening for breast cancer noted that population statistics could be used to see the mortality benefit from screening that was expected on the basis of results from randomised trials.[13] We did not see this expected effect in Denmark.

We compared open cohorts because our data did not allow identification of individual women. We could not therefore take account of migration between screened and non-screened regions. However, mobility in the screened age groups is limited in Denmark. We also note that our open cohort design cannot be used to explain why breast cancer mortality declined in the non-screened areas at a similar rate as in the screened areas, and that the decline was larger in women who were too young to have benefited from screening. We consider it unlikely that there were regional differences in the use of hormone replacement therapy that could explain our findings because Denmark is a homogeneous country and the screened and the non-screened areas had a similar proportion of cities and rural areas.

Comparison with previous studies

Olsen et al reported the results of a complicated statistical model, and the choice of model can have a substantial impact on the results. Some of the same authors have more recently reported results from several models, one of which showed an increase in breast cancer mortality in Copenhagen among screened women relative to women in the non-screened areas.[14] The authors asserted that the model they published originally, which gave the most favourable result for screening, should be preferred, but did not explain why. None of the models was validated, and it is not clear whether the preferred model was selected after other models had been tried first. Our study does not use a complicated statistical model; instead we present the raw data and simple analyses.

Olsen et al assumed that women in the screened areas and those in the non-screened areas received identical care because national guidelines for breast cancer treatment have been in use in Denmark since 1977.[4] Guidelines, however, may not be used to the letter in clinical practice. In January 2007, for example, several women in one of the non-screened regions were compensated financially for having received treatment that did not live up to "best specialist standards."[15 16] If the standard of care were lower in the non-screened areas, it would only strengthen our findings that screening cannot be responsible for the declines in breast cancer mortality we observed.

All breast cancer treatment in Copenhagen takes place at university hospitals that provide specialised care and have a high volume of patients, whereas care is more variable in Funen, and there has been considerable pressure to centralise breast cancer treatment in other regions.[15] The reduction in breast cancer mortality in Copenhagen started earlier than expected after screening was introduced and the reduction in breast cancer mortality in Funen began before organised screening started (see web extra); therefore the mortality difference between Copenhagen and non-screened regions found in the previous study might partly reflect better organisation of treatment and earlier implementation of improvements in therapy (for example, use of tamoxifen).

Olsen et al calculated that the reduction in breast cancer mortality among those who actually attended screening was 37%.[4] However, there was no relevant control group to compare those who actually attended screening with, because it is impossible to know which women in the non-screened areas would have attended screening had it been offered. Such results are invalid because of the "healthy screenee effect." People who attend screening are more healthy in general than those who choose not to participate, and have been described as "healthy, well educated, affluent, physically fit, fruit and vegetable eating, non-smokers with long lived parents."[17]

It is common for mortality estimates to be adjusted for attendance to mammography screening, but this measure is equivalent to preferring a per protocol analysis over an intention to treat analysis. By comparison, one does not adjust for compliance in drug trials because such adjustments are bias prone. For example, in a trial that failed to find an effect of clofibrate on cardiac mortality, the authors reported a large effect among those who took at least 80% of the drug (P=0.0001) but found a similar "effect" among compliers in the placebo group ($P=5\times10^{-16}$).[18]

The handbook on breast cancer screening from the International Agency for Research on Cancer advises that observational studies should not be regarded as providing evidence of an effect of screening.[3] We agree that positive evidence for an effect should come from randomised trials. The effect of screening is equivocal and has been estimated to be only about 15-16% in the two most comprehensive systematic reviews of randomised trials.[1 2] Small effect sizes render observational studies particularly problematic, but observational studies are useful for monitoring the effect in clinical practice.[12] Contrary to expectations, a study

in Europe found that declines in breast cancer mortality were of a similar magnitude in countries not offering screening as in those offering screening, with the greatest declines among women who were too young to be offered screening, which is similar to our findings.[19]

Many studies have used population statistics to estimate the effect of mammography screening programmes.[20-23] Like the study by Olsen et al, most of them include only women in the age group that could benefit from screening and do not compare trends in breast cancer mortality with those in an unscreened group, thus disregarding the effects of other important factors that could change in the screening period (such as treatment).

These studies also often claim to have compensated for lead time and length bias, with highly variable assumptions of their size. This is not surprising, as no one knows exactly how large lead time and length bias for breast cancer screening are. Such shortcomings question the conclusions in these studies.

Comparison with other countries

Results from other countries[19] support our findings. In the UK, where screening started in 1988, the decline in breast cancer mortality from 1989 until 2007 was 41% in women aged 40-49 years, who were not invited to screening, 41% in women aged 50-64 years, who were invited to screening from 1988, and 38% in women aged 65-69 years, who were invited from 2002 (fig 2).[24] Furthermore, the drop in breast cancer mortality in the relevant age group began before the screening programme started, and was largest in the age group that was too young to be invited (40-49 years) if the whole observation period is considered (1971-2007).[25]

In the United States, a particularly pronounced trend shift in breast cancer mortality has been observed, with a substantial decline since the middle of the 1980s.[27] However, the starting point for the decline is probably a random high, and there have been large changes in the use of surgery and chemotherapy that might affect the drop.[28] Groups of epidemiologists analysing these data independently arrived at a median estimate of the effect of screening of only 15%.[27]

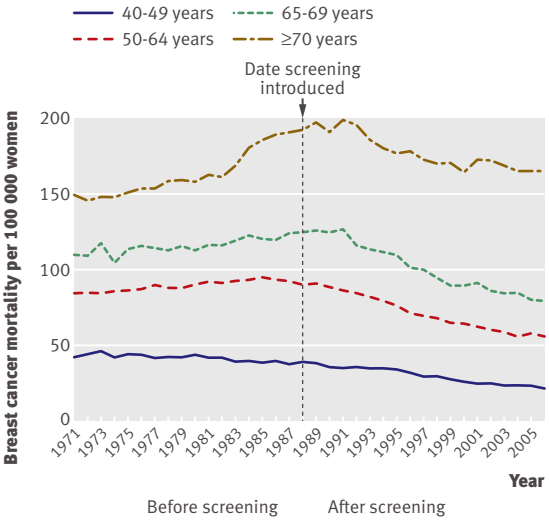

Fig 2 | Age adjusted breast cancer mortality rates in the United Kingdom for screened and non-screened age groups. Data from Cancer Research UK[26]

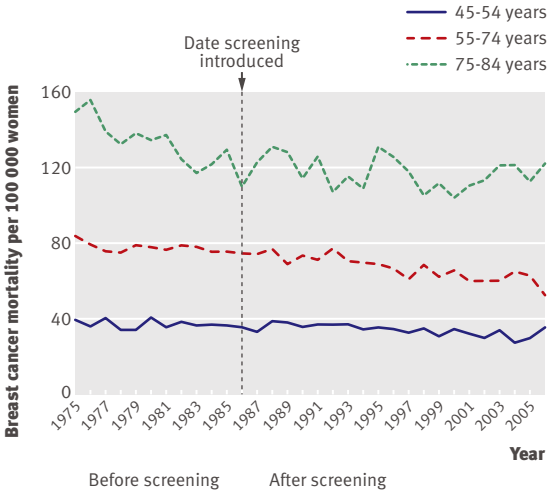

Fig 3 | Unadjusted breast cancer mortality rates in Sweden for screened and non-screened age groups. Data from Statistics Sweden (http://www.scb.se/default____2154.aspx)

In countries with a less pronounced trend shift following the introduction of mammography screening, or no shift at all,[19] such analyses would likely fail to find an overall positive effect of screening on breast cancer mortality. We note, for example, that in Sweden, where screening started in 1986 and where uptake rates are very high, the mortality curves for the relevant age groups (45-55 years and 55-74 years) show a constant decline through the decades (fig 3). This decline started before screening was introduced, which does not suggest a screening effect.

Furthermore, the decline in the youngest age group (45-54 years, some of whom are offered screening in some areas in Sweden) is similar to that in the age group that would be expected to benefit the most from screening (55-74 years, who stand to benefit from screening in all counties). Somewhat surprisingly, there was a pronounced decline in breast cancer mortality in the oldest age group (75-84 years) that stopped when screening was introduced (fig 3). This is contrary to what would be expected and is unlikely to have anything to do with screening.

Conclusions

We were unable to find an effect of the Danish screening programme on breast cancer mortality. The reductions in breast cancer mortality we observed in screened regions were similar or larger in non-screened regions and in age groups younger than that screened. The mortality reduction is therefore more likely to be explained by changes in risk factors and by improved treatment than by screening mammography. Our results are similar to what has been observed in other countries with nationally organised programmes. We believe it is

WHAT IS ALREADY KNOWN ON THIS TOPIC

A Danish study has estimated that breast cancer mortality in Copenhagen has fallen by 25% since 1991 following the introduction of screening mammography

However, the full mortality reduction appeared three years after screening started (that is, several years earlier than expected), the study did not describe breast cancer mortality rates in women who were too young or too old to have benefited from screening, and only one of two available screening regions was included

If the reduction in breast cancer mortality in Copenhagen was due to screening, a similar reduction should be seen in the other region of Denmark that used screening, but not in non-screened areas or in age groups other than those that could potentially have benefited

WHAT THIS STUDY ADDS

Among women who could benefit from screening (ages 55-74 years), there was a similar or larger decline in breast cancer mortality among women in areas that did not use screening than in those that did

The reductions in breast cancer mortality among women too young to benefit from screening (ages 35-54 years) were much larger than those among women in the screened age groups

The reductions in breast cancer mortality we observed are more likely explained by changes in risk factors and by improved treatment than by screening mammography

time to question whether screening has delivered the promised effect on breast cancer mortality.

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Ethical approval: No approval from an ethical committee or informed consent was needed.
Data sharing: The mortality data used in our calculations and graphs are available from the corresponding author at kj@cochrane.dk.

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