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The efficacy of mammographic screening for breast cancer in elderly women

De effectiviteit van mammografische screening naar borstkanker bij oudere vrouwen

Een wetenschappelijke proeve op het
gebied van de Medische Wetenschappen

Proefschrift

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door

José Antonia Augusta Maria van Dijck

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Voor mam en moeder

"De wereld der mensheid bezit twee vleugels:
de mannelijke en vrouwelijke.
Zolang deze twee vleugels niet even sterk zijn,
zal de vogel niet vliegen.
Als de twee vleugels even sterk worden
doordat zij dezelfde voorrechten genieten,
zal de vlucht die de mensheid neemt,
uitermate verheven en uitzonderlijk zijn."

'Abdu'l-Bahá

Contents

Chapter 1

Background and motivation

Breast cancer is the most frequent form of cancer in women.[1] Recent calculations have shown that approximately 10% of the women in the United States will be diagnosed with breast cancer before the age of 85 years.[2] Table 1.1 shows incidence rates in the mid-1980s for several countries.[3] After the United States and Switzerland, the incidence is highest in the Netherlands with about 73 cases of breast cancer cases diagnosed annually per 100,000 woman-years after age-standardization according to the population of the world. About 1 in 12 women will be diagnosed with invasive breast cancer before the age of 75 years. In Table 1.1, the mortality rates from breast cancer are also shown. Again, the Netherlands rank very high, with approximately 27 breast cancer deaths annually per 100,000 woman-years. Some of the countries with a lower incidence rate than the Netherlands, however, have a higher mortality rate, *e g* the United Kingdom and Denmark. In these countries with a higher ratio of mortality to incidence (Table 1.1), breast cancer is probably diagnosed at a relatively late stage. Early detection by screening can be expected to have a larger effect on mortality in these countries.

Table 1 1 *Age-standardized (world population) incidence and mortality rates of female breast cancer in selected countries, and ratio of mortality to incidence, ranked by incidence rate*

Country	Incidence rate#	Mortality rate#	M/I* (%)
United States, Seattle	94 2	22 3	25 2
United States, Utah	75 4	17.9	25 2
Switzerland, Geneva	73 5	27 4	42 6
Netherlands, Eindhoven	72 7	26 3	38 8
Canada	71 1	24 2	35 6
Denmark	68 6	27 8	46 2
Netherlands, Maastricht	68 1	27 2	42 7
France, Bas Rhin	66 3	20 6	36 7
Italy, Florence	65 4	20 8	35 1
Sweden	62 5	18 9	32 6
Australia, Victoria	61 7	22 2	38 5
United Kingdom, England & Wales	56 1	30 3	59 0
Norway	54 8	18 7	37 8
German Democratic Republic	46 3	18 2	41 4
Czechia, Slovakia	34 5	18 8	56 2
India, Bombay	24 6	8 8	35 9
Japan, Osaka	21 9	6 4	29 9

Source "Cancer incidence in five Continents (Volume VI)[3]" period 1983-1987
 # per 100,000 woman-years
** ratio of mortality to incidence rate*

Table 1.2 *Number of new cases of breast cancer and number of breast cancer deaths in 1989 in the Netherlands according to age*

Age at diagnosis/death (years)	Number diagnosed	Number of deaths
< 50	2049 (26%)	454 (14%)
50-69	3392 (43%)	1283 (38%)
70+	2527 (32%)	1628 (48%)
Total	7968 (100%)	3365 (100%)

Source the Netherlands Cancer Registry[4]

Table 1.2 shows the number of newly diagnosed cases and the number of breast cancer deaths in the Netherlands in 1989, in 3 age categories.[4] In the whole population, there were almost 8000 newly diagnosed cases of breast cancer, one third of them were 70 years or older. The number of deaths from breast cancer was almost 3400. Approximately half of the deaths from breast cancer occurred in patients aged 70 years or older.

In 1963, the first trial on the effectiveness of breast cancer screening was started. The research question in this Health Insurance Plan (HIP) trial in Greater New York was whether breast cancer mortality could be reduced by annual screening with two-view mammography combined with physical breast examination.[5] For the study, 62,000 women aged 40-64 years were allocated at random in the ratio 1:1 to one of two groups who received an invitation for screening or not. The results reported in 1971 were promising: 31 deaths from breast cancer in the study group compared to 52 in the control group.

The high mortality rate in the Netherlands and the promising results of the HIP study formed the motivation to seek financial support for a screening project in Nijmegen.[6] The project was organized with a grant from the Prevention Fund in order to study the effect of population screening for breast cancer with modern mammography (*i.e.* using dedicated mammography equipment with a molybdenum anode and a so-called low-dose film-screen combination) as the only screening method. The project was started in 1975 with biennial one-view mammography for women aged 35 years and older. After 6 years of follow-up, the effect of screening on breast cancer mortality was analysed by means of comparing the mortality rate in the participants to that in the non-participants (using the so-called case-referent or case-control method).[7] Beast cancer mortality in the women who did participate was 52% lower than in those who did not

participate.[8] The 95% confidence interval (CI) was 0%-77% reduction. The underlying incidences in the self-selected populations of screened and unscreened women were estimated to be the same. With an additional year of follow-up, the reduction in breast cancer mortality was 49% (95% CI 1%-74%).[9]

In the meantime, several other studies, including some randomized controlled trials in the United States and Europe, have also demonstrated a screening-related reduction in breast cancer mortality with different screening methods (*e.g.* one or two-view mammography sometimes combined with physical examination) and different intervals between screening rounds (one, two or three years).[10-13] Extensive meta-analyses of the results of these studies have lead to the conclusion that in the whole population of women aged 50-70 years, mortality from breast cancer can be reduced by about 30%.[14-17] In participants, the reduction may be as large as 45%.[18] Screening seemed to be effective at least up to the age of 75 years, but more research was needed to confirm this.[15,19,20]

In 1989, a national breast screening programme was started in the Netherlands for women aged 50 to 70 years. Women who reached the age of 70 years were permitted to continue to participate at their own request.[21] From 1993 onwards, however, women aged 70 years or older were excluded from the screening programme. The motivations for this decision were the absence of any evidence that screening had a beneficial effect in this age category and concern that negative side-effects may outweigh the possible positive effect.[22] Abroad, there is no consensus either about the upper age limit for breast cancer screening.[15,20,23] In various countries that promote screening for breast cancer, the guidelines for an upper limit vary from 64, 69, 74, 84 years to no age limit, i.e. up to a very advanced age in women with a good general life expectancy.[23-25]

The decision about whether or not to set an upper age limit, and at what age, should be made by carefully balancing the effects against the side-effects. However, little is known about the extent of most (side-) effects. Worldwide, only two trials have systematically invited elderly women: the randomized two-county trial in Sweden and the Nijmegen screening project.[8,26] In the former study, women aged 70 and older at the start of the trial received invitations for two screening rounds. Results have been reported for women of up to 74 years, but the older women were excluded from the analyses because the participation rate was considered to be too low (51%).

The purpose of the present study was to investigate whether screening of women aged 65 years and older affects the stage at diagnosis and breast cancer mortality.

The setting for the various studies described below is the Nijmegen screening project. It is the only long-term project in the world that includes elderly women.

Chapter 2 is a review of the literature on the anticipated effect of screening in elderly women. The relation between age and epidemiological and biological factors of breast cancer are discussed, as well as the impact of these factors on mammography as a screening test. Furthermore, the screening-related mortality reduction in studies that included elderly women was examined.

Chapter 3 presents studies on the validity of mammography as a screening test for breast cancer. To determine the detectability of breast cancer by modern mammography, the previous negative screening mammogram of a group of screen-detected patients and interval cancer patients was reviewed. These mammograms were checked for the presence of signs and whether they were considered as mammographic signs for breast cancer. Chapter 3 also deals with the quality of one-view mammography compared to two-view mammography for initial screening. To achieve a reduction in breast cancer mortality, the sensitivity of the screening test must be optimal, that is, most of the cancers should preferably be detected in their preclinically detectable phase. At the same time the specificity should be high to prevent healthy women from being referred for unnecessary further diagnostic tests. This issue was addressed by means of reviewing the literature.

Chapter 4 describes the early outcomes of mammographic screening in elderly women, such as the number of screen-detected cancers per 1000 women and their stage at diagnosis. Chapters 5 and 6 deal with the key issue: does screening elderly women affect breast cancer mortality. In the two studies outlined in Chapter 5, a case-referent design was used, comparing breast cancer mortality between women who participated in the screening and those who did not. These two studies differed with regard to the length of follow-up and the definition of the relevant screening histories. The final discussion section of the Chapter addresses the differences between the screening histories as well as the impact of bias due to self-selection. Chapter 6 makes a comparison between breast cancer mortality in the invited population from Nijmegen, regardless of participation, and that in an unscreened population from the neighbouring city of Arnhem. This design was used to avoid self-selection bias. Chapter 7 reviews the evidence and formulates issues for future research.

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Chapter 2

Review of the literature

Screening for breast cancer after the age of 70 years: a further reduction in breast cancer mortality?

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Screening for breast cancer after the age of 70 years: a further reduction in breast cancer mortality?

JAAM van Dijck, ALM Verbeek, JHCL Hendriks, R Holland

Introduction

The Dutch national screening programme for breast cancer was set for women aged 50 to 70 years. Once a woman had reached the age of 70 years, she was permitted to continue participating if she wished. In 1993, however, the latter policy was halted because the cost of the programme was exceeding the budget. Arguments included uncertainty about a possible reduction in breast cancer mortality by screening older women. Furthermore, there would be more negative side-effects, such as an increased number of person-years that a woman would have to live with the knowledge that she has the disease. This applies especially to screen-detected breast cancer patients who would die of another disease before the breast cancer would otherwise have been diagnosed on clinical grounds.[1]

There is still no consensus about the upper age limit for breast screening in the Netherlands and abroad. In the various countries, guidelines vary from no upper age limit to an upper limit of 64, 69, 74 or 84 years.[2] A forum "On breast cancer screening in older women" recommended that annual physical examination and biennial mammography should be continued up to the age of 75 years and up to a very advanced age in women with a good general life expectancy.[3]

In the following sections, epidemiological and biological aspects of breast cancer in elderly women are discussed. Besides, results of several trials on the effectiveness of screening are being reviewed, especially the Nijmegen programme which started in 1975 with biennial mammography for women aged 35-65 years. From the second round (1977) and on also women over age 65 were invited.

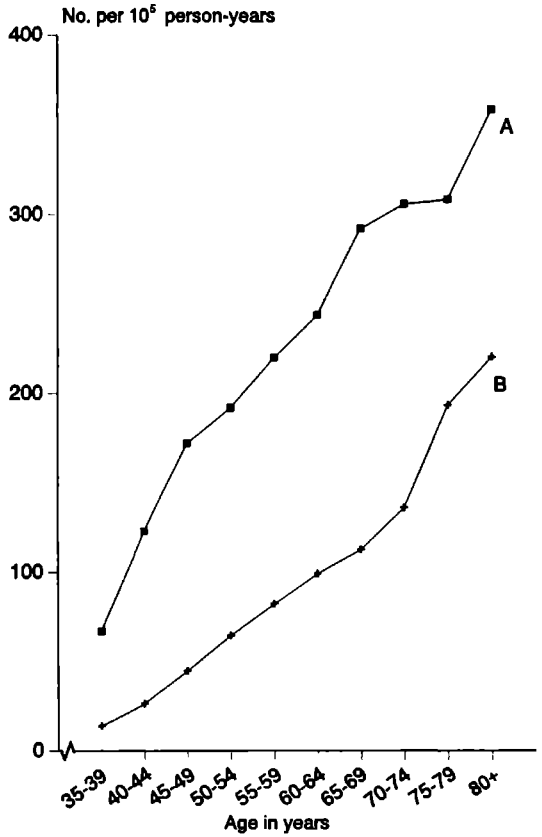
Epidemiology

Incidence

For several decades, the age-specific incidence of breast cancer has been rising worldwide, especially among elderly women. Further increases in the

1980s in both the United States and the Netherlands were attributed to an increase in the use of mammography.[4] Figure 2.1 shows the age-specific numbers of newly diagnosed breast cancers and deaths from breast cancer per 100,000 women in 1989 in the Netherlands.[5] In that year, almost 8000 invasive breast cancers were diagnosed; 25% of the patients were younger than 50 years, 43% were aged 50-69 years and 32% were 70 years and older (Table 2.1).[5] Owing to the increasing proportion of older women in the population, it is expected that the number of newly diagnosed cases of breast cancer will increase further to over 11,000 in the year 2010 (Table 2.1).

Figure 2.1 *Incidence (A) of breast cancer and mortality (B) in the Netherlands per age category, 1989*[5]



It has been suggested that the incidence of breast cancer in elderly women who were regular participants in the breast screening becomes so low that it no

longer justifies continuation of the screening. However, the opposite can be seen in Table 2.2, which shows the detection rates among screened Nijmegen women aged 70 and older. At the first screening (round 2 for this age category) about 10 breast cancers were detected in 1000 screened women. At successive screenings, the detection rate stabilized at about 8 cancers per 1000 screened women.

Table 2.1 *Number of newly diagnosed cases of breast cancer per age category (at diagnosis) in 1989 and the predicted numbers in 2000 and 2010*

Age at diagnosis (years)	Number of newly diagnosed breast cancers in		
	1989*	2000†	2010†
<50	2,049 (25%)	2,371 (26%)	2,456 (23%)
50-69	3,392 (43%)	3,893 (42%)	4,775 (45%)
70+	2,527 (32%)	3,021 (33%)	3,285 (31%)
Total	7,968 (100%)	9,285 (100%)	10,516 (100%)

* *Source: the Netherlands Cancer Registry 1989 (5)*
† *Age-specific incidence rate in 1989 applied to the midvariant of the population prognosis of the Dutch Central Bureau of Statistics (1989)*

Table 2.2 *Detection rates per screening round of the Nijmegen programme in the age category 70 years and older at invitation*

Screening-round*	Number of women screened	Number of screen-detected cancers	Detection rate per 1000 screened women
2	2,288	23	10.1
3	1,783	12	6.7
4	1,711	15	8.8
5	1,672	11	6.6
6	1,898	16	8.4
7	2,069	17	8.2
8	1,936	14	7.2
9	1,274	12	9.4

* *Round 2 was the first screening for women aged 70 years and older, while the subsequent rounds concerned almost exclusively successive screenings*

Life expectancy

Life-tables of the Dutch Central Bureau of Statistics (CBS) show that in 1991, the life expectancy of 70 and 80-year-old women was about 15 and 8 years, respectively. Life expectancy reflects the risk of dying at a certain age and depends on the presence of chronic comorbid disease. A healthy 70-year-old woman can be expected to live longer than the 15 years that are expected for all 70-year-olds.

Biological aspects

Breast tissue

Growing older is associated with physiological changes in the breast; these actually facilitate the detection of abnormalities with mammographic screening. After the menopause, the glandular tissue is gradually replaced by fat. Due to the fact that fat absorbs less radiation than glandular tissue, there will be greater contrast between breast tissue and tumour tissue, which increases the sensitivity of mammography. Moreover, the frequency of benign breast disease is lower, which increases the chance that a newly developed lesion shadow on the mammogram will be a carcinoma. This may in turn increase the specificity.

Table 2.3 *Results of the Nijmegen programme for two age categories. Mean values of the results of rounds 4-9*

Result	Age at invitation	
	50-69 yrs	70+ yrs
Rate of screen-detected cancers	3.6 ‰	8.1 ‰
Rate of interval cancers*†	2.1 ‰	3.3 ‰
Referral rate	6.2 ‰	12.2 ‰
Sensitivity‡†	62.4 %	70.1 %
Specificity	99.7 %	99.6 %
Positive predictive value of referral	59.0 %	68.3 %
Positive predictive value of biopsy	70.4 %	79.8 %

* *Interval cancer diagnosed within 2 years of a negative screening result*
† *Average of rounds 4-8*
‡ *Sensitivity = (screen-detected cancers)/(screen-detected + interval cancers)*

Table 2.3 shows the average values for several characteristics of Nijmegen screening mammography in rounds 5 to 9. These rounds almost exclusively concern successive screening. Sensitivity, calculated as the percentage of screen-detected cancers versus the sum of screen-detected and interval cancers, was slightly higher for women aged 70 years and older. This was also true for the predictive values for referral and biopsy. (Interval cancers are diagnosed clinically after a negative screening result, but before the next invitation 2 years later). Specificity was roughly the same for the respective age categories.

Tumour biology

The biological characteristics of breast cancer are prognostically better in older women than in younger ones. This is due to better histological differentiation and a larger proportion of the tumours are positive for oestrogen and progesterone receptors.[6] Furthermore, the growth rate of breast cancer is slower in older age. In the Nijmegen screening patients, tumour volume doubling times were calculated from the tumour sizes measured on serial mammograms. The median doubling time was 80 days in patients of younger than 50 at diagnosis, 157 days in patients aged 50-70 years and 188 days in patients older than 70 years.[7] Due to the slower tumour growth rate, which also contributes to the higher sensitivity of mammography, breast cancer can be diagnosed at an even earlier stage. For women aged 50-70 years, the lead-time has been estimated at 3.5 years. Due to the small difference in growth rate between the age categories 50-69 and $\geq$70 years, the lead-time will be about 4 years.

Disease-specific survival

In several studies, disease-specific survival was slightly poorer for older breast cancer patients.[8,9] This was mainly caused by the more advanced stage of the disease at diagnosis; elderly patients were more prone to having a large tumour and distant metastases.[5,8-10] Survival is also influenced adversely by the presence of (several) comorbid diseases and a poor physical condition.[9,11] The effect of early diagnosis may even be lost in breast cancer patients with serious comorbidity, who have an increased risk of dying from causes other than breast cancer.[11] Furthermore, it is the general trend to perform fewer operations or less extensive operations on older breast cancer patients and to administer hormone therapy as adjuvant treatment instead of radiotherapy. A large proportion of these patients receive hormone therapy alone.[8,9,11] Less

intensive treatment, however, does not seem to influence the disease-specific survival.[9]

Owing to the slower growth rate of breast cancer in older women, the diagnosis can be brought forward even further. If this results in a smaller proportion of patients with positive axillary lymph nodes at diagnosis, the reduction in breast cancer mortality may increase. However, as more patients will die from unrelated causes, the increase in life expectancy may be only minimal. Even if life expectancy is unchanged, some patients will benefit from screening, for example in terms of quality of life. This applies to patients who, without screening would have had distant metastases at diagnosis, but who die without metastases because of screening.

The combination of a slower growth rate and the shorter life expectancy will have a negative effect on the side-effects of the screening. Women who, without screening would not have been diagnosed with breast cancer because they died of another cause in the preclinical phase of breast cancer, will be confronted with the diagnosis breast cancer and possibly even be treated. The increase in the number of years lived with the knowledge that breast cancer is present may be even larger than the number of life years gained.

Studies on the effect of screening

Several studies have investigated the effect of mammographic screening on breast cancer mortality and many reviews of the available evidence have been published. Generally, it is concluded that in women aged 50 to 70 years, mammographic screening with or without palpation with an interval of one or two years, reduces breast cancer mortality,[12-15] while for invited women, the reduction in breast cancer mortality is estimated to be 23 to 40%.[12-14] For participants, the reduction may be as large as 45%.[13] The few authors that reviewed screening in elderly women concluded that screening may be effective up to the age of 75 years, but that more research is needed to confirm this.[15,16]

Table 2.4 shows the most important characteristics and results of Dutch screening projects and those of foreign studies that included women aged 70 years and older. The results suggest that, although not statistically significant due to the small numbers of screened women, screening after the age of 70 had a beneficial effect. It should be noted, however, that in most studies, age was defined as age at entry into the trial or age at diagnosis.

Table 2.4 *Studies on the effect of mammographic screening*

Study	Year of start	Design	Screening test	Interval between screenings (yrs)	Endpoint	Follow-up (yrs)	Age at start	Risk ratio (95% CI)
Two county, Sweden[17]	1977	randomized, 77,000 women invited, 56,000 controls	mammography (obl)	2-3	death from breast cancer	8	50-59 60-69 70-74 total 40-74	0.60 (0.40-0.90) 0.65 (0.44-0.95) 0.77 (0.47-1.27) 0.70 (0.55-0.88)
Overview 4 Swedish trials[18] *	1976-82	randomized, 157,000 women invited, 126,000 controls	mammography (obl or cc+obl)	1½-3	breast cancer present at death	5-13	50-59* 60-69* 70-74@ total 40-74	0.71 (0.57-0.89) 0.71 (0.56-0.91) 0.94 (0.60-1.46) 0.76 (0.66-0.87)
Nijmegen[19]	1975	30,000 Nijmegen women invited, case-control study	mammography (obl#)	2	death from breast cancer	7	50-64 65+ total 35+	0.26 (0.10-0.67) 0.81 (0.23-2.75) 0.51 (0.26-0.99)
Utrecht[20]	1974	21,000 Utrecht women invited, case-control study	xerography (cc+lat) + palpation	1, 1½, 2 and 4&	death from breast cancer	11	60-64 total 50-64	0.38 (0.18-0.83) 0.52 (0.32-0.83)
BCDDP[21]	1973	283,222' volunteers, cohort study	mammography (cc+lat) and palpation	1	death from breast cancer	9	50-59 60-74 total 35-74	0.76 (?) 0.74 (?) 0.80 (?)
Duke Tumor Registry[22]	no screening programme	no screening programme, case-control study	any "screening" mammogram	not applicable	metastases from breast can cer	7	60+!	0.73 (0.25-2.14)

BCDDP = Breast Cancer Detection Demonstration Project
mammography: cc = cranio-caudal view, lat = lateral view, obl = medio-latero-oblique view
* *including the two-county trial*
@ *only from the two-county trial*
\# *up to round 3 lateral view*
& *five rounds with different intervals*
! *age at diagnosis*

This does not necessarily correspond with age at the screening examination. The reduction in breast cancer mortality in women aged 50-69 years at entry may be partly due to screening after the age of 69 years.

Methods used to analyse the screening histories leave much to be desired. The randomized trials compared breast cancer mortality in the invited population to that in the non-invited population.[17,18] Participation rates had a very strong influence on the results. The reduction in breast cancer mortality among the screened women will be larger than among invited (participant and non-participant) women. The case-control studies compared breast cancer mortality in "ever screened" and "never screened" women.[19,20,22] "Ever screened", however, may have meant that a woman rejected the screening in the period that the disease was in the preclinical detectable phase, which would have reduced the effect.

Misclassification of the end-point, "death due to breast cancer", may bias the results. Older women often have comorbid disease, which complicates the classification of the cause of death. This may lead to underestimation of the real effect of screening. Breast cancer as an underlying cause of death may be over-reported in screened women, because the disease did not go unnoticed and therefore may be regarded as the cause of death. In the overview of the Swedish trials, the end point used was "breast cancer present at death". Although it was shown that the results were the same whether this end point was used or "death due to breast cancer",[18] there may have been a discrepancy in the elderly women because of the increased risk of death from another cause, with or without breast cancer. This may be an explanation for the disappointing results after 13 years of follow-up in women aged 70-74 years at randomization (a reduction in breast cancer mortality of 6%).[18] After 8 years, a reduction of 23% was found for the end-point "death due to breast cancer".[17]

Continuation of the screening

The most important question for the Dutch national programme, i.e. whether *continuation* of screening after the age of 70 years will further reduce breast cancer mortality, has been studied recently in the Nijmegen programme.[23] A case-referent study was conducted on 33 cases who had died from breast cancer and five referents per case with an identical age at their first invitation and the same number of previous invitations. Eligibility criteria were having been invited at least twice before the diagnosis of breast cancer and age over

64 years at the most recent invitation. In the women aged 65-74, breast cancer mortality in the women who had participated just prior to the diagnosis of the case, relative to those who had not, was reduced by 66% (rate ratio = 0.34, 95% CI 0.12-0.97). Participation before and after the age of 65 years relative to participation before the age of 65 only, was associated with a reduction of 74% (rate ratio 0.26, 95% CI 0.05-1.32). In participants before and after the age of 70 years relative to participants before the age of 70 only, the reduction was 62% (rate ratio 0.38, 95% CI 0.03-4.15). Additional analyses showed that self-selection bias was present in the data. Non-participants (diagnosed after the start of the screening) had a lower mortality rate from breast cancer than was expected on the basis of the Arnhem mortality data. The underlying breast cancer mortality in the participants must have been higher. Therefore, the self-selection bias could not explain our results. It was concluded that continuation of mammographic screening up to the age of 75 years may further reduce breast cancer mortality, whereas the effect of continuation after 75 years remains unclear.

Table 2.5 *Participation rates in round 9 of the Nijmegen programme according to age at invitation*

Age at invitation to round 9 (yrs)	All invited women			Women who had also participated in round 8		
	no. invited	no. screened	participation	no. invited	no. screened	participation
40-49	3,841	2,621	68.2%	2,741	2,322	84.7%
50-59	7,499	5,114	68.2%	5,154	4,499	87.3%
60-69	6,807	4,192	61.6%	4,267	3,692	86.5%
70-74	3,340	806	24.1%	1,605	710	44.2%
75-79	2,042	296	14.5%	683	246	36.0%
80+	2,906	172	5.9%	337	114	33.8%
Total	26,435	13,201	50%	14,787	11,583	78%

Participation

The participation rate in breast screening decreases with increasing age. A variety of factors may be responsible for this. An important one may be the presence of comorbid disease, which decreases a woman's motivation and mobility and dampens her expectations. Table 2.5 shows the Nijmegen participation rates in round 9 according to age at invitation. These rates decrease sharply with increasing age. However, participation was much higher in the women who participated in the previous round.

Cost-effectiveness

De Koning and colleagues[24] calculated that in the Netherlands, biennial mammographic screening of women aged 50-70 years will cost 466 million Dutch guilders in the period 1990-2017. If women aged 70-75 years are included in the target population, the cost will increase by Dfl 64 million.[24] The cost divided by the number of life years gained gave a cost-effect ratio of roughly Dfl. 7650 and Dfl. 8200 per life year gained for the first and second alternatives, respectively. The cost for each quality adjusted life year gained was estimated to be Dfl. 8100 and Dfl. 8900, respectively.[24]

However, the higher cost per life year gained by screening after the age of 70 years may not be a valid argument for establishing an upper age limit, because it encourages age discrimination.[25,26] It should be considered whether the total cost of expanding the target population would make to high a claim on the total budget for the health service and obstruct the implementation of other health facilities.

Conclusion

The incidence of breast cancer is highest among women aged 70 years and older. Compared to younger women, elderly women are more likely to have distant metastases at diagnosis and the disease-specific survival of disseminated breast cancer seems to be poor. Even if breast cancer is diagnosed at an early stage, it will not improve the survival of patients with several chronic co-existing diseases.

The value of screening for breast cancer in women of over 70 years depends on several factors. In this age category, mammography is a good screening test. Trials indicate a possible breast cancer mortality reduction due to (the continuation of) biennial screening up to the age of 75 years. The magnitude of the mortality reduction, however, remains unclear.

Owing to the shorter life expectancy and a slower tumour growth rate, over-diagnosis and over-treatment may occur. The number of years that a woman has to live with the knowledge that she has breast cancer may increase even more than the number of life years gained. A longer screening interval (e.g. 3 years) may reduce both the cost and side-effects.

In women with several comorbid diseases, screening for breast cancer will not improve survival. It is very likely that selective participation will occur: mainly the women in whom benefit can be expected, will continue to participate. Lack of evidence prevents us from drawing any conclusions about how long they should continue to participate.

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Chapter 3

Validity of mammography

The current detectability of breast cancer in a mammographic screening programme: a review of the previous mammograms of interval and screen-detected cancers

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Cancer 1993; 72: 1933-8

One versus two-view mammography in baseline screening for breast cancer: a review

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Introduction

In Chapter 2, the effect of increasing age on the quality of mammography as a screening test was outlined. The sensitivity may increase in the elderly because glandular tissue is gradually replaced by fat, while the specificity may increase because the frequency of benign breast disease is lower. This Chapter presents a study on the detectability of breast cancer with mammography, published in *Cancer 1993; 72: 1933-8*. Previous negative mammograms of screen-detected patients and interval cancer patients were reviewed. It was recorded whether or not mammographic signs of the cancer were visible on the previous, negative, mammogram, and if so, whether or not the signs could have led to the diagnosis of breast cancer. At the end of this Chapter, in the section "Age-specific detectability" (page 53) the relation between age at screening and the classification of the previous mammogram is discussed.

Usually, signs of benign breast diseases are also visible on a mammogram, but it may be very difficult to discriminate between "benign" and "malignant" signs. This results in the referral of women without breast cancer for diagnostic work-up, which reduces the specificity of mammographic screening. Both the sensitivity and the specificity may increase if two-view mammography is used instead of one-view. However, the financial cost and the exposure to radiation will also increase. The literature was reviewed on the effect of one-view and two-view mammography in baseline screening (*The British Journal of Radiology 1992; 65: 971-6*). This study in perspective with very recent publications on the subject is also included in this Chapter (page 42 and page 54, respectively).

The current detectability of breast cancer in a mammographic screening programme: A review of the previous mammograms of interval and screen-detected cancers

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Abstract

The occurrence of an interval cancer in a mammographic screening programme is indicative of a suboptimum effect on mortality, because the very aim of the screening is to detect as many cancers as possible and at their earliest possible stage. In several studies, the previous screening mammograms of patients with an interval cancer were reviewed and the reasons for the "missed diagnosis" were classified into four categories: "screening error" (20-29%), "minimal sign present" (30-40%), "radiographically occult" (33-58%), or "radiographically occult at diagnosis" (occult both at previous screening and diagnosis; 7-16%). A similar procedure was followed in the Nijmegen screening project with patients recently diagnosed as having interval cancer or screen-detected cancer.

The previous screening mammograms of 40 interval and 44 screen-detected cases from the breast cancer screening programme in Nijmegen were reviewed and categorised as specified above. These breast cancers were diagnosed clinically before the patient was invited to the eighth screening round (interval cancer) or were detected at the eighth screening round (screen-detected cancer). All these patients had been screened in the seventh round (1987-88).

Thirteen percent of all cases were classified as "screening error", 38% as "minimal sign present", 43% as "radiographically occult", and 6% as "radiographically occult at diagnosis". In nearly half of the screen-detected cancers, minimal signs appeared to be present on the previous screening mammogram 2 years befor the diagnosis.

Annual instead of biennial screening may advance detection in most of the "screening error" cases as well as in some in the categories "minimal sign present" and "radiographically occult" at the previous screening. Meticulous analysis of the radiological characteristics of the "minimal sign present" cases may very well lead to results showing that earlier detection is possible without a significant decrease in the specificity of the screening test.

Introduction

Over the past few years, the technical quality of mammography, currently the most reliable screening test for the early detection of breast cancer,[1] has been improved considerably. This apparently increased the number of breast cancer cases detected and decreased the number of cancers missed at the screening. Consequently, this development may have had a beneficial effect on breast cancer mortality.

So far, only the results of studies on interval cancers, that is, cancers which were clinically diagnosed after a "negative" screening examination and before the next scheduled screening, have been reported. Reasons for the missed diagnosis of these cancers were revealed by a review of the "negative" mammograms taken at the previous screening examination.[2-6] They were classified as screening errors, minimal or non-specific sign present, radiographically occult, and radiographically occult both at the previous screening and at diagnosis (Table 3.1). This classification of the previous "negative" screening mammograms can also be applied to the screen-detected cases, with the exception of the category "radiographically occult at diagnosis", if mammography is the sole screening test.

Table 3.1 *Classification of previous screening mammograms of patients with interval cancer in the literature*

Reference	No. of cases	Classification of previous screening mammograms			
		Screening error (%)	Minimal sign (%)	Radiograph occult (%)	Radiograph occult at diagnosis (%)
Martin et al.[3]	48	29	38	33	—
Von Rosen et al.[4]	42	24	33	36	7
Frisell et al.[5]	60	20	28	52	—
Peeters et al.[6]	153	26	—	58	16

In the current study, we reviewed the previous "negative" screening mammograms of patients with recently diagnosed breast cancers. The study population comprised, in addition to the interval cancers, the screen-detected cases of the Nijmegen screening programme.

Patients, mammograms, and methods

Since 1975, a population-based mammographic breast cancer screening has been in progress in the city of Nijmegen, The Netherlands. Single-view mammography is applied biennially as the only screening modality. Results of the first six screening rounds have been reported earlier.[7]

The objective of the current study was to review the previous screening mammograms of recently diagnosed breast cancer patients. Two groups of patients were studied. The first group comprised 41 interval cancer cases that had been clinically diagnosed with primary breast cancer after a negative screening result in the seventh round (1987-88), but before their invitation to the eighth round. One of these patients had to be excluded because both the mammogram and the report were no longer available. The second group consisted of 57 primary breast cancer cases that were detected on the mammogram taken in round 8 (1989-90). Thirteen cases were excluded because they had not attended the screening in round 7. Patients with the sole histologic tumor type of "lobular carcinoma in situ" were also excluded. Thus, a total of 84 patients was studied.

The mammogram at diagnosis of each patient was reviewed by the radiologist (JH). (In four cases the mammogram was missing and only the report was available.) Then the previous mammograms, taken during the seventh screening examination, were reviewed with knowledge of the site and radiologic signs of the tumor. The cases were classified into one of the following four groups:

Screening error: (1) if malignant signs were present that had not been perceived or had been misinterpreted (i.e., present but interpreted as benign); (2) if the tumor, visible at diagnosis, had been outside the imaging field because of faulty positioning; or (3) if the malignant signs could not have been noticed because of a technically poor mammogram.

Minimal sign present: if a radiological sign had been observed that was considered to be nonspecific for the presence of a malignant tumor (i.e., that it did not necessitate a further diagnostic evaluation).

Radiographically occult: if no changes at all could be seen on the previous mammogram.

Radiographically occult at diagnosis: if no signs suspicious of malig nancy could be identified on both the diagnostic and the previous screening mammogram; these cases were detected by physical examination.

At the review, the radiologic characteristics such as tumor localization and size, as well as the density of the breast parenchyma according to Wolfe's classification,[8] were recorded. The screening history and histologic characteristics of the tumor were available from the screening and hospital files.

Results

Thirteen percent of the previous mammograms (Table 3.2) were classified as "screening error", 38% as "minimal sign present", 43% as "radiographically occult" and 6% as "radiographically occult at diagnosis".

The categories are outlined separately below.

Table 3.2 *Classification of previous screening mammograms of 84 patients with breast cancer*

Group	No. of cases (%)	Classification of previous mammogram			
		Screening error (%)	Minimal sign present (%)	Radiograph occult (%)	Radiograph occult at diagnosis (%)
All cancers	84 (100)	11 (13)	32 (38)	36 (43)	5 (6)
Interval cancer	40 (100)	7 (18)	11 (28)	17 (42)	5 (12)
Screen-detected cancer	44 (100)	4 (9)	21 (48)	19 (43)	Not applicable

Screening Error

In 11 patients, the diagnosis had been missed as a result of errors made in the screening process. In two of them, technical errors had been responsible, due to poor positioning in one case and poor technical quality in the other. In the remaining nine cases, one lesion had been misinterpreted, whereas eight lesions had not been perceived. Table 3.3 shows the radiologic signs present on the patients' previous mammograms. Most of them had a tumor mass with a malignant appearance. All the cancers were invasive and 55% of the patients had axillary lymph node involvement (Table 3.4).

Table 3.3 *Radiologic signs on the previous screening mammogram for "screening error" and "minimal sign present"*

Radiologic sign	Classification of previous mammogram	
	Screening error (%)	Minimal sign present (%)
Vague density		15 (47)
Density	7 (70)	5 (16)
Microcalcifications	2 (20)	8 (25)
Density + microcalcifications	0 (0)	1 (3)
Distortion of architecture	1 (10)	3 (9)
Total	10 (100)*	32 (100)

* *One value missing because of poor positioning*

Minimal Sign Present

Twenty-eight percent of the patients with interval cancers and 48% with screen-detected cancers showed minimal signs on the previous screening mammogram (Table 3.2).

At diagnosis, these tumors appeared to be larger and had a higher prevalence of axillary node involvement than those classified as "radiographically occult" (Table 3.4).

Table 3.3 shows the type of radiologic signs visible on the patients' previous mammograms, the majority of which (almost 50%) consisted of vague densities.

Radiographically occult

Forty-three percent of the tumors (Table 3.2) were "radiographically occult" on the previous mammogram. Some tumors in this category must have been fast growing and therefore may have been smaller than the threshold size of radiologic detection, whereas others may have been masked by dense breast tissue.[9] Nevertheless, many of these tumors were located in fatty tissue (61%), suggesting a fast growth.

The tumor stage at diagnosis in this category was the most favorable: 31% of the tumors had a diameter of 1 cm or less at diagnosis, compared to only 9%, 11% and 0% in the other categories, respectively (Table 3.4). Axillary node involvement was 31% and almost 50%, respectively (Table 3.4).

Table 3.4 *Characteristics of tumor and breast parenchyma in 84 breast cancer patients by review category*

Characteristic	Total (%)	Classification of previous mammogram			
		Screening error (%)	Minimal sign present (%)	Radio-graph occult (%)	Radiog-raph occult at diagnosis (%)
No.	84	11	32	36	5
Interval cancer	40 (48)	7 (64)	11 (34)	17 (47)	5 (100)
Screen-detected cancer	44 (52)	4 (36)	21 (66)	19 (53)	0 (0)
Tumor					
Main sign on diagnostic mammogram:					
Density	79				
Microcalcifications	50 (63)	8 (73)	20 (63)	22 (61)	—
Density + microcalcifications	13 (16)	0 (0)	7 (22)	6 (17)	—
Distortion of architecture	10 (13)	2 (18)	4 (13)	4 (11)	—
	6 (8)	1 (9)	1 (3)	4 (11)	—
Histologic type:	83				
Ductal in situ	9 (11)	0 (0)	5 (16)	4 (11)	0 (0)
Ductal invasive	52 (63)	8 (73)	19 (59)	23 (64)	2 (50)
Lobular invasive	15 (18)	2 (18)	6 (19)	5 (14)	2 (50)
Other	7 (8)	1 (9)	2 (6)	4 (11)	0 (0)
Tumor size on diagnostic mammogram (mm)*,†:	74				
≤10	14 (19)	1 (9)	3 (11)	10 (31)	0 (0)
11-20	32 (43)	4 (36)	12 (44)	14 (44)	2 (50)
>20	28 (38)	6 (55)	12 (44)	8 (25)	2 (50)
Axillary lymph nodes*:	74				
Positive	31 (42)	6 (55)	13 (48)	10 (31)	2 (50)
Negative	43 (58)	5 (45)	14 (52)	22 (69)	2 (50)
Breast parenchyma					
Wolfe previous mammogram:	84				
N1, P1	45 (54)	5 (45)	16 (50)	22 (61)	2 (40)
P2, DY	39 (46)	6 (55)	16 (50)	14 (39)	3 (60)

* *Invasive tumors only.*

† *Histologic tumor size if no mammographic size could be measured.*

Radiographically occult at diagnosis

This category comprised 6% of all the cases. Their histologic type was "invasive ductal" (n = 2) or "invasive lobular" (n = 2). It is known that these latter are difficult to detect by mammography owing to their diffuse growth pattern and poor desmoplastic reaction.[9] The two lobular carcinomas were situated in breast tissue classified as Wolfe's N1 and P1, whereas the two ductal carcinomas were situated in P1 and P2 breast parenchyma, respectively.

At diagnosis, the tumors were large and had a high prevalence of positive axillary nodes (50%). This advanced stage may have been due to the late diagnosis because of the shortcomings of the mammographical technique in these types of cancer. They might very well remain undetected at the screening unless palpation were part of the test.

Discussion

Currently, mammography is the most valuable test for diagnosing early breast cancer, especially if it is applied at regular intervals within a screening programme.[1] False-negative screening test results (i.e., negative results despite of the presence of malignant signs that should have been noticed) cause a delay in treatment and may jeopardize the effectiveness of the screening. It has been recognized that interval cancers may represent potential false-negative results,[2-4,6,10] whereas screen-detected cancers always were considered to be the true-positive results. In the current study of the Nijmegen breast cancer screening programme, the previous mammograms of the patients not only with interval cancers but also with screen-detected cancers were reviewed and categorised. In 9% of the screen-detected patients, the previous screening result was true false-negative (classified as "screening error" in Table 3.2) which had delayed the diagnosis by two years.

Since the introduction of breast cancer screening in Nijmegen in 1975, both the experience of the radiologist in reading mammograms and the technical quality have increased considerably. This should have improved the detection capability and reduced the occurrence of interval cancers. The detection rates of the successive screening rounds since 1975, however, have not increased, nor the proportion of interval cancers declined (Table 3.5). An explanation may be that although more lesions become visible because of the improved resolving power of the mammography, our criteria for referral for diagnostic evaluation have become stricter as a consequence of our policy to reduce the number of false-positive results. This assumption is supported by the increase in the specificity rates (calculated according to Brecht and Robra[11]) over the progressive screening rounds (Table 3.5).

In our earlier study on interval cancers,[6] a somewhat different categorisation was used compared to that of the current study, which makes it difficult to judge whether the recent technical improvements have influenced at all the distribution among the various categories. This distribution not only depends

on the categories actually used but also on the definition of the (fairly subjective) cutoff point for a positive test result. If an aggressive screening strategy is applied (i.e., emphasis is laid on the detection of as many cancers as possible) then some "minimal sign present" cases will be classified as "screening errors". If the differences in classification are taken into account, the results of the patients with interval cancer in the current study agree fairly well with those published in these papers (Tables 3.1, 3.2).[3-6]

Table 3.5 *Result of eight successive screening rounds in the Nijmegen programme*

Round	No of women screened	Positive test result	Screen-detected cancer*	Cancer detection rate†	Specificity rate‖ (%)	Interval cancer*	Interval cancer rate†	% interval cancer‡
1	19,702	254	75	3 81	99 09	31	1 57	29
2	19,787	198	77	3 89	99 39	36	1 82	32
3	16,629	122	49	2 95	99 56	32	1 92	35
4	15,091	125	45	3 11	99 47	35	2 32	43
5	16,169	110	56	3 46	99 66	26	1.61	32
6	16,478	81	61	3 82	99 88	37	2.24	37
7	16,464	98	57	3 46	99 75	41	2 49	42
8	15,184	82	54	3 75	99 81	14§	—	—

* *Lobular carcinoma in situ not included*
† *Per 1000 women screened*
‡ *Relative to screen-detected + interval cancers*
§ *Follow-up period not yet completed*

No reports are available on screen-detected cases for comparison with our results. In almost 10% of these cases, the diagnosis was delayed by 2 years because of a false-negative screening result. Furthermore, the percentage of "minimal sign present" cases (48%) was striking. Only 43% of the screen-detected cases did not show any radiologic signs at all on their previous mammogram (Table 3.2).

A reduction of the screening interval from 2 years to 1 year may reduce the number of interval cancers and advance the time of detection of some of the screen-detected cases. All "screening error" cases without clinically suspect signs in the interscreening period probably would be discovered at the next screening, 1 year later. Thus, in our population the diagnosis would have been made 1 to 7 months earlier in six out of the seven interval cancers, and 1 year

earlier in the four screen-detected cancers. In addition, some cases in the categories "minimal sign present" and "radiographically occult" at the previous screening may have shown clear malignant signs 1 year later. In the patients with interval cancer, however, 55% of the "minimal sign present" cases and 25% of the "radiographically occult" cases were diagnosed clinically within a year, so annual screening would not have been of any benefit to them. It is not clear if advancing the diagnosis with a maximum of 1 year would have any effect in further reducing the breast cancer mortality.

Obviously, screening errors should be prevented as much as possible. This can be achieved in various ways —for example by thorough training of the radiologists and mammography radiographers, by ensuring a high technical quality of the mammography films and by applying double reading.[12]

It may be wondered whether not at least a proportion of the "minimal sign present" cases might have been detected at the previous screening round. If less specific signs had been accepted for a positive test result, the increase in false-positive results would have been considerably greater than the increase in true-positive ones. This is illustrated by Moskowitz in a study of 40,431 mammographic screening examinations.[13] If "benign appearing masses" had been included in the definition of a positive screening result, the number of false-positives would have increased by approximately 600, whereas 6 additional cancers (true-positive results) would have been detected.

Insight into the magnitude of the increase in sensitivity and the decrease in specificity might be obtained by studying the prevalence of minimal signs on the screening mammograms, and relating the outcome to the diagnosis. A radiological analysis of these cancers is necessary to find out whether these signs can be specified in such a way that the sensitivity is improved without any significant decrease in the specificity of the mammographic screening test.

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One versus two-view mammography in baseline screening for breast cancer: a review

JAAM van Dijck, ALM Verbeek, JHCL Hendriks, R Holland

Abstract

Two-view mammography is generally preferred as an initial screening examination because the number of missed carcinomas and false positive results in one-view mammography is considered to be large. The present review was performed to assess the difference in screening quality between one- and two-view mammography. Nineteen previous studies were reviewed and differences in sensitivity as well as specificity of two-view and one-view mammography were calculated. The results ranged from - 5.7% to 19.4% (median 3.9%), and 2.7% to 36.1% (median 14.8%), respectively, and indicate a higher screening quality of two-view mammography. However, in the studies considered there is a large variation in study population, screening tests used and assessment of disease outcome, which makes the numerical results less conclusive. None of the studies provided adequate information for deciding whether two-view mammography in baseline screening for breast cancer is preferable to one-view mammography. If a screening programme using one-view mammography has already achieved high sensitivity and specificity, the value of an additional craniocaudal view is only marginal.

Introduction

The maximum reduction in breast cancer mortality that can be reached by mammographic screening depends to a large extent on the quality of the screening test. Ideally all women with preclinical breast cancer should show positive, and all others negative, screening test results.

Since the introduction of mammography in breast cancer screening, the number of views to be used, particularly for the first screening examination, has been debated. Two-view mammography, *i.e.* mediolateral oblique and craniocaudal projections of each breast, has been criticized because compared with one-view, *i.e.* the oblique projection, the radiation dose is twice as high,

the costs are higher, and it takes longer to perform and interpret. However, sensitivity and specificity may both decrease if only one view is used.

In theory, if two independent screening tests instead of one are used, more cases of the disease will be detected (higher sensitivity), and more women without the disease will have a false positive test result (lower specificity) because the combined result is positive if both tests are positive as well as if either one of the tests is positive.[14] The test result of a two-view mammogram, however, is not the same as the combined result of an oblique and craniocaudal projection read separately because further evaluation of the lesion on the second view may lead to a negative two-view result. This means that the sensitivity of two-view mammography is not necessarily higher and the specificity is not necessarily lower than that of one-view.

Different studies on this subject have reached different conclusions. Some authors recommend one-view mammography because only very few cancers would be missed.[15-17] Others argue that in one-view mammography the number of false negative results or the number of false positive results is too high,[18-23] especially in women with dense breast tissue.[24,25] The extensive and expensive diagnostic tests which will follow a false positive screening result may cause severe strain or physical harm to women and will lead to extra costs.

The best way to evaluate the screening quality of one-view versus two-view mammography would be to conduct a randomized controlled trial. Random allocation of the target population, *i.e.* women who are having a baseline screening for breast cancer, to one or two-view mammography would ensure comparability of populations in terms of prevalence and spectrum of malignant and benign breast disease as well as breast parenchyma. Only one screening centre and one radiologist should be involved, to avoid variation in technical quality of the mammograms and between observers. Follow-up for a year should allow for clinical diagnosis of those with false negative results.

The population of such a study would have to be very large to be able to estimate the sensitivities and specificities with acceptable precision because breast cancer is a relatively rare disease (at initial screening about seven breast cancer cases may be detected in 1000 women screened). Before deciding whether or not such a large-scale randomized study is justified, the difference in sensitivity and specificity between two-view and one-view mammography was quantified in the present literature review, with special emphasis on design and study population.

Studies and methods

Identification and selection of published studies

A list of published studies was compiled by checking literature references and by performing a MEDLINE CD-ROM search covering the period up to July 1991. The index terms used were "breast neoplasms" and "mammography", followed by a search for "view(s)" and "projection(s)" in title and abstract. Studies could only be included if the test results had been related to the diagnosis and if the numbers of true and false positive results and true and false negative results of both mammographic tests had been presented. Nineteen studies were included. All the studies were reviewed for the methods of sampling the study population, the mammographic tests compared, and the proper assessment of disease outcome of the study population (particularly women with a negative screening test result).

Test characteristics of two against one-view mammography

If the tests are evaluated in the same population, the respective numbers of women with and without the disease are equal for the two and one-view situations: A+C = a+c and B+D = b+d (Table 3.6).

Test results reported in more than two alternatives, for instance "negative", "additional views required" and "positive" or "negative", "probably malignant" and "malignant", were made dichotomous by regarding "negative" as the negative test result, and all other alternatives as positive.

The percentage difference in sensitivity between two- and one-view mammography, D_{sens}, was calculated as the difference in true positive results divided by the number of breast cancer patients, multiplied by 100 (see Equation (1), Table 3.6). The percentage difference in specificity between the two- and one-view test, D_{spec}, was calculated as the difference in true negative results divided by the number of "non-cases", multiplied by 100 (see Equation (2), Table 3.6).

The reciprocal of the number of cases [1/(A+C)] and the reciprocal of the number of non-cases [1/(B+D)] were defined as indicators of the precision of D_{sens} and D_{spec}, respectively, and were calculated. If in any study two or more radiologists had read both the one- and two-view mammograms, a combined difference in sensitivity and specificity was calculated, using the mean difference in true positives and true negatives, respectively.

Table 3.6 *Sensitivity and specificity of two-view and one-view screening test*

Two-view mammography

Test result	Breast cancer: yes	Breast cancer: no
+	A	B
−	C	D
	A+C	B+D

$$\text{Sensitivity} = \frac{A}{A+C}$$

$$\text{Specificity} = \frac{D}{B+D}$$

One-view mammography

Test result	Breast cancer: yes	Breast cancer: no
+	a	b
−	c	d
	a+c	b+d

$$\text{Sensitivity} = \frac{a}{a+c}$$

$$\text{Specificity} = \frac{d}{b+d}$$

$$D_{sens} = \frac{A-a}{A+C} \times 100\% = \frac{A-a}{a+c} \times 100\%$$

$$D_{spec} = \frac{D-d}{B+D} \times 100\% = \frac{D-d}{b+d} \times 100\%$$

D_{sens}: *Difference in sensitivity between two-view and one-view mammography.*
D_{spec}: *Difference in specificity between two-view and one view mammography.*

Results

Eighteen publications were selected. Buchanan & Jager[26] described 2 substudies, both of which were included; Muir and colleages[21] reported 3 substudies of which only the first one could be used, so that in all, we included a total of 19 studies. Table 3.7 summarizes the studies according to population size, age, and modifiers of D_{sens} and D_{spec}. These modifiers include population characteristics, such as screening or patient population, tests applied and assessment of disease outcome, on which the sensitivity and specificity are dependent. By implication, D_{sens} and D_{spec} will depend on these factors as well. A more detailed description of these modifiers is given in the Discussion section, below.

All studies can be criticized with regard to at least one modifier. The studies listed in the upper part of Table 3.7 report on populations or compare tests that are inadequate to answer the question posed by this review.

Table 3 7 *Studies according to population size, age and modifiers of D_{sens} and D_{spec}*

Study	No of cases	No of "non-cases"	Age (yrs)	Population				Tests applied					Out come*
				A	B	C	D	E	F	G	H	I	
Weishaar 1976[16]	223	0	nm	—	—	—	nr	—	+	—	+	+	nr
Locker 1988[17]	352	0	nm	—	—	+	nr	+	+	±	+	+	nr
Moskowitz 1977[18]	31	119	nm	+	—	—	—	—	—	—	+	+	±
Andersson 1978[19]	478	0	nm	—	—	+	nr	+	+	±	+	+	nr
Bassett 1983[27]	80	0	33-87	—	—	—	nr	+	+	±	+	+	nr
Muir 1984[21]	0	303	45 64	—	—	nr	+	+	+	+	+	+	—
Bassett 1987[28]	169	194	28-94	—	—	+	—	+	+	+	+	—	+
Bassett 1989[23]	169	0	nm	—	—	+	nr	+	+	±	—	+	nr
Cukier 1977[24]	106	0	nm	±	—	—	nr	—	—	+	+	+	nr
Buchanan 1977[26] 1st	160	0	nm	±	—	—	nr	—	—	—	+	—	nr
Buchanan 1977[26] 2nd	50	30	nm	±	—	+	nr	—	—	—	+	—	+
Huppe 1977[29]	277	0	nm	—	—	—	nr	+	+	+	+	+	nr
Libshitz 1976[30]	88	0	nm	—	—	+	nr	—	—	—	—	—	nr
Pagani 1980[31]	53	20	nm	—	—	+	nr	—	+	+	+	+	+
Lundgren 1976[15]	34	860	35+	+	+	—	—	—	+	+	+	+	—
Andersson 1981[20]	117	100	45-69	+	+	—	—	+	+	—	+	+	±
Sickles 1986[22]	27	2473	nm	+	+	+	+	+	+	+	+	+	—
Anttinen 1989[32]	34	269	50-52	+	+	—	+	+	+	+	+	+	+
Ikeda 1988[25]	5	995	av 57	+	—	nr	+	+	+	+	—	+	—

+ = yes, — = no, ± = partly, nm not mentioned, nr not relevant (in column D and J because no non-cases were included, in column C because D_{sens} was not calculated), av average

***A** asymptomatic population (breast cancer screening programme), **B** baseline screening, **C** cases include those with initially false negative results, **D** non-cases randomly sampled from initially true negatives and false positives **E** cc+oblique versus oblique (if — lateral view or three-view), **F** film-mammography (if — xero), **G** revision of both tests (if ± two-view results by combining separately read oblique and craniocaudal views), **H** revision without additional information, **I** no use of "additional views requested/equivocal"*

** Diagnostic work-up/follow-up of the screening test negatives (if ± women with false positive one-view result were free of breast cancer)*

NOTE Bassett 1987[28] and Bassett 1989[23] based on the same patients and including the 80 patients of Bassett 1983[27]

Table 3.8 *Sensitivity of two-view mammography, D_{sens}, two-view specificity and D_{spec} according to study*

Study	Sensitivity 2-view	D_{sens}*	Specificity 2-view	D_{spec}*
Weishaar 1976[16]	100%†	1.3% (0.004)	—	—
Locker 1988[17]	81.8%	3.9% (0.003)	—	—
Moskowitz 1977[18]	100%†	19.4% (0.032)	100%†	36.1% (0.008)
Andersson 1978[19]	94.3%	4.7 (0.002)	—	—
Bassett 1983[27]	100%	1.3% (0.013)	—	—
Muir 1984[21]	—	—	95.7%	5.3% (0.003)
Bassett 1987[28]	84%	−5.7% (0.006)	87.7%	26.3% (0.005)
Bassett 1989[23]	91.9%	6.4% (0.006)	—	—
Cukier 1977[24]	99.1%	1.4% (0.009)	—	—
Buchanan 1977[26] 1st	100%†	1.3% (0.006)	—	—
Buchanan 1977[26] 2nd	96.0%†	−2.0% (0.020)	90.0%†	21.0 (0.033)
Hüppe 1977[29]	96.4%	8.7% (0.004)	—	—
Libshitz 1976[30]	96.6%†	3.4% (0.0011)	—	—
Pagani 1980[31] ‡	81.6%	8.5% (0.019)	—	—
Lundgren 1976[15]	100%	0% (0.029)	93.8%	14.8% (0.001)
Andersson 1981[20]	100%†	6.3% (0.009)	97.4%†	4.4% (0.010)
Sickles 1986[22]	100%	7.4% (0.037)	93.9%	18.8% (0.0004)
Anttinen 1989[32]	87.5%	18.4 (0.029)	66.9%	2.7% (0.004)
Ikeda 1988[25] §	—	—	98.8%	4.9% (0.001)

* *In parentheses: precision of D_{sens} (1/(A+C): see text) and D_{spec} (1/(B+D): see text)*
† *Based on original screening or diagnostic test result*
‡ *D_{spec} not calculated because no test results of the non-cases were given by the author*
§ *D_{sens} not calculated because of small number of cases*

Table 3.8 shows sensitivity and specificity of two-view mammography, as well as D_{sens} and D_{spec}. D_{sens} was calculated from 17 studies and ranged from -5.7% to 19.4% (median 3.9%, mean 5.0%, standard deviation 6.5%). D_{spec} was calculated from nine studies and varied from 2.7% to 36.1% (median 14.8%, mean 14.9%, standard deviation 11.6%).

Figure 3.1 shows D_{sens} (vertical axis) in relation to the precision (horizontal axis). In 14 out of 17 studies the sensitivity of two-view was higher than that of one-view ($D_{sens}>0\%$), while one study showed no difference. In two studies D_{sens} was very high (18.4% and 19.4%), but these studies lacked precision. In the studies listed in the lower part of Table 3.8 D_{sens} does not seem to differ from the values for the studies in the upper part, although tending to be less precise.

Figure 3.2 shows D_{spec} (vertical axis) against precision (horizontal axis). The variation is very large. In 4 studies D_{spec} varies from 2.5% to 5.5%, but in 5 other studies it varies from 14.8% to 36.1%. D_{spec} tends to be larger and less precise for the studies listed in the upper part of Tables 3.7 and 3.8.

Figure 3.3 shows D_{sens} and D_{spec} simultaneously for those studies that report both sensitivity and specificity (only 7 studies do so). No relation between D_{sens} and D_{spec} can be observed.

Figure 3.1 *D_{sens} (%) and corresponding precision in 17 studies*

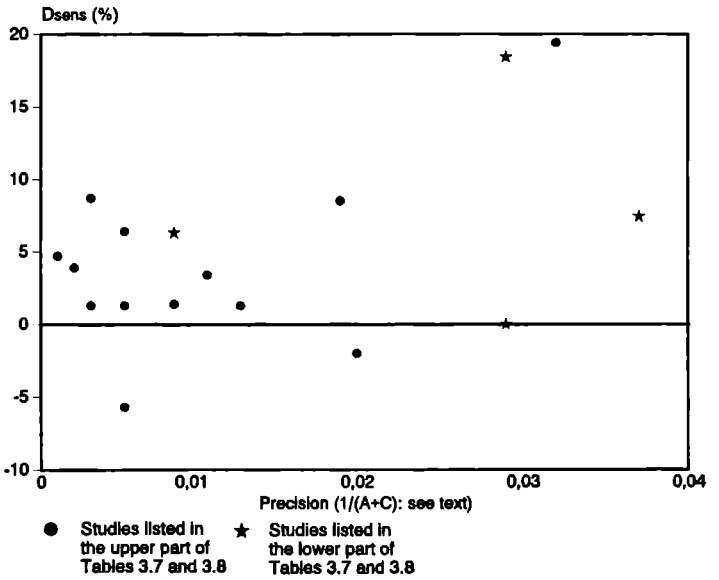


Figure 3.2 D_{spec} *(%) and corresponding precision in 9 studies*

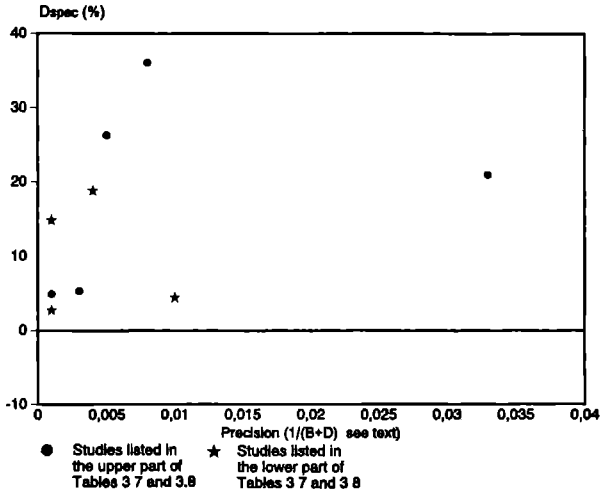
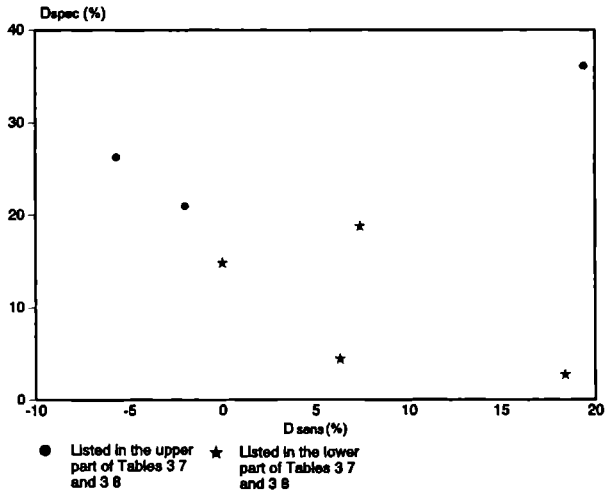


Figure 3.3 D_{sens} *(%) and* D_{spec} *(%) in 7 studies reporting both sensitivity and specificity*



Discussion

The sensitivity and specificity of a screening test are influenced by characteristics of the study population, the test applied, and the assessment of disease outcome. As a consequence, D_{sens} and D_{spec} may also be affected by these modifiers. Table 3.7 presents the studies according to numbers of breast cancer cases and "non-cases", age (which was rarely mentioned), and presence (+) or absence (-) of several items on which the modifiers were scored.

First, study populations should be samples from the general population and not taken from a clinic where women present with breast complaints. The larger tumor size at diagnosis yields higher sensitivities and the presence of benign breast disease yields lower specificities, which increases the likelihood of differences in D_{sens} and D_{spec}. Furthermore, cases as well as controls should be included. In populations of breast cancer cases only the sensitivity cannot be assessed properly because visibility of the tumor on one projection will almost certainly lead to a positive test result if the radiologist is aware of the diagnosis of breast cancer for the whole set of cases. Also, case series should include women with false negative mammographic screening results, whereas control series should be a random sample of all "non-cases" (those with initially true negative or false positive results). In populations of only women with initially (true or false) positive test results some kind of lesion will be present on all mammograms, which will make it very difficult to decide which are negative. Even if a large sample of screen-negatives are included the results will be biased, as can be illustrated by Lundgren and Jakobsson's study.[15] Here 210 women with positive one-view screening results, 65 women with a positive history and 618 of 5804 with negative screening results had three-view mammography. One and three-view mammograms were reviewed by a blinded radiologist. In this study population, specificities were 79.5% and 94.3%, respectively, but in the unselected screening population, one-view specificity was as high as 97.0%. In conclusion, unbiased estimates of D_{spec} can only be obtained if the "non-cases" are a random sample of those with initially true negative or false positive screening results.

The technical quality of the mammograms and the reading ability of the reviewing radiologists vary between the studies. Interobserver variation can be illustrated by Anttinen's study in which four radiologists read the same mammograms.[32] Radiologist 1's reading of one-view mammograms had a higher sensitivity than radiologist 4's reading of two-view. However, Radi-

ologist 1's specificity on two-view reading was much lower than that of Radiologist 4 on one-view reading.

Furthermore, the use of xerography, three-view mammography, the lateral view, or the availability of previous mammograms will influence the study result. Moreover, if in any study only the oblique view is reviewed and the results are compared with the screening results of two-view mammography, work-up bias and inter-observer variation can occur. Finally, in some studies one of the alternative qualifications was "additional views required for confirmation of malignancy" or "equivocal". It will be clear that many more verdicts of "additional views required" are found at one-view readings. If the radiologist must choose between "positive" and "negative" without the option of "additional views", they will sometimes choose "negative", which leads to different cut-off points for a positive test for one- and two-view mammography.

A final modifier of D_{sens} and D_{spec} is the assesment of disease outcome. The definitive diagnosis (presence of absence of breast cancer), which is required for the calculation of sensitivity and specificity, will be known for women whose screening yielded positive results who then underwent diagnostic tests. Those whose test results were negative, on the other hand, are not tested further; and some may be falsely negative because not all breast cancers show mammographically suspect signs at the screening examination.[6] D_{spec} will hardly change because the number of true negatives is usually large and constant. Therefore, follow-up data must be available to provide information on the number of cancers missed at the screening but diagnosed clinically later on, allowing for an unbiased estimation of D_{sens}.

Tables 3.7 and 3.8 show two groups of studies. Those in the upper part of the Tables reported on the population and/or applied tests which were not very suitable in answering the question of this review. The median D_{sens} of the studies of the lower part of Table 3.8 was 6.9%. The negative sign for D_{sens} and the very large D_{spec} in Bassett's[28] and Buchanan's[26] studies have probably been caused by the use of the alternative score "additional views required". In Lundgren and Jakobsson's study[15] D_{sens} might have been larger than zero if follow-up data had been available to adjust for cancers missed at one-view screening but detectable at two-view.

According to Figure 3.2, all nine studies had fewer false positive results with two-view mammography. D_{spec} was largest in studies listed in the upper part of Table 3.8. Considering only studies listed in the lower part of Table 3.8, the median for D_{spec} was 4.9%. Assuming D_{spec} = 5% and a two-view

specificity of 90%, then of 10,000 women screened 1,000 will have a false positive result on two-view mammography and 1,500 on one-view mammography. If the two-view specificity is 99%, then these numbers are 100 and 600, respectively. In both examples the difference is 500 false positive results, but in the first, one-view yields 50% more false positive results and in the second 500%.

It can be concluded that two-view mammography detects more cases and reduces the number of unnecessary diagnostic tests. However, the differences can hardly be assessed. Probably the gain in sensitivity and specificity by the addition of the craniocaudal view is highest for radiologists who are relatively inexperienced in reading mammograms. They may not be able to reach a high sensitivity as well as a high specificity even with two views available.

Whether the two-view screening test is more effective depends not only on D_{sens} and D_{spec}, but also on the sensitivities and specificities themselves. For example, Peeters and colleagues reported a sensitivity of 93% and a specificity of 99% of a screening test consisting of one-view mammography only.[7] If with the oblique view alone 93% of the breast cancer cases can be detected and only 1% of the women without breast cancer must undergo unnecessary diagnostic tests, it may be concluded that although two-view may yield more true positive and true negative results, it will probably be less cost-effective. If the baseline mammograms are read by less experienced radiologists, the specificity of one-view mammography may be too low, and then two-view may be more cost-effective.

Acknowledgements

We thank F. de Groot for his comments.

Discussion

Age-specific detectability

In the detectability study, the previous mammogram was studied for tumour characteristics and breast parenchyma. This section makes a secondary analysis of the detectability study, in order to examine the association with age at the screening examination reviewed. Table 3.9 shows the classification of 84 previous mammograms according to age at invitation to the previous screening. In the interval cancer patients, the results for the age categories 55-64 and 65-79 years are comparable, whereas in the younger age category, the proportion of "radiographically occult at previous screening" is larger and the proportion of "minimal signs present" is smaller than in the older age categories, although the numbers are too small to reach statistical significance. Probably, these minimal signs are more difficult to detect in younger women with denser breasts. Furthermore, the growth rate of breast cancer in younger women may be faster and thereby the preclinically detectable phase of the tumour may be shorter.[33] In patients with screen-detected cancers, there were no differences in the classification of the previous mammogram according to age.

Table 3.9 *Classification of previous screening mammograms of 84 breast cancer patients, according to age when the previous mammogram was taken*

Cancer and age category	No. of cases	Classification of previous mammogram in %			
		Screening error	Minimal sign	Radio-graphically occult	Radiographi-cally occult at diagnosis
Interval cancer	**40**	**18%**	**28%**	**42%**	**12%**
42-54 yrs	14	14%	14%	50%	21%
55-64 yrs	19	21%	37%	37%	5%
65-79 yrs	7	14%	29%	43%	14%
Screen-detected cancer	**44**	**9%**	**48%**	**43%**	**n.a.**
42-54 yrs	12	8%	50%	42%	n.a.
55-64 yrs	11	9%	45%	45%	n.a.
65-79 yrs	21	10%	48%	43%	n.a.

The publication of our detectability study in Cancer encouraged researchers in the Florence programme to review the previous screening mammograms of 134 patients using the same design and criteria.[34] The previous mammograms were classified as 16% "screening error", 27% "minimal sign present", 54% "radiographically occult" and 7% "radiographically occult at diagnosis" (compared to 13%, 38%, 43% and 6% in the Nijmegen study, respectively). The differences in the proportion classified as "minimal signs" and "radiographically occult" show that the classification is subjective even when the same categories are used. Explanations for this are variation in the visual observation and perception and in the threshold of concern about perceived abnormalities.[35] In a retrospective review of 73 "negative" mammograms in patients who later developed breast cancer, the classification of 3 radiologists showed disagreement in as many as 19% of the cases.[36]

The most common reason for screening errors is related to perception error. Of the 11 screening errors in the detectability study, 8 had not been perceived by the radiologists, despite the fact that these mammograms had been double read. Recent research is focussing on computer-assisted reading of mammograms. It may be possible to develop software that can detect lesions that a radiologist would overlook, but it will not be able to interprete the lesions. Computerized pre-screening in the function of one of the double readers may be helpful to detect and mark visible lesions in large series of screening mammograms, so that the radiologist as the second reader can concentrate on his interpretation.

One versus two-view mammography: an update of the review

The hypothesis in our review that the sensitivity and specificity of two-view mammography for initial screening would be higher than one-view mammography, could not be quantified because of the poor study designs. Recently, several well-designed studies have been published. Thurfjell and colleagues[37] conducted a study on 12,636 women aged 40-54 years who underwent two-view mammography in their initial screening round. One radiologist examined the single oblique view and later on in the day both views. The recall rates for one- and two-view mammography were 4.3‰ and 2.8‰, the biopsy rates were 4.8‰ and 5.7‰ and the number of cancers detected were 31 and 32, respectively. None of the differences were statistically significant.

In London, a study was carried out on 26,430 women aged 50-64 years who had been screened with two-view mammography.[38] One of the views and the two-view mammograms were read independently by the same radiologist and resulted in recall rates of 9.1% and 6.7% (McNemar's test $P<0.001$) and detection rates of 7.8‰ to 8.3‰ (McNemar's test $P<0.01$), respectively. The reduction in the cost due to the decreased recall rate was not sufficiently large to neutralize the extra cost of the second view.

Wald and associates[39] reported on a large randomized controlled trial that was set up to study the difference in screening results between one-view and two-view mammography. A total of 40,163 women aged 50-64 years at their first screening were recruited from 9 English screening centres. At each centre, the women were assigned at random to one of three groups in the ratio 1:1:2. Group 1 were screened with one-view and groups 2 and 3 with two-view mammography. The oblique view of groups 1 and 3 were read by reader X, whereas the two views in groups 2 and 3 were read by reader Y, independently from X. Every month X and Y switched groups. Twenty-one readers took part, 19 of them were radiologists. In groups 1 and 2, the recall rates were 8.2 and 7.0 per 100 women screened, the biopsy rates were 7.5 and 7.4 per 1000 women screened and the detection rates were 5.6 and 6.5 per 1000 women screened, respectively. In group 3, in which 115 cancers were detected, the results for one-view and two-view mammography were recall rates of 8.5% and 6.3%, biopsy rates of 7.5‰ and 7.4‰ and detection rates of 5.5‰ and 6.8‰, respectively. In group 3, 24 of the 115 cancers had been detected by only 1 method: 23 by two-view and 1 by one-view (McNemar's test: $P<0.0001$). The cost of two-view screening was higher, but the average cost per cancer detected was about equal. The authors concluded that two-view screening is more effective and has similar cost-effectiveness.

These studies support the opinion that a cranio-caudal view should be performed in addition to the oblique view for initial screening. The gain in sensitivity and specificity seems to be much larger than anticipated. It must be stressed, however, that these results will depend on the specific programme. In the first round of the Dutch programme, the rate of referral for diagnostic work-up a hospital was much lower (1.3%)[40] than in Wald's trial, which was situated in the UK programme, although in both the programmes two-view mammography was used. Probably, the increase in sensitivity of two-view mammography was the same in the Dutch programme but the decrease in the referral rates may have differed because of the lower referral rates with one-view mammography.

The question remains as to whether two-view mammography is also preferable for subsequent screening. Wald et al[39] speculated that the decrease in recall rate (and thus specificity) at subsequent screening may be smaller than at initial screening and the interpretation of benign lesions would be facilitated by previous two-view mammography. The gain in sensitivity would be as large as it was at initial screening, because the detection of malignant lesions would not be affected by the previous mammogram. One could argue, however, that the identification of malignant lesions will also be facilitated by the availability of previous two-view mammography, so that the increase in sensitivity due to the cranio-caudal view would also be less. Future research could assess the gain in quality of two-view mammography over one-view for subsequent screening.

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Chapter 4

Outcomes of mammographic screening

Mammographic screening after the age of 65 years: early outcomes in the Nijmegen programme

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Mammographic screening after the age of 65 years: early outcomes in the Nijmegen programme

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Abstract

We studied outcomes of mammographic screening in women older than 65 years. In 1975, breast cancer screening was started in Nijmegen, the Netherlands, for women aged 35 to 65 years. Since 1977, approximately 7700 older women have also been invited for biennial one-view mammography. This report is based on 10 screening rounds from 1975 to 1994. The results of the subsequent screening rounds in the age groups 65-69, 70-74 and 75 years and older were: participation rates 55%, 39% and 15%, screen-detected cancer rates 5.6‰, 6.9‰ and 7.8‰, interval cancer rates 2.0‰ 1.8‰ and 3.5‰, predictive values of referral 62%, 64% and 62%, respectively. In all age groups, screen-detected patients had smaller tumours and a lower prevalence of axillary lymph node involvement than unscreened patients. Our conclusion is that in women aged 65 years and older, breast cancer can be detected at an earlier stage by biennial mammographic screening.

Introduction

Breast cancer is the commonest malignancy in women. The incidence of invasive breast cancer in the Netherlands rises with age to about 340 new diagnoses annually per 100 000 women aged 70 years and older.[1] Approximately one out of three new cases of invasive breast cancer is diagnosed in this age group. Although it has often been argued that this disease is more indolent in older women, their relative survival is no better than for younger women.[2]

Several trials have been conducted and reviews of the results show that mammographic screening can reduce breast cancer mortality by approximately 30%.[3-5] Recently, it was shown that mammographic screening of women aged 65-74 years can also reduce breast cancer mortality.[6-8]

To evaluate screening programmes that may have differently aged target populations, background material is necessary in order to assess the early

results. For women aged 50-69 years, this information is available from several regional and national programmes,[9-12] but for the older age groups, the information is limited.

The aim of the present study was to determine age-specific outcomes of mammographic screening, with emphasis on women aged 65 years and older, in the Nijmegen programme, which is the only long-running trial in the world that did include women over 75 years of age.[13]

Study population and methods

In 1975, a population-based screening programme for breast cancer was started in Nijmegen, The Netherlands. In 1975 and 1976, approximately 30000 women aged 35-65 years received their first invitation to participate in the mass mammographic screening. From the second round onwards, some 7700 older women were also invited for biennial one-view mammography. From 1975-1994, ten screening rounds were carried out. Details of the programme and the round-specific results up to round 9 are published elsewhere.[13]

The present analyses included primary breast cancer patients diagnosed before December 1994. Excluded were patients with lobular carcinoma *in situ*, patients diagnosed before their first invitation to screening, and women under the age of 50. Age, defined as the age on the date of invitation, was categorised as 50-64, 65-69, 70-74 and 75 years and older.

The following indicators were studied for first and subsequent invitations separately: participation rate (i.e. number of accepted invitations per 100 invitations), referral rate (i.e. number of referrals for diagnostic work-up per 1000 accepted invitations), screen-detected cancer rate (i.e. number of screen-detected patients per 1000 accepted invitations), interval cancer rate (i.e. number of patients diagnosed clinically after a negative screening result but before the next scheduled invitation 2 years later per 1000 accepted invitations) and non-participant cancer rate (i.e. number of cancers diagnosed clinically in non-participants per 1000 rejected invitations). The predictive value of referral (i.e. the number of diagnosed breast cancer patients per 100 referred women) and the ratio of screen-detected patients to screen-detected plus interval cancer patients were also calculated. Tumour size and lymph node status were studied according to the detection mode: (1) detected at first screening (including screen-detected patients who had rejected the invitation 2 years earlier), (2) detected at repeated screening (i.e. in women who had also par-

ticipated in the previous round), (3) diagnosed clinically as an interval cancer and (4) diagnosed clinically in non-participants (i.e. in women who had rejected the most recent invitation). Tumour size was measured in millimetres (mm) as the largest measurable size on the mammogram, or on the specimen radiography and histological slides if the tumour had vague margins or was radiographically occult. Axillary lymph node status was studied in patients diagnosed after 31 December 1980. Before this date, axillary lymph node dissection was not performed as a routine procedure and, as a result, the lymph node status was missing in 34% of the patients. From 1981 onwards, the axillary lymph node status was missing in 10% of the patients.

The statistical tests used were the Kruskall Wallis test to analyse differences in median tumour size and the chi-square-test for contingency tables to test differences in proportions. The analyses were performed with the statistical software package SAS.

Results

Table 4.1 shows the number of invitations and the participation rates, referral rates and cancer rates for the first invitation. The participation rates for the first invitation decreased dramatically at older ages from 81% in women aged 50-64 years to 24% in women aged 75 years and older, while those for the subsequent invitations were some 10% lower at all ages. Table 4.2 shows corresponding details for subsequent invitations. The initial high rates of referral and detection (18% and 9%) dropped in the subsequent invitations to levels of about 10 and 6 per 1000 accepted invitations in women aged 65 years and older. The breast cancer detection rates in women who had been screened regularly (i.e. those also screened in the previous round) remained fairly high at 3.0, 5.5, 6.0 and 6.3 per 1000 accepted invitations for the four age groups, respectively (not included in the tables). Interval cancer rates were slightly higher after subsequent invitations than after the first invitation. The non-participant cancer rates did not increase in the older age groups. The predictive value of referral was very high. At subsequent invitations, breast cancer was diagnosed in two out of three referred women aged 65 and older. The ratio of screen-detected cancers to the sum of screen-detected plus interval cancers was 0.69 or higher in women older than age 65.

Table 4.3 shows the tumour size of invasive cancers, categorised as ≤ 10 mm, 11-20 mm and >20 mm, according to the detection mode and age. The

Table 4.1 *First invitations: screening results according to age at invitation*

Screening result		Age at invitation (years)				Total
		50-64	65-69	70-74	75+	
No. of invited women		13149	2328	3122	4253	22852
No. of participants		10591	1440	1450	1009	14490
Participation rate (%)		81	62	46	24	63
Referrals	No.	158	22	27	20	227
	Rate[a]	14.9	15.3	18.6	19.8	15.7
Screen-det. cancers	No.	60[4]	8[1]	15[2]	13[1]	96[8]
	Rate[a]	5.7	5.6	10.3	12.9	6.6
Interval cancers	No.	17[1]	2[1]	3	2	24[2]
	Rate[a]	1.6	1.4	2.1	2.0	1.7
Non-particip. cancers	No.	14[1]	3	5	13	35[1]
	Rate[b]	5.5	3.4	3.0	4.0	4.2
Predictive value of referral (%)		38	36	56	65	42
Ratio screen-detected to screen-detected+interval		0.78	0.80	0.83	0.87	0.80

Superscript denotes number of ductal carcinoma in situ included
[a] *per 1000 accepted invitations*
[b] *per 1000 rejected invitations*

median tumour sizes (with 25th and 75th centiles) are also presented. In each age group, the median size was smallest in the cancers detected at repeat screening and largest in non-participant cases (P values < 0.001). The proportion of large tumours detected at first screening or those diagnosed in non-participants was somewhat larger in the oldest age groups (chi-square=5.62, d.f.=3, P=0.13; chi-square=5.82, d.f.=3, P=0.12), while the proportion of large interval cancers was slightly smaller in the oldest women (chi-square=5.17, d.f.=3, P=0.16).

Table 4.4 shows the lymph node status of women diagnosed between 1981 and 1994. Overall, the percentage 'unknown' was 5%, 6%, 5% and 30% in the four age groups, respectively (chi-square=92.4, d.f.=3, P<0.001). Breast cancer specific survival was poorest in patients with an unknown lymph

node status; the 10 year breast cancer specific survival rate was 0.40 for patients with unknown lymph node status, whereas it was 0.61 for patients with positive nodes and 0.92 for patients with negative nodes. This illustrates the importance of considering all diagnosed patients instead of only those with a known lymph node status as the denominator for the proportion of patients with negative nodes. The proportion of lymph node negative patients differed according to the detection mode (chi-square=65.8, d.f.=3, P<0.001). In the patients detected at repeat screening it was 74% while in non-participants it was 41%. In non-participants aged 75 years and older, the proportion of lymph node negatives was smaller than in the younger non-participants (34% and 47%, respectively, P=0.03).

Table 4.2 *Subsequent invitations: screening results according to age at invitation*

Screening result		Age at invitation (years)				Total
		50-64	65-69	70-74	75+	
No. of invitations		98851	28398	21079	33949	182277
No. of participations		66073	15708	8116	5129	95026
Participation rate (%)		67	55	39	15	52
Referrals	No	401	143	87	65	696
	Rate[a]	6.1	9.1	10.7	12.7	7.3
Screen-det. cancers	No.	220[41]	88[8]	56[6]	40[5]	404[60]
	Rate[a]	3.3	5.6	6.9	7.8	4.3
Interval cancers	No.	132[6]	32[2]	15	18[1]	197[9]
	Rate[a]	2.0	2.0	1.8	3.5	2.1
Non-particip. cancers	No.	107[3]	51[2]	49[2]	122[3]	329[10]
	Rate[b]	3.3	4.0	3.8	4.2	3.8
Predictive value of referral (%)		55	62	64	62	58
Ratio screen-detected to screen-detected+interval		0.63	0.73	0.79	0.69	0.67

Superscript denotes number of ductal carcinoma in situ included
[a] *per 1000 accepted invitations*
[b] *per 1000 rejected invitations*

Table 4.3 *Tumour size of invasive cancers according to detection mode and age at invitation*

Detection mode and tumour size	Age at invitation (years)				Total
	50-64	65-69	70-74	75+	
Detected at first screening[a]					
≤10 mm	25 (28)	5 (29)	4 (16)	5 (21)	39 (25)
11-20 mm	46 (51)	10 (59)	16 (64)	9 (38)	81 (52)
>20 mm	19 (21)	2 (12)	5 (20)	10 (41)	36 (23)
Total	90	17	25	24	156
Median (25-75 centile)	15 (10-20)	15 (10-15)	20 (15-20)	20 (14-27)	15 (11-20)
Detected at repeat screening					
≤10 mm	57 (39)	27 (38)	14 (38)	11 (48)	109 (40)
10-20 mm	66 (46)	35 (49)	21 (55)	7 (30)	129 (47)
>20 mm	22 (13)	9 (13)	2 (6)	5 (22)	39 (14)
Total	145	71[1]	37[1]	23	276[2]
Median (25-75 centile)	15 (10-18)	15 (10-20)	15 (10-18)	12 (7-20)	15 (10-20)
Diagnosed as interval cancer					
≤10 mm≤10 mm	19 (14)	3 (10)	4 (24)	4 (24)	30 (15)
10-20 mm	65 (46)	14 (45)	11 (65)	8 (47)	98 (48)
>20 mm	56 (40)	14 (45)	2 (12)	5 (29)	77 (38)
Total	140[2]	31	17[1]	17[2]	205[5]
Median (25-75 centile)	20 (15-30)	20 (15-30)	15 (15-20)	20 (13-25)	20 (15-30)
Diagnosed in non-participants					
≤10 mm≤10 mm	12 (11)	4 (8)	2 (4)	5 (4)	23 (7)
10-20 mm11-20	30 (28)	13 (27)	18 (35)	27 (23)	88 (27)
>20 mm>20 mm	66 (61)	32 (65)	31 (61)	88 (73)	217 (66)
TotalTotal	108[9]	49[1]	51[1]	120[12]	328[23]
Median (25-75 centile)	25 (19-35)	26 (20-35)	25 (15-35)	30 (20-40)	30 (20-35)

Percentage between parenthesis
Superscript indicates the number of missing values
[a] *Includes screen-detected patients who had rejected the previous screen invitation*

Table 4.4 *Axillary lymph node status of women diagnosed after 1980 according to detection mode and age at most recent invitation*

Detection mode and lymph nodes	Age at invitation (years)				Total
	50-64	65-69	70-74	75+	
Detected at first screening[a]					
Negative[b]	22 (61)	7 (70)	13 (76)	6 (55)	48 (65)
Positive	13 (36)	3 (30)	3 (18)	3 (27)	22 (30)
Not examined	1 (3)	0 (0)	1 (6)	2 (18)	4 (5)
Total	36	10	17	11	74
Detected at repeat screening					
Negative[b]	107 (78)	44 (69)	30 (77)	14 (64)	195 (74)
Positive	27 (20)	19 (30)	9 (23)	4 (18)	59 (23)
Not examined	3 (2)	1 (2)	0 (0)	4 (18)	8 (3)
Total	137	64	39	22	262
Diagnosed as interval cancer					
Negative[b]	69 (63)	19 (66)	7 (50)	12 (67)	107 (63)
Positive	34 (31)	10 (34)	3 (21)	4 (22)	51 (30)
Not examined	6 (6)	0 (0)	4 (29)	2 (11)	12 (7)
Total	109	29	14	18	170
Diagnosed in non-participants					
Negative[b]	44 (46)	20 (48)	21 (47)	41 (34)	126 (42)
Positive	45 (47)	15 (36)	23 (51)	36 (30)	119 (39)
Not examined	7 (7)	7 (17)	1 (2)	43 (36)	58 (19)
Total	96	42	45	120	303

[a] *Includes screen-detected patients who had rejected the previous screen invitation*
[b] *women with DCIS included as negative*

Discussion

Mammographic screening can obviously only reduce the mortality of breast cancer in the population if at least a part of the invitees participates. The participation rates in women for the first invitation (65-69 years, 81%; 70-74 years, 67% and 51% for older women), declined for subsequent invitations (64% for ages 50-69, 39% for ages 70-74, and 15% for older women). These rates were very disappointing compared to the two-county trial in Sweden, in which, among women aged 70-74 years, 72% participated after subsequent invitations.[14]

The effect of screening in the women who actually do participate may appear fairly large because the women who continue to participate have a longer life-expectancy. In another study, we found a marked difference in survival of women who continued to participate at the age of 65-66 years compared to those who discontinued. The 10 year cumulative survival rates were 0.87 and 0.73, respectively.[7] In Stockholm, similar results were reported in participants and non-participants aged 40-64 years.[15] It is possible that participants had fewer co-existing diseases or they were less severe. There may even be an interaction between breast cancer and certain co-existing diseases. In breast cancer patients with localised or regional disease, Satariano and Ragland[16] found that the probability of survival decreased with an increasing number of co-existing conditions, whereas in patients with distant metastases, the 3 year survival rate did not depend on the number of other conditions. They concluded that women with severe co-existing diseases would not have a survival advantage because of early diagnosis.

One of the reasons for participation may be awareness of the presence of risk factors for breast cancer. If this is true, non-participants will be at less risk of breast cancer. The finding that the non-participant cancer rates did not increase with increasing age, in contrast with the screen-detected cancer rates and interval cancer rates, supports this hypothesis. In women over the age of 65, these non-participant cancer rates were approximately 2 per 1000 rejected invitations per annum, whereas the annual incidence of breast cancer in the Netherlands is about 3.5 per 1000 women.[1] In another study, we also observed that the incidence of breast cancer in the non-participants was lower than would have been expected on the basis of a population without mass screening.[7] This means that one explanation for the high incidence in elderly participants, which was 4.5 per 1000 accepted subsequent invitations per annum at ages 65+ (calculated by the summation of screen-detected cancer and interval

cancer rates in Table II) may be that the women who participate at a more advanced age are at greater risk for breast cancer. However, part of the increased incidence in participants may be artificial, because some of the detected cancers may never have become clinically detectable.

As the breast cancer incidence increases with increasing age, it was expected that screen-detected cancer rates and interval cancer rates would also show the same pattern. Owing to the slower growth rate[17] it was expected that the ratio of screen-detected to screen-detected plus interval cancers would increase with increasing age. In the 75+ group, however, the proportion of interval cancers was relatively high. In order to find an explanation for this result we reviewed the previous screening mammograms of 17 out of the 18 interval cancers. Two tumours (12%) had been missed at the previous screening examination; five tumours (29%) were visible in retrospect, but the signs were not specific enough for referral; and ten tumours (59%) had been radiographically occult at the previous screening. These findings are in agreement with the results of our study in 1993 and do not provide an explanation for the high interval cancer rate.[18]

Two indicators of stage, i.e. tumour size and lymph node status, were studied. In all age groups, screen-detected tumours were the smallest. Tumours detected at repeat screening had a median size of roughly 15 mm, whereas in non-participants the median size was 25 to 30 mm. In all age groups there was a similar increase in the proportion of patients with negative axillary nodes due to detection at repeat screening *vs* clinical detection in non-participants. Thus, it may be concluded that, through periodic screening with mammography in women over the age of 65, breast cancer can be detected at a similar early stage as in those aged 50-64 years.

In summary, our data show that, in women aged 65 years and older, breast cancer can be diagnosed at an earlier stage by mammographic screening. This does not imply that the life-expectancy of all screen-detected patients will be longer. First, a larger proportion of the screen-detected cancers may have remained undiagnosed without screening because of the slow growth rate.[17] Second, women of 75 have a life expectancy of 11 years and those of 85 of 6 years.[19] The duration of the detectable preclinical phase in women aged 70 years and older has been estimated at 4.5 years.[20] It is thus unlikely that many breast cancer deaths can be prevented in patients screened at age 75 years and older, but the quality of life may be increased if screening can prevent them from having to live for years with metastases.

We conclude that there is reason to continue mammographic screening until at least the age of 75 years. The beneficial effects of mammographic screening on breast cancer mortality and the quality of life may outweigh the negative side-effects until the age when life expectancy is shorter than the detectable preclinical phase of the disease.

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Chapter 5

Assessment of the reduction in breast cancer mortality: case-referent studies

Efficacy of mammographic screening of the elderly: a case-referent study in the Nijmegen programme in The Netherlands

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Mammographic screening after the age of 65 years: evidence for a reduction in breast cancer mortality

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Introduction

Assessment of the effect of mammographic screening on breast cancer mortality is most straight forward in randomized controlled trials. Comparability of the population with regard to underlying breast cancer mortality is guaranteed by the random assignment of the study population to an invitation group and a non-invitation group and analysing the results according to the randomization groups. Usually, the ratio is calculated between the risk of dying from breast cancer in the invited group and the risk in the non-invited group.

The Nijmegen screening project, however, was not set up as a randomized study. All the female inhabitants of Nijmegen aged 35 years and older were invited for screening. A useful method to perform effect measurements in such a non-randomized study is the case-referent approach. The ratio can be calculated between the breast cancer mortality rates of screened versus unscreened women. Using such a design, the study population consists of all the patients who were invited for screening and died from breast cancer in the study period (the cases), and a sample of all invited women (the referents). All the study subjects are classified according to participation in the screening. Next, the ratio of the "quasi-rates" is calculated as the number of screened cases to the number of screened population referents divided by the number of unscreened cases to the number of unscreened population referents. Although the absolute mortality rates for screened and unscreened women remain unknown (the true denominators, which consist of the number of woman-years of observation in each group, are unknown), this ratio of "quasi-rates" is a valid estimator of the ratio of the true mortality rates.

This Chapter contains two such case-referent studies which have been published in *The Journal of the National Cancer Institute 1994; 86: 934-8* and *The International Journal of Cancer 1996; 66: 727-31*, respectively. The difference between these studies with regard to the definition of the relevant screening histories is outlined in the Discussion section of this Chapter (page 93). Furthermore, bias due to self-selection is discussed, which forms a major limitation in case-referent studies to assess the reduction in mortality due to screening.

Efficacy of mammographic screening of the elderly: a case-referent study in the Nijmegen programme in The Netherlands

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Abstract

Only a few small studies have been conducted to examine the usefulness of mammographic screening in elderly women. These studies suggest that the screening-related reduction in breast cancer mortality rates is less than the estimated 20-40% reduction observed for women aged 50-70 years at the time of their first screening. We have studied the efficacy of continued mammographic screening for breast cancer of elderly women within our screening programme.

In 1975, a breast cancer screening programme was started in the city of Nijmegen, The Netherlands. During each biennial screening round, approximately 30 000 women aged 40 years and older were personally invited to participate. Single-view mammography was administered. The present study was conducted using a case-referent design. In order to be eligible for inclusion in this study, women had to have been invited to participate in the mammography screening programme at least twice, with the most recent invitation having occurred when each woman was 65 years or older. The cases studied comprised 33 women in this group who had died of breast cancer at some point during 1977 through 1988. Referents were matched for age at last invitation to screening prior to the diagnosis of breast cancer and for the number of previous invitations to screenings. Five referents were randomly selected for each case. Breast cancer mortality rate ratios (RR) were calculated for several categories of attendance to the screening.

The RR of those who attended the last screening versus those who failed to do so was 0.58 (95% confidence interval [CI] = 0.24-1.41); for women aged 65-74, the RR was 0.34 (95% CI = 0.12-0.97) and for women aged 75 or over, 2.87 (95% CI = 0.62-13.2). The RR of those who attended the screening before and after the age of 65 relative to those who attended before 65 only, was 0.26 (95% CI = 0.05-1.32).

Although self-selection bias was present in our data, it was not likely to be responsible for the beneficial effect in women aged 65-74 at the time of invitation to screenings. It probably was responsible for the reversed RR (RR > 1) in the group of women 75 years and older. Continuation of

mammographic screening until at least the age of 75 years may lead to a reduction of breast cancer mortality among elderly women.

Introduction

Mammographic screening for breast cancer is at present the most effective method in reducing breast cancer mortality. In various reviews of published studies it was concluded that breast cancer mortality may be reduced by approximately 20-40% in women aged 50-70 years at time of entry into the screening programme, whereas for women under 50 years of age, no reduction was evident.[1-3] Currently, it is a matter of considerable debate whether the elderly should be screened. Most studies on the effect of mammographic screening have focused on women younger than 70 years at entry.[4-10] The few studies that did report on the elderly are indicative of an effect of mammographic screening somewhat smaller than that in the younger age group, with the degree of reduction in breast cancer mortality being in the range of 15 to 20%.[11-14] However, several questions remain unanswered, such as if continuation of screening after the age of 70 has the potential to reduce mortality, and whether or not an upper age limit should be set.[15]

In the Netherlands, mammographic screening for breast cancer is now being introduced nationwide.[16] Women aged 50-69 years are personally invited every 2 years. Women aged 70 years and older are not invited because evidence of a reduction in breast cancer mortality for this group is still lacking. The lack of evidence for benefit from such screening, however, does not imply that a beneficial effect does not, in fact, exist. On the other hand, there will be a certain age above which the number of women who die of causes other than breast cancer before the date at which breast cancer would have been diagnosed without screening inevitably becomes unacceptably high.

The most important issue, i.e. whether or not screening should be continued in the elderly, has never been studied. Therefore, we decided to investigate the efficacy of screening women aged 65 years and older for breast cancer using a population that had already been included in the mammographic screening programme previously. The two most important differences between the present study and earlier studies were the following: 1) The subjects should have had at least two invitations to the screening before the diagnosis of breast cancer, and 2) age was defined as "age at invitation to the screening examination under study" instead of "age at entry in the screening programme".

Study population and methods

Study setting

In 1975, a breast cancer screening programme was started in the city of Nijmegen, the Netherlands. Biennially, single view mammography was administered. Single view mammography consisted of the latero-medial view in rounds 1 to 3, and the medio-lateral oblique view thereafter. At every screening round, approximately 30,000 women aged 40 and over were personally invited to participate. Details of the programme have been previously published.[17] In Table 5.1 the attendance rates of round 7 (1987-88), which can be regarded as representative of a steady state period regarding attendance rates, are presented. With increasing age, a strong decline in attendance was evident, whereas for those women who had already participated in round 6, attendance was much higher.

Table 5.1 *Attendance rates of round 7 of the Nijmegen breast cancer screening programme (separately for all invited women and participants in round 6) by age at invitation*

Age at invitation round 7, y	All invited women			Already participated in round 6		
	No. invited	No. screened	Attendance rate, %	No. invited	No. screened	Attendance rate, %
40-49	7,634	5,359	70,2	4,546	3,973	87.4
50-64	10,908	7,227	66,3	7,092	6,387	90.1
65-69	3,382	1,815	53,7	1,841	1,569	85.2
70-74	2,995	1,282	42,8	1,356	1,057	77.9
75-79	2,482	594	23,9	699	477	68.2
≥ 80	2,756	187	6,8	251	130	51.8
Total	30,157	16,464	54,6	15,785	13,593	86.1

Study design and population

The present study was designed as a case-referent study, with the odds ratio (OR) as the estimator of the ratio of the breast cancer mortality rates (rate ratio, [RR]) of women who had accepted the invitation to the screening relative to those who had not.[18] Because our aim was to examine the effect of a continuation of the screening in the elderly, only those women were included

in the study who had been invited to participate at least twice, most recently at the age of 65 years or over.

Case patients were defined as women who had died of breast cancer before 1989. The cause of death, classified by a panel of physicians, was based on the clinical course of the disease as well as on the death certificates. Breast cancer was defined as the cause of death if the following evidence existed: 1) the disease had progressed to distant sites, 2) this progression was ultimately responsible for the death of the patient, and 3) other causes of death could be excluded. Using this set of criteria, we identified 33 cases.

Referents were individually matched with each case patient for age at last invitation to participate before the diagnosis and for the number of previous invitations to screenings. Using the following criteria, we selected a set of eligible referents to match each case[19] *(a)* alive and residing in Nijmegen at the time of death of the case patient, *(b)* free of breast cancer at the invitation to the last screening before the diagnosis of breast cancer in the case patient, *(c)* having the same age as the case patient at the invitation to the last screening before the diagnosis, and *(d)* having been invited to the same screening rounds as the case patients before the diagnosis. Five referents were selected randomly from each set, resulting in 165 referents.

Data analysis

We calculated breast cancer mortality RRs with 95% confidence intervals (CIs) by maximum likelihood estimation through conditional logistic regression analysis[13,14] with the statistical package EGRET (Statistics and Epidemiology Research Corporation, Seattle, Wash.). First, we calculated the RR of those who had attended the screening after the last invitation before the diagnosis of breast cancer the case patient relative to those who had failed to attend. (This was the same screening round for a case patient and her 5 referents). In this analysis the indicator for screening was "1" if the subject had undergone mammographic screening after the last invitation and "0" if the subject had not undergone screening in response to the last invitation to participate.

Next, the mammographic screening history of each woman was divided into four categories of participation: 1) participation before the age of 65 only, 2) participation before and after the age of 65, 3) participation after the age of 65 only, and 4) no participation at all. Because of our interest in the effect of a continuation of the screening, category 1 (participation before 65 only) was chosen as the reference category. Indicators for the three other categories of participation were included in the regression model. This latter model was also

analyzed for indicators of participation before and/or after the ages of 70 and 75 years, respectively, in order to estimate the effect of a continuation of the screening above these age limits as well.

Self-selection bias

Self-selection bias is a major problem in case-referent studies on intended effects, because the reasons for participation may be associated with the outcome. The extent of a possible bias was studied by calculating the ratio of observed and expected breast cancer deaths in the nonparticipating population over a 10-year period. A ratio of 1 suggests absence of bias, whereas a ratio smaller than 1 indicates that the real effect is underestimated (RR closer to 1) or reversed (RR > 1).

The population of the neighbouring city of Arnhem was used as the reference population because in the period of 1970-1974, it had the same age-adjusted incidence and mortality rates of breast cancer as those in Nijmegen,[15] and because no mass screening programme had ever been implemented in Arnhem. Since 1975, data on Arnhem patients diagnosed as having primary breast cancer have been carefully recorded by the Carcinoma Werkgroep Arnhem. The cause of death was ascertained using the same criteria described for the case patients. The age-specific mortality rates of breast cancer in this reference population in the period 1978 to 1988 (deaths were counted only if breast cancer had been diagnosed after the start of the screening in Nijmegen) were applied to the woman-years of observation of the nonparticipants (i.e., the time between the refused first invitation to screening up to the first attendance, up to relocation from Nijmegen, up to death, or up to the end date, December 31, 1988). Thus, the expected numbers of breast cancer deaths in Nijmegen were calculated. The standardized mortality ratio is defined by the ratio of observed and expected numbers of breast cancer death.[23]

We also used this procedure to calculate the standardized morbidity ratio; however, the numbers of primary breast cancer cases were assessed instead of breast cancer deaths for the years from 1977 to 1988.

Results

Table 5.2 shows the attendance of the 33 case-referent sets after the last invitation to the screening as well as the RR. The numbers refer to the number of case-referent sets. For example in the age category 65-74, there were no sets

with the case and zero, one, four, or five out of five referents screened just before diagnosis of the case, one set with the case and two out of five referents screened, and four sets with the case and three out of five referents screened. The overall RR was 0.58 (95% CI 0.24-1.41). For women aged 65-74 years at invitation to screening, the RR was 0.34 (95% CI 0.12-0.97), and for women aged 75 years or more, the RR was 2.87 (95% CI 0.62-13.2).

Table 5.2 *Case-referent sets according to attendance at the screening after the last invitation before diagnosis and RR (95% CI) according to age at invitation*

Age at invitation, years	Case attended	No. of referents who attended*						Total No. of cases	RR+ (95% CI)
		0	1	2	3	4	5		
65-74	Yes	0	0	1	4	0	0	5	0.34 (0.12-0.97)
	No	2	2	3	7	2	0	16	
≥75	Yes	2	1	0	0	0	0	3	2.87 (0.62-13.2)
	No	5	3	1	0	0	0	9	
Total	Yes	2	1	1	4	0	0	8	0.58 (0.24-1.41)
	No	7	5	4	7	2	0	25	

* *Cell entries denote the number of sets of one case and five referents, arranged according to attendance to the last screening. For example, in the age-category 65-74 years in the fourth column, there are four sets with the case and three out of five referents screened just before the diagnosis of the case.*

\+ *Breast cancer mortality rate ratio, calculated by maximum likelihood estimation.*

Table 5.3 displays some model specifications, the numbers of cases in each category and the results of the analysis of a continuation of the screening after age 65. The RR of participants before and after age 65 relative to participants before age 65 only, was 0.26 (95% CI 0.05-1.32). Participation before and after age 70 relative to participation before age 70 only, resulted in a RR of 0.38 (95% CI 0.03-4.15), and for participation before and after age 75 versus before age 75 years only, it was 8.92 (95% CI 0.86-92.1).

Table 5.4 shows the age-specific mortality rates in Arnhem, the observed (O) and expected (E) numbers of breast cancer deaths in the Nijmegen nonparticipants, and the ratio of O to E. The O/E ratio was larger than 1 in the younger age categories and smaller than 1 in the highest age categories [test for heterogeneity of ratios:[17] chi square = 16.9, d.f. = 3, P = 0.001]. Because of this heterogeneity of ratios, no standardized mortality rate ratio was calculated. The very high O/E in the age category 70-74 is probably due

to the surprisingly low mortality rate in Arnhem. The most striking finding in Table 5.4 is the very low ratio of observed and expected deaths in women 80 years and older, although the observed numbers of deaths in Nijmegen were very small.

Table 5.3 *Model specifications and results of the conditional logistic regression analysis of the continuation of the screening after age 65*

Indicator	Index category*	Definition	Results		
			b+	SE(b)	P-value
X_1	participation before and after 65 (n = 3)	X_1 = 1 if yes X_1 = 0 if no	-1.33+	0.82	0.11
X_2	participation after 65 only (n = 8)	X_2 = 1 if yes X_2 = 0 if no	-0.21	1.05	0.84
X_3	no participation at all (n = 18)	X_3 = 1 if yes X_3 = 0 if no	0.59	0.93	0.53

The number of cases in each category are shown in parentheses.
* *Reference category: participation before 65 only (n=4)*
\+ *b = estimated parameter of exposure category X_i in the logistic regression model*
\+ *RR = 0.26 (95% CI 0.05-1.32). Participation before and after age 70 versus before age 70 only, RR = 0.38 (95% CI = 0.03-4.15). Participation before and after age 75 versus before age 75 only, RR = 8.92 (95% CI = 0.80-92.1)*

Table 5.4 *Age-specific breast cancer mortality of reference population in Arnhem: observed and expected numbers of breast cancer deaths in the Nijmegen nonparticipants by age in the period 1978-1987*

Age at death, years	Population of Arnhem			Nijmegen nonparticipants			
	No. of breast cancer deaths*	Woman years	Mortality rate x10^{-5} WY	Woman years at risk+	Breast cancer deaths		O/E
					Obs. (O)	Exp. (E)	
65-69	24	33,321	72.0	4,893	4	3.5	1.14
70-74	12	29,439	40.8	7,753	7	3.2	2.18
75-79	18	22,460	80.1	9,509	7	7.6	0.92
≥80	37	23,547	157.1	13,293	6	20.9	0.29
Total	91	108,767	83.7	35,448	24	35.3	0.68+

* *Only if diagnosed after the start of the screening in Nijmegen.*
\+ *Adjusted for deaths, removals, and participation to the next invitation.*
\+ *Test for heterogeneity of ratios[24]: chi square = 16.9; d.f. = 3, P = 0.001*

The observed number of cases of primary breast cancer was lower than expected in all strata of age (range of ratios, 0.54-0.89; test for heterogeneity of ratios: chi square = 3.95, d.f. = 3, $p > 0.10$). The standardized morbidity ratio was 0.68 (95% CI 0.53-0.88).

Discussion

Several studies showed a beneficial effect of screening in the elderly, but no single result proved to be statistically significant.[11-14] In an earlier study of the Nijmegen programme, based on 16 cases and 80 age-matched referents of age 65 and over at first invitation to screening, an OR of 0.81 (95% CI 0.23-2.75) was found after 7 years of follow-up.[11]

In a two county trial conducted in Sweden, an RR of 0.77 was reported after 8 years of follow-up (95% CI 0.47-1.27) in the age category 70-74 at entry.[12] A recent update of this trial with 13 years of follow-up showed an RR of only 0.94 (95% CI 0.60-1.46) in the same population but with the end point "breast cancer present at death" in stead of "death due to breast cancer".

In the Breast Cancer Detection Demonstration Project (BCDDP), another study including elderly women, the RR was analysed by means of a comparison with population-based data from the Surveillance, Epidemiology and End Results Program,* and a value of nearly 25% (no confidence bounds provided) was calculated for the ages 60-74 at entry.[13]

Another study was published based on data from the Duke Tumor Registry.[14] This study included 109 case subjects who were 60 years and older at diagnosis and who had developed metastatic breast cancer as well as 211 controls who had been selected by random sampling from the same tumor registry. Only 6% of the controls had ever been screened. The OR, adjusted for several risk factors, was 0.73 (95% CI 0.25-2.14).

All of these studies showed some beneficial effects of mammographic screening in the elderly, but none of them addressed the effect of a *continuation* of mammographic screening. The screening history was divided into the categories of "ever" screened and "never" screened in the former Nijmegen[11,22] and Duke Tumor Registry studies.[14] Women who had been previously screened, however, may have failed to participate in the more recent screenings, and these were the screenings that should have caused the reduction in mortality. The Swedish studies compared the RR of the invited populations with that of the uninvited populations.[12,25] The differences in attendance

rates between women aged 70-74 years at entry in the study and those aged 60-69 years (79% and 91%, respectively) may largely explain the differences in the estimated effects after 8 years (RR = 0.77 and 0.65, respectively).[2] Moreover, age was defined in all of these studies as age at entry in the programme or at diagnosis, in spite of the fact that the actual age at screening may be quite different. In addition, three of the studies included self-selected populations,[11,13,14] but they failed to control for this selection in the analysis. However, the extent of the self-selection bias was studied in the Nijmegen[11] and BCDDP[13] studies. In these two studies, it was argued that the calculated effect must have been smaller than the real effect because of the self-selection bias.

Finally, misclassification of the end-point may have played an important role in all of these studies. With increasing age, the increase in co-morbidity frustrates the determination of the cause of death and increases in the chance of a misclassification, thus resulting in a RR closer to 1. In addition, once breast cancer has been diagnosed, death may be attributed to the disease. This may lead to an overreporting of death due to breast cancer in the screened population, in contrast to death in the unscreened population, and thus may result in a RR closer to 1.

It is likely that the overview of the Swedish trials may have suffered from misclassification because the end point "breast cancer present at death" was used.[25] That study reported that the RR calculated on this end-point was similar to that calculated on the end-point "breast cancer as primary cause of death", 0.77 and 0.78, respectively. These RRs were calculated in the whole study population in the age group 40-74 years. There may, however, have been a substantial difference for the elderly. As pointed out above, more breast cancer cases are bound to be diagnosed in the invited group, thus more women may die "with breast cancer present", resulting in an underestimation of the RR.

In the present study, participation in the screening just before diagnosis resulted in a reduction of the breast cancer mortality rate of 42%, although this result was not very precise. In the categories encompassing 65-74, the effect was greater (66%) and more precise. Also, the effect of a continuation of the screening on the breast cancer mortality was calculated. It was not possible to compare different screening strategies (i.e. screening until the age-limit versus continuation of screening), because all women had been invited and had decided themselves whether or not to continue participation. The results are suggestive of a beneficial effect of the continuation of the screening

both after the age of 65 (RR = 0.26, 95% CI 0.05-1.32), and after the age of 70 (RR = 0.38, 95% CI 0.03-4.15). However, after the age of 75 the effect is reversed (RR = 8.92, 95% CI 0.86-92.1).

Besides the misclassification of the cause of death, self-selection bias could be an explanation for the RR greater than 1 found in the oldest age group. Attendance rates decreased strongly with increasing age, even in women who had attended the previous round (Table 5.1). Attendance may be associated with an increased risk (e.g. as a result of the presence of a palpable mass or other symptoms), which would explain a higher underlying incidence and mortality rate in the screened group. The incidence rates in the nonparticipants aged 65 or older as well as the mortality rates in the nonparticipants aged 75 or older were lower than expected on the basis of the data from Arnhem (Table 5.4). Although the number of observed deaths was larger than expected in the age group 65-74, this has little meaning for the interpretation of our study because of the difference in the definition of age (age at death, whereas the analyses were done according to age at time of invitation). Assuming that the incidence and mortality rates in Nijmegen and Arnhem were identical in the absence of screening, the underlying incidence and mortality rates in the participants of the same ages must be higher. Because of this self-selection bias, the effect will be diluted or even reversed, i.e. a beneficial effect in women aged 75 years or older may not be excluded, although unlikely.

Incidence and mortality rates of breast cancer continue to rise with increasing age and about 30% of invasive breast cancer is diagnosed in women aged 70 and over.[26,27] In this age group the likelihood of being diagnosed with metastatic disease is highest[28] and the relative survival is worst.[26,27] As the tumor growth rate decreases,[29] the lead time will be longer and the disease may be diagnosed even earlier because of screening. Thus, a greater effect of the screening may be expected, although this is more difficult to assess because of the complications in determining the cause of death. Breast cancer detection by mammography is enhanced,[30] and interval cancer rates are lower in older women than in younger women.[17] On the other hand, the extent of overdiagnosis may increase because more women with breast cancer will die in the lead time period from causes other than breast cancer. Even then, however, early detection may improve the quality of life, because less women will be diagnosed with metastatic disease.[30]

Unfortunately, the present study, is not helpful in determining the upper age-limit for mammographic screening. It, however, indicates that continued screening of women up to the age of 75 might be beneficial. It is important to

note that, because of the self-selection bias and the increased likelihood of misclassification of the cause of death of women aged 75 and older, a beneficial effect of mammographic screening for these women cannot be excluded. We conclude that a continuation of the mammographic screening until the age of 75 may reduce breast cancer mortality.

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Notes

*Editor's note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited and made available for analysis.

Mammographic screening after the age of 65 years: evidence for a reduction in breast cancer mortality

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Abstract

We evaluated whether regular mammographic screening of women aged 65 years or older affected breast cancer mortality.

In Nijmegen, a population-based screening programme for breast cancer was started in 1975, with biennial mammography for women aged 35-64 years. Since 1977, elderly women have also been participating. For the present case-control study, women were selected who were over 64 years of age at the most recent invitation. Eighty-two of them had died from breast cancer. For these cases, 410 age-matched population controls were selected.

The ratio of breast cancer mortality rates of the women who had participated regularly (*i.e.*, in the 2 most recent screening rounds prior to diagnosis) vs. the women who had not participated in the screening was 0.56 (95% CI = 0.28-1.13). The rate ratio was 0.45 in the women aged 65-74 years at the most recent invitation (95% CI = 0.20-1.02), whereas it was 1.05 in the women aged 75 years and older (95% CI = 0.27-4.14).

While the breast cancer survival rate of the non-participant patients was fairly equal to that of patients from a control population, the underlying incidence rate of breast cancer was higher in the participants than in the non-participants. Therefore, we conclude that bias was present, but that it had decreased our effect estimate. The real reduction in breast cancer mortality due to regular screening will be even larger. Regular mammographic screening of women over age 65 (at least up to 75 years) can reduce breast cancer mortality by approximately 45%.

Introduction

In women, the life time risk of developing breast cancer has been estimated at 8.4 to 9.4%.[31] For women aged 65-69 years the probability of developing breast cancer before the age of 85 years is 1 in 16 and for those aged 70-74

years 1 in 20.[32] Thus even in the very elderly, many cases of breast cancer are diagnosed. The proportion of patients who die from this disease is as large as it is in younger women.[33] In patients aged 65-84 years, 5-year relative survival rates vary from about 90% for those with localized disease, to 66-69% for those with regional disease and to 17-20% for those with distant disease.[28]

In the past few decades, several randomized and non-randomized trials have been undertaken to evaluate the effect of mammographic screening on breast cancer mortality. Extensive evaluations on the available evidence have led to the conclusion that a 30 to 40% reduction in breast cancer mortality can be achieved by periodic screening of women aged 50 to 65 or 70 years.[1-3,25,34,35] In women over the age of 70 years, evidence for a possible reduction in breast cancer mortality due to screening is lacking, because most trials did not include elderly women.[34,36]

In the late eighties and the early nineties, national screening programmes were initiated in several European countries, such as the UK, the Netherlands and Sweden.[37] The lack of data showing that screening was of benefit to elderly women was the principal argument for not inviting women aged 65 years and more to screening programmes in the UK[38] and for excluding women aged 70 years and older from programmes in the Netherlands.[39] Nevertheless, the question still remains as to whether continuing to screen women after they have reached these upper age limits will further reduce beast cancer mortality. With 18 years of follow-up data available in our Nijmegen screening programme from the first screening round up to 31 December 1993, we elected to conduct a case-control study on the effect of long-term participation after the age of 65 years on breast cancer mortality.

Study population and methods

Study setting

In the city of Nijmegen, population-based screening for breast cancer has been ongoing since 1975. Biennially, nearly 30,000 women aged 40 years and older are personally invited to have a one-view mammogram. From round 2 (1977-1978) onwards, about 10,000 women aged 65 years and older have also been invited to participate. At each screening round, individual data on invitation and participation are stored in a computer file. Another file is kept on all Nijmegen breast cancer patients diagnosed within and outside the programme. The follow-up of the population is registered with the help of the local author-

ities, who provide weekly lists of deceased women and those who have moved out of Nijmegen. Details of the programme have been reported previously.[40,41]

Study design and population

Within the Nijmegen population of invited women, we conducted a case-control study in order to investigate the effect of regular participation in the screening programme from age 65 years onwards on breast cancer mortality. The study population consisted of women who (1) had been invited to participate at the age of 65 years or older and (2) had been free of breast cancer at the first screening invitation at age 65 years or older.

The *cases* were the patients who had died of breast cancer before January 1, 1994. The cause of death was classified by a panel of physicians who were unaware of the screening history of the patients and was based on the clinical course of the disease and information about serious co-morbidity. Breast cancer was defined as the cause of death if the disease had progressed to distant sites and this progression was ultimately responsible for the death of the patient, or if in the presence of advanced disease other causes of death could be excluded. Patients with advanced breast cancer who died of other, unrelated causes were not included as cases. The study population comprised 82 cases. The screening round in which the case had received the most recent invitation just before the diagnosis of primary breast cancer was defined as the index round. For screen-detected cases the round in which the cancer had been detected was the index round.

For each case, a group of eligible population controls were selected who (1) were alive and residing in Nijmegen at the time of death of the case, (2) had been invited to participate in the index round of the case, (3) were free of breast cancer at their index invitation, (4) were of the same age as the case at the index invitation. At random, 5 controls were selected for each case. Thus, the total number of controls was 410.

Definition of contrasted screening histories

A history of *no screening* was defined as no participation in the 5 most recent screening rounds up to and including the index round. Women in this category represented the reference category. A history of *regular screening* was defined as participation in the index round and having had a negative screening examination one round (approximately 2 years) earlier. Histories that did not meet the criteria for "no screening" or "regular screening", were classified as *otherwise* and formed a category we took no interest in. Cases and controls

were classified according to these categories of screening histories.

Statistical analysis

We calculated the odds ratio with its 95% confidence interval (95% CI) as an estimator of the ratio of breast cancer mortality rates (RR) in women with a history of regular screening versus those with a history of no screening.[18] Owing to the matched design, we used conditional logistic regression analysis with the software package EGRET.

Results

Age at the index invitation was identical for cases and their matched controls (range from 65 to 92 years). At the index invitation, 33% of the study population were 65-69 years old, 24% were 70-74 years, 32% were 75-79 years and 11% were 80 years or older.

The number of invitations was virtually the same for the cases and controls. Up to and including the index round, 23% of the cases and 21% of the controls had been invited only once, 35% and 41% had been invited 2 to 4 times, respectively, whereas 41% and 39% had been invited 5-8 times, respectively.

Table 5.5 *Breast cancer mortality rate ratio for screening history according to age at index invitation*

Age at index invitation (years)	Screening history	Number of cases/controls	Breast cancer mortality rate ratio (95% CI)
All ages	no screening[1]	40/166	1
	regular screening[2]	15/101	0.56 (0.28-1.13)
	otherwise[3]	27/143	0.77 (0.44-1.34)
65-74	no screening	20/ 69	1
	regular screening	12/ 87	0.45 (0.20-1.02)
	otherwise	15/ 79	0.64 (0.30-1.38)
75 and older	no screening	20/ 97	1
	regular screening	3/ 14	1.05 (0.27-4.14)
	otherwise	12/ 64	0.90 (0.40-2.02)

[1] *No participation in index round and 4 preceding rounds*
[2] *Participation in index round and negative mammogram in preceding round*
[3] *Not meeting the criteria for "unscreened" or "screened"*

Table 5.5 shows the results of the conditional logistic regression analysis. The ratio of the breast cancer mortality rates (RR) of regularly screened women vs. unscreened women was 0.56 (95% CI = 0.28-1.13). In women aged 65-74 years at the index invitation the RR was 0.45 (95% CI = 0.20-1.02); in the women aged 75 and older, the RR was 1.05 (95% CI = 0.27-4.14).

Discussion

All over the world, the age-specific incidence of breast cancer is rising, especially among elderly women.[42] At the time of diagnosis, elderly patients are more likely to have distant metastases or unknown stage disease than younger women.[28,43] In the Nijmegen group of non-participants with ages 70 years and older, 85% had stage II or stage II+ cancer, in contrast with 77% of those aged 50-69 years. Among the regular participants, these percentages were 33 and 30, respectively.[40]

After menopause, a large proportion of the fibroglandular breast tissue is replaced by fatty tissue, with greater radiological transparency,[15] thereby facilitating the detection of breast cancer by mammography. In addition, the proportion of false-positive screening results will be lower because of the decreased frequency of benign breast disease. The growth rate of breast cancer is relatively low in elderly women. Peer et al.[29] estimated that the median tumour volume doubling time is 80 days in patients younger than 50 years, 157 days in patients aged 50-70 years and 188 days in older patients. The lower growth rate is in concordance with the higher rate of steroid-positive tumours.[44] Life expectancy is relatively long, about 14 years at age 70 and about 8.5 years at age 80 years.[45] For the reasons given above, an important reduction in breast cancer mortality can also be expected in elderly women due to mammographic screening.

The few studies on the effect of breast cancer screening in women aged 65 years and older are small and have methodological flaws. For instance, age specific analyses involve age at entry to the screening programme instead of age at screening and the comparisons are made between the "invited group" and the "control group" or between women "screened once" and those "never screened" [11,13,14,22,46,47] The most recent results from the Swedish 2 county trial for women aged 70-74 years at their first invitation for screening showed for the invited women a relative risk of 0.79 for death from breast cancer (95%

CI = 0.51-1.22), compared to the noninvited women.[46] Analysis of the women aged 65-74 years at their first invitation revealed RR = 0.68 (95% CI = 0.51-0.89).[47] In the Nijmegen programme, a case-control study was conducted on women who had been invited at least twice.[48] In this study, 33 cases and 165 controls aged 65 years and over at the index invitation were included. For women who had participated in the index screening, compared with those who had not participated, the RR was 0.58 (0.24-1.41). For women aged 65-74 years at the index invitation, the RR was 0.34 (95% CI = 0.12-0.97); whereas in the older women, an excess of mortality was found which could be attributed to self-selection bias.[48] In the present study, with 5 more years of follow-up and twice as many patients, the RR for women screened regularly compared with those not screened, was 0.56 (95% CI = 0.28-1.13); for women aged 65-74, the RR was 0.45 (95% CI = 0.20-1.02) and for women aged 75 or over, 1.05 (95% CI = 0.27-4.14). The agreement in the results, in spite of the difference in the definition of the relevant screening histories (participation in the index round for the former study and participation in both the index round and one round earlier in the present study), is noteworthy.

Screening can only improve the prognosis of breast cancer if it can detect more breast cancer cases in a curable phase than can be diagnosed without screening. Maximum benefit can only be expected if a woman participates on a regular basis. In our study, the definition of a regular screening history applied to women who continued to participate up to and including the index round and had had a negative screening mammogram approximately 2 years earlier. This definition guaranteed that in regularly screened patients, breast cancer had been diagnosed as early as possible in the given screening programme. Screening mammograms performed 2 or more rounds before the index invitation were not expected to have any influence on the diagnosis of breast cancer and were therefore not taken into consideration. The reference category with a history of *no screening* was also designed explicitly. After a negative screening result, a woman's risk of developing breast cancer is low initially, but it approaches that of unscreened women after several years. After about 10 years, preceding screening can be expected to have lost its effect. We therefore defined a history of no screening as being present if a woman had never participated at all, or if she had rejected the index invitation and the 4 preceding ones. With this carefully designed contrast, we estimated that in women aged 65 years and older the reduction in breast cancer mortality for regularly screened women relative to the unscreened women was 44%.

Non-randomized studies are liable to self-selection bias that may (in part)

explain the breast cancer mortality rate ratio observed in the screened vs. the unscreened group. Besides age, which was controlled for by matching, we only reviewed the information on previous referral for diagnostic work-up. Only 3 controls and no cases had been referred previously, so this cannot have caused any bias. However, there may have been a difference in the underlying breast cancer mortality between the screened and unscreened groups that had biased our results. To gain an insight into the direction of the bias, we first calculated the survival rate (Kaplan-Meier method) from diagnosis to death from breast cancer for the Nijmegen non-participant patients and compared it with that of Arnhem patients. Arnhem is a neighbouring city with a similar population size as in Nijmegen, where population screening for breast cancer was started in 1989. The cause of death of the Arnhem patients was determined in the same way as in Nijmegen. We selected patients aged 65 years or older at diagnosis who were diagnosed in 1977 to 1989. Figure 5.1 shows that the curve for the 99 Nijmegen non-participants was fairly similar to that of the 372 Arnhem patients.

Next, we compared the incidence rate of breast cancer in Nijmegen with that in Arnhem. In the period from 1 January 1979 (after the Nijmegen population had undergone its first round of screening) to 31 December 1988, the incidence rate of breast cancer in Nijmegen equalled that in Arnhem (RR = 0.97; 95% CI = 0.83-1.14). We used log-linear modelling with the computer package GLIM and adjusted for age in 5-year categories: 65-69, 70-74, 75-79, 80-84 and 85+. Subsequently, the Nijmegen population was restricted to non-participants. For the Nijmegen non-participants compared with the Arnhem population, the RR was 0.72 (95% CI = 0.56-0.93). In the participants, the incidence of breast cancer must have been much higher than in the non-participants. Therefore, we conclude that the bias had reduced the estimated mortality reduction; the real effect must have been larger.

In a study on the survival of breast cancer patients, Satariano and Ragland[49] found that women with severe co-morbid conditions did not have a survival advantage because of early diagnosis. Death from other causes than breast cancer was the reason for this observation. We studied the overall survival rate from the date of invitation to round 3 (1979-80) in women aged 65-66 years at this invitation, who had participated in round 2 (Kaplan-Meier method). Figure 5.2 shows that the women who participated in round 3 (n = 720) had a far higher survival rate than those who did not (n = 198). Obviously, the participants had fewer co-morbid diseases or they were less severe. This means that the participants were at risk of dying from breast cancer for a

longer period. Moreover, we conclude that the women who chose to continue to participate in the screening are those who may benefit from a survival advantage because of early diagnosis.

Figure 5.1 *Breast cancer survival in Nijmegen non-participants and Arnhem patients*

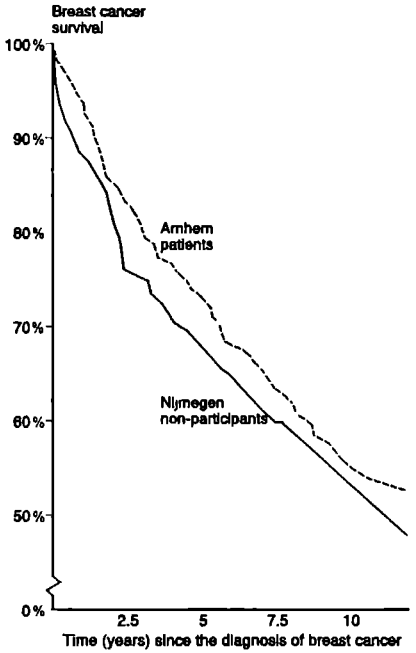
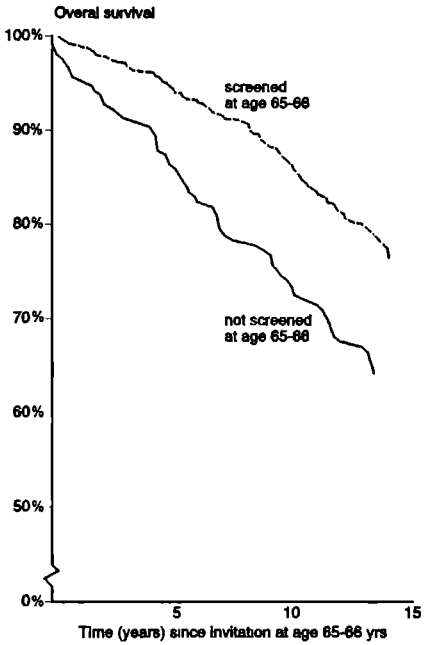


Figure 5.2 *Overall survival of women screened at age 63-64 years and invited at age 65-66 years*



Classification of the cause of death of deceased breast cancer patients is difficult. Especially in elderly women, some degree of misclassification is unavoidable because of the presence of co-morbid conditions, including other malignancies. In many patients, the origin of newly diagnosed metastases was not confirmed histologically. Autopsy had been performed in 11% of the deceased patients only. This means that a new malignancy for example of the lung, may have been misdiagnosed as metastases originating from the breast cancer.[50] To avoid different misclassification for screened and unscreened patients, the classification procedure was blinded for screening history. Misclassification that occurs independently of the screening history may have reduced the estimated mortality reduction.

Conclusion

We conclude that continuing breast cancer screening after the age of 65 years, at least up to 75 years, will lead to a reduction in breast cancer mortality in elderly women. No effect of screening after 75 years was found, but only 8% of these women had participated regularly. However, the extent of harmful side effects of breast cancer screening increases with increasing age. Because the overall death rate is higher, some screen-detected patients may even die before the tumour would have become detectable clinically. The magnitude of both the effects and the side-effects of continued mammographic screening after 65 years of age need to be evaluated. As a reduction in breast cancer mortality of 45% can be achieved in women over age 65 years, it seems unfair to exclude these women from national screening programmes. A policy of screening elderly women free of charge if they request it, as is the case in the UK, seems preferable to excluding them totally.

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Discussion

Contrasted screening histories

There was remarkable correspondence between the results of the two case-referent studies, although the contrasted screening histories were different. All the study subjects had been invited at least twice in the first case-referent study, and at least once in the second study. In the first study, the women who participated in the index screening (just before the diagnosis of breast cancer in the case) were contrasted with those who did not. Previous participations were not taken into consideration. In the second study, contrast was made between women screened regularly (*i.e.* at the index screening and 2 years prior to that) and those who had not been screened in the previous 10 years (regardless of the number of previous invitations). This definition of regular screening, which involved the fewest possible screening rounds, guaranteed that in the regularly screened patients, breast cancer had been diagnosed at the earliest possible stage. The reference category was designed to reflect breast cancer mortality in a population from an area without a screening programme.

In the first study, the ratio of the breast cancer mortality rates (RR) was 0.58 (95% CI = 0.24-1.41); in women aged 65-74 years, RR = 0.34 (95% CI = 0.12-0.97) and in women aged 75 or older, RR = 2.87 (95% CI = 0.62-13.2). The results in the second study were RR = 0.56 (95% CI = 0.28-1.13); in those aged 65-74 years, RR = 0.45 (95% CI = 0.20-1.02) and in those aged 75 years, RR = 1.05 (95% CI = 0.27-4.14).

Bias due to self-selection

Case-referent studies may produce biased results because the contrasted populations, i.e. the screened and unscreened women, may differ in terms of the baseline risk of death from breast cancer.[51,52] Because each woman makes her own choice about whether or not to participate, these self-selected populations may differ with regard to several unknown factors related to a woman's risk of dying from breast cancer. These unknown confounders may be either determinants of breast cancer incidence (risk factors for the disease) or prognostic factors. In the two case-referent studies, analyses were performed that showed the presence of confounding due to self-selection, and specifically a higher underlying breast cancer mortality in the participants than in the non-participants. This bias diluted the reduction in breast cancer mortality and controlling for confounding would have increased the reduction. Other trials have also reported an increased breast cancer incidence in the participant population.[53,54]

Healthy screenee bias

A specific source of bias has been called healthy screenee bias.[52] Women with a previous negative screening test have a lower chance that breast cancer is present in the detectable preclinical phase than those not screened before. This form of bias needs to be taken into consideration when repeated participation is considered, as was the case in the second case-referent study in which a positive screening history was defined as participation in two screening rounds. To study the extent of healthy screenee bias, the ratio of the incidence rates of invasive breast cancer of women screened regularly relative to non-participant women was calculated. The incidence rate in women screened regularly was calculated as the number of invasive cancers (both screen-detected and interval cancers) per 1000 accepted invitations, whereas in non-participants it was calculated as the number of invasive cancers per 1000 refused invitations. In women aged 50-64, 65-69, 70-74 and 75+, the ratios of the incidence rates in regular participants versus those in non-participants were 1.3 (95% CI = 1.2-1.5), 1.8 (95% CI = 1.3-2.5), 2.0 (95% CI = 1.4-2.8) and 2.1 (95% CI = 1.4-3.0), respectively. The presence of "healthy screenee bias" would have resulted in rate ratios of smaller than 1. Presumably, the bias due to self-selection was much stronger than the bias due to the healthy screenee effect.

Misclassification of the cause of death

A form of bias that may have occurred is misclassification of the cause of death. Non-differential misclassification of the outcome may give biased results, especially if the outcome is rare.[55] More precisely, screening may not be found to affect death from breast cancer even if screening reduces mortality. In the elderly, it is extremely difficult to make a correct classification of the cause of death. If metastases are diagnosed, the histological origin is not always verified. This leaves the possibility that metastases that were judged to originate from breast cancer, in fact had another origin, or may be a second primary cancer.[50] In the Malmö trial that included women aged 45-70 years, 193 breast cancer patients had breast cancer as the underlying cause of death according to the clinical information after 8 years of follow-up.[5] Forty-one of these patients had at least one other malignancy, which was judged to be the cause of death in 31 of them. Autopsy had been performed on 26 of these 41, 3 of whom appeared to have an additional previously unknown cancer as the cause of death, whereas 2 had died of the second malignancy. Between 1989 and 1993, autopsy had been performed on 11% of the Nijmegen and Arnhem

patients, which involves a fairly large risk of misclassification of the cause of death.

In order to evaluate misclassification of the cause of death in relation to age and screening history, a cross classification was made between the cause of death according to the death certificates, which were available for 640 Nijmegen and Arnhem patients who had died in the period 1975-1988, and the reviewed cause of death. The reviewed cause of death (breast cancer as underlying cause yes/no) was classified by a panel of physicians who were unaware of the screening history of the Nijmegen patients and was based on the clinical course of the disease and information about serious co-morbidity. Breast cancer was defined as the cause of death if the disease had progressed to distant sites and this progression was ultimately responsible for the death of the patient, or if in the presence of advanced disease other causes of death could be excluded. Patients with advanced breast cancer who died from other, unrelated causes were not classified as deaths from breast cancer. Table 5.6 shows the sensitivity and specificity of the death certificates using the cause of death determined during the review, as the golden standard. The sensitivity was 91%, which means that 91% of the patients who had died from breast cancer according to the review also had breast cancer as the primary cause of death on their death certificate. The specificity was 83%, which means that 17% of the patients who had died from another cause according to the review had breast cancer as the primary cause of death on the death certificate. It should be mentioned that although the reviewed classification of the cause of death was based on all the available clinical data it may have been inaccurate in an unknown proportion of the patients.

Table 5.6 *Cause of death on death certificate against reviewed cause of death*

Cause of death on death certificate	Death due to breast cancer at review		Total reviewed
	Yes	No	
Breast cancer primary cause	393 (91%)	36 (17%)	429 (66%)
Breast cancer secondary cause	9 (2%)	29 (14%)	38 (6%)
No breast cancer	29 (7%)	144 (69%)	181 (28%)
Total	431 (100%)	209 (100%)	651 (100%)

Sensitivity: 393/431 = 91%
Specificity: 173/209 = 83%

The data were also analysed according to age at death because with increasing age, an increase in co-morbidity may obscure the cause of death and lead to an increased misclassification. Table 5.7 shows the results of these analyses. Sensitivity and specificity of the death certificate decreased slightly with increasing age. Nyström et al[56] also reported more uncertainty about determining the reviewed cause of death in older women: the reviewers disagreed on the cause of death in 5% of the cases aged 40-59 years at randomization, in 13% aged 60-69 and in 19% aged 70-74 years. In the UK trial, however, no relation was found between the accuracy of the cause of death on the death certificates and age.[57]

Table 5.7 *Sensitivity and specificity of death certificates according to age, screening history*

Determinant	Sensitivity	Specificity
Age at death (yrs)		
35-59	94% (164)	94% (16)
60-69	91% (92)	83% (29)
70-79	88% (93)	83% (66)
80+	88% (76)	81% (98)
Participation in index screening		
yes	90% (91)	91% (53)[1]
no	91% (69)	77% (31)[1]

In parentheses the denominator of the percentage
[1] *Difference in specificities = 14% (95% CI = -4% to 30%)*

Another analysis was performed according to participation in the index screening (Nijmegen patients only) was performed because it was suspected that death from breast cancer may have been overreported in the screened population, in contrast with the unscreened population. If more cases of breast cancer are diagnosed, more deaths may be attributed to the disease in the screened population. The sensitivity of the death certificates, however, was identical, whereas the specificity was much lower in the non-participants (difference = 14%; 95% CI = -4% to 30%) than in the participants (Table 5.7). This means that there may have been overreporting of breast cancer deaths in the unscreened women. This decreased specificity may reflect the fact a larger proportion of the that non-participant patients had comorbid diseases which complicated the classification of the cause of death. The end-point used in the case-referent studies was the reviewed cause of death, which was probably

fairly accurate. However, it cannot be excluded with certainty that misclassification occurred more often in patients not screened at the index screening. If it were present, the proportion of patients who had died of other causes but had been classified as cases (*i.e.* death from breast cancer), may have been larger in the unscreened patients than in the screened patients, which would have overestimated the mortality reduction due to screening.

Case-referent studies on screening efficacy

A case-referent study may be a useful means to assess the efficacy of early detection and treatment for breast cancer.[58] Several important aspects must be dealt with for the results to be valid, such as the definition of the cases and population referents,[58,59] the definition of the relevant screening histories and last but not least, the elimination of bias due to self-selection.[51-53] Bias due to misclassification of the cause of death is a problem that can occur in any study on the efficacy of screening with death as the end-point.

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Chapter 6

Assessment of the reduction in breast cancer mortality: a non-randomized trial

Breast cancer mortality in a non-randomized trial on mammographic screening in women over age 65

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Abstract

Recent case-referent studies in the Nijmegen breast screening programme have shown a reduction in breast cancer mortality of approximately 50% due to screening of women aged 65 years and older. In this type of study, however, the results may be biased because of self-selection. The purpose of the study was to compare the breast cancer mortality rate in a population invited for screening with that of a reference population from an area without a screening programme.

In 1977-1978, 6773 women aged 68-83 years were enrolled in the mammographic screening programme in Nijmegen, the Netherlands. The women were followed-up until 31 December, 1990. The reference population consisted of women from the same birth cohort from Arnhem, a neighbouring city without mass screening, for whom the entry date was 1 January, 1978. The ratios of the Nijmegen and Arnhem breast cancer mortality rates with 95% confidence intervals (CI) were calculated.

In the study period, 173 patients were diagnosed with primary breast cancer in Nijmegen versus 183 in Arnhem; 40 Nijmegen patients had died of breast cancer versus 51 Arnhem patients. The cumulative mortality rate ratio was 0.80 (95% CI = 0.53-1.22). In the periods 1978-1981, 1982-1985 and 1986-1990, the mortality rate ratios were 1.44 (95% CI = 0.67-3.10), 0.81 (95% CI = 0.37-1.79) and 0.53 (95% CI = 0.27-1.04), respectively.

After adjustment for the difference in incidence rate that existed between the Nijmegen and Arnhem populations, mammographic screening of women older than 65 can be expected to yield a 40 per cent reduction in breast cancer mortality after 10 years.

Introduction

Unlike most malignancies, the course of breast cancer can be altered by early detection and treatment. In women over the age of 50 years, trials have shown

a reduction of breast cancer mortality of some 25 to 30% in populations that were offered screening versus unscreened populations.[1-4] The screening intervals used in these studies ranged form 12-33 months and the screening test consisted of one or two view mammography, sometimes in combination with physical examination.

More recently, a reduction in mortality has been demonstrated in women up to the age of 75 years.[5-7] The results of the Swedish two-county study, which was a randomized trial, showed a decrease in breast cancer mortality due to the screening of women aged 65-74 years at entry.[7] After 14 years of follow-up, a statistically significant 32% reduction in the risk of death from breast cancer was observed in the population invited for screening. In Nijmegen, two case-referent studies included women aged 65 years and older at the index invitation (*i.e.* the most recent invitation to screening just prior to the diagnosis of breast cancer in the case). The estimated reductions in breast cancer mortality in women screened at the index invitation relative to those unscreened at that time were 42% and 44% after 13 and 18 years of follow-up, respectively.[5,6] There has been debate, however, on the validity of case-referent studies as a method to evaluate screening efficacy, because the results may be biased due to self-selection for screening.[8,9] The present study used an external reference population to evaluate whether including elderly women in a screening programme affects breast cancer mortality.

Study population and methods

In 1975, a breast cancer screening programme was started in the city of Nijmegen, the Netherlands.[10] Initially, women born between 1910-1939 (aged 35-66 years) were invited for one-view mammography. Since the second round of screening, 1977-1978, women born before 1910, aged 67 years and older at their first invitation, have also been invited biennially to participate in the screening. The present study included all Nijmegen women born between 1895-1909 who had been invited to screening before the end of 1990. In this way, 6773 women entered the screening programme in round 2, while 488 women, who had come to live in Nijmegen after round 2, joined the programme between 1979 and 1990.

Information about invitation and participation of the invited women was stored in a computer file. With the aid of the local authorities, follow-up could be recorded. All the patients diagnosed with breast cancer (screen-detected and

clinically diagnosed) at either of the two Nijmegen hospitals were registered at the Department of Radiology of the University Hospital. Clinical information about deceased patients was obtained from their medical files and reviewed by a panel of physicians who were unaware of the screening history of the patients. The cause of death was ascertained based on the clinical course of the disease and information about any serious co-morbidity. Breast cancer was defined as the cause of death if the disease had progressed to distant sites and this progression could not be ruled out as the cause of death of the patient.

The reference population consisted of inhabitants of Arnhem, a city located 20 kilometres north of Nijmegen, where mass screening was started in 1989 for women aged 50-69 years as part of the national programme in the Netherlands. The Arnhem patients were registered by the "Carcinoma Work Group", which operated until 1991. With the aid of the local authorities, patients who had died or moved away from Arnhem could be identified. The cause of death of deceased patients was established in the same manner as that described above and by the same physicians as in Nijmegen.

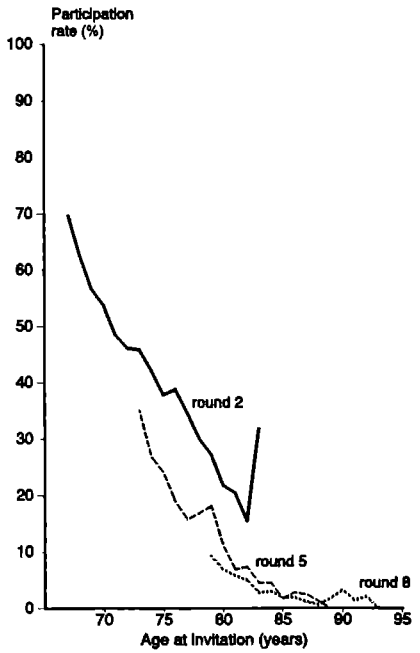
For Arnhem, person-years of observation had to be calculated from the official census statistics published annually by the Dutch Central Bureau of Statistics. These statistics keep track of the number of inhabitants of each sex, by year of birth, on 1 January of each calendar year. Although data for Nijmegen were available on an individual basis woman-years were also calculated on the basis of the census statistics for the sake of comparability of the information. For each calendar year up to and including 1990, the mid-year population size was calculated as the number of woman-years of observation in that year.

Breast cancer mortality rates in Nijmegen were based on data from patients in whom breast cancer had been diagnosed after the invitation to the first round of screening in 1977-1978. For 1977 and 1978, a population-time correction was made according to the exact entry dates. The mortality rates in Arnhem were based on data from patients diagnosed from 1 January, 1978 onwards, because this was close to the median date of the first invitation for the Nijmegen population (55% had been invited by then). Patients diagnosed with breast cancer before this date were excluded from the analysis. The ratio of the cumulative breast cancer mortality rates (*i.e.* number of breast cancer deaths in the entire study period divided by the total number of woman-years) was calculated, as well as the ratios of breast cancer mortality rate over three periods. Confidence intervals were calculated using the method based on the standard deviation of the log-transformed point estimates.[11]

Results

In Nijmegen, 7261 women born between 1895-1909 had been invited for screening in the period 1977-1990. A total of 46% had participated in the screening programme at least once and half of these women had taken part more than once. A marked decrease in the participation rate was observed as the round number and age increased, which is illustrated in Figure 6.1 for rounds 2, 5 and 8. In rounds 2-8, the overall participation rates were 43%, 29%, 22%, 15%, 12%, 10% and 4%, respectively.

Figure 6.1 *Participation rate according to age at invitation for screening rounds 2,5 and 8*



In Nijmegen, 173 patients were diagnosed as having breast cancer, versus 183 in Arnhem. Breast cancer had been diagnosed in Nijmegen: (1) after a positive screening examination in 57 patients, (2) after a negative screening mammogram (interval cancer) in 21 patients, (3) before the first invitation in 4 patients who had moved to Nijmegen after 1977, and (4) after a refused invitation in 91 non-participant cases.

Table 6.1 shows the number of patients who had died from breast cancer as well as the woman-years of observation for each calendar year. Two deaths

occurred in patients diagnosed before their first invitation who had moved to Nijmegen after 1978. For both populations, the breast cancer mortality rates (5-year moving average) are displayed in Figure 6.2. Up to 6 years after the start of screening, the breast cancer mortality rate in Nijmegen was higher than that in Arnhem. In the subsequent years, the Nijmegen breast cancer mortality rate stabilized, but an increase was observed in the late eighties. In Arnhem, the rate reached its maximum after 10 years and continued to decrease afterwards.

Table 6.1 *Number of breast cancer deaths and woman-years of observation by calendar year and city*

Calendar year	Nijmegen		Arnhem	
	breast cancer deaths[a]	woman-years	breast cancer deaths[b]	woman-years
1978	1	6823[c]	1	6502
1979	1	6248	3	6222
1980	8[d]	5947	1	5961
1981	6[d]	5620	6	5725
1982	3	5284	1	5455
1983	4	4967	3	5155
1984	2	4669	6	4836
1985	2	4378	4	4494
1986	1	3988	9	4174
1987	3	3567	6	3863
1988	5[e]	3224	6	3526
1989	3[f]	2944	5	3156
1990	1	2656	0	2765
1977-1990	40	60313	51	61832

[a] *only if diagnosed after first invitation in round 2*
[b] *only if diagnosed after 31 December 1977*
[c] *including 1977*
[d] *including 1 death in patient diagnosed before enrollment, but after round 2*
[e] *including 1 death with breast cancer metastases*
[f] *including 3 deaths with breast cancer metastases*
Cumulative mortality rate ratio 0.80 (95% CI = 0.53-1.22)

Figure 6.2 *Breast cancer mortality rates (5-year moving average) in Nijmegen, if diagnosed after first invitation in 1977-1978, and in Arnhem, if diagnosed from 1-1-1978 onwards*

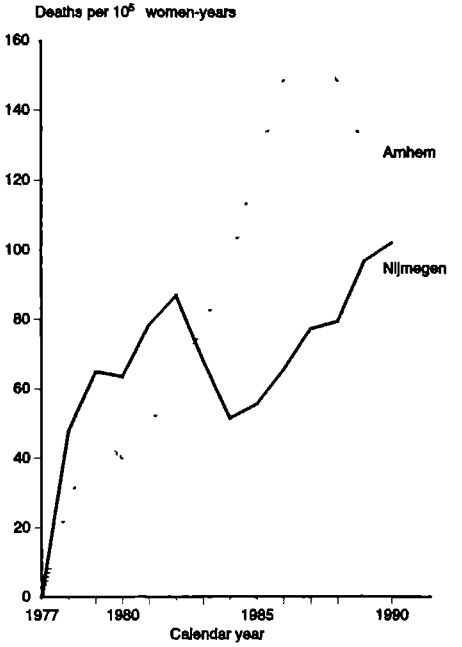


Table 6.2. *Breast cancer deaths and woman-years in Nijmegen and Arnhem in three specified periods and the mortality rate ratio (95% CI)*

Period	Nijmegen		Arnhem		Mortality rate ratio (95% CI)
	Deaths[a]	Woman-years	Deaths[b]	Woman-years	
1978-1990	16[c]	60325	51	61845	0.80 (0.53-1.22)
1978-1981	16	24641	11	24415	1.44 (0.67-3.10)
1982-1985	11	19301	14	19943	0.81 (0.37-1.79)
1986-1990	13[c]	16383	26	17487	0 53 (0 27-1.04)

[a] *if diagnosed after first invitation*
[b] *if diagnosed from 1-1-1978 onwards*
[c] *including 4 deaths with breast cancer metastases*

Over the entire study period, the breast cancer mortality in Nijmegen was lower than that in Arnhem: cumulative mortality rate ratio = 0.80 (95% CI = 0.53-1.22). Table 6.2 shows the ratio of the breast cancer mortality rates with 95% CI over several periods. In the first period of four years, the mortality rate ratio was 1.44, in the second period of 4 years it was 0.81, whereas in the relevant observation period, 9 to 13 years after the start of screening, it was 0.53 (95% CI 0.27-1.04).

Discussion

According to the results, the effect of screening manifests itself approximately 7 years after the start of the programme and reaches its maximum after about 10 years. This is what one would expect if analyses only include patients in whom breast cancer was diagnosed after the start of the screening programme. The proportion of women who participated in the programme decreased gradually, so the effect of screening on breast cancer mortality can also be expected to decrease gradually. It is likely that the effect will have diminished 15-20 years after the start of screening.

Could the observed mortality reduction be due to screening 46% of the population only, while half of these women had been screened at least twice? In an earlier study, the incidence of breast cancer in Nijmegen and Arnhem was compared in women aged 65 years and older. In the period 1979-1988, the incidence rate of breast cancer in Nijmegen (adjusted for age in 5-year categories: 65-69, 70-74, 75-79, 80-84 and 85+) equalled that in Arnhem (RR = 0.97; 95% CI = 0.83-1.14), whereas in the Nijmegen non-participants, the incidence was much lower than that in Arnhem (RR = 0.72, 95% CI = 0.56-0.93). Therefore, the incidence of breast cancer in the participants must have been much higher than in the non-participants.[6] We concluded that the women who do participate in the screening are at increased risk for breast cancer. As a consequence, actual participation may have a relatively large effect on breast cancer mortality in the population.

An important question is whether the populations of Nijmegen and Arnhem would have had the same breast cancer mortality in the absence of screening. This cannot be derived directly, but it can be analysed using an indirect approach by comparing the incidence of breast cancer. For the period 1975-1990, Figure 6.3 shows the incidence rates of primary breast cancer (5-year moving averages) in Nijmegen and Arnhem in women born between 1895-

1909. In almost every calendar year, the incidence in Nijmegen was lower than in Arnhem. It was only higher in Nijmegen in 1977-1981, when rounds 1 and 2 took place for this birth cohort. In the early eighties, the incidence rate in Nijmegen declined, possibly due to the start of screening in the late 1970s.

Figure 6.3 *Breast cancer incidence rates (5-year moving average) in the Nijmegen and Arnhem populations born between 1895 and 1909*

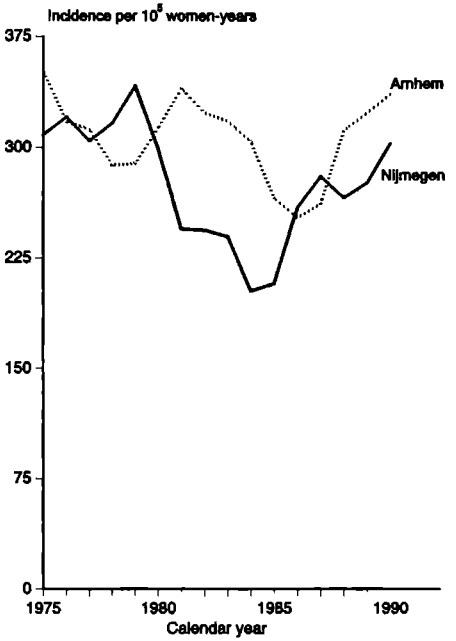


Table 6.3 shows the number of diagnosed patients and the woman-years of observation, as well as the incidence rate ratio for four periods. The incidence rate ratio was 0.90 (95% CI 0.75-1.07), adjusted for these 4 periods (directly weighted pooled estimate.[12,13] Correction of the mortality rate ratio over the relevant observation period 1986-1990 gave an estimate of 0.59 (95% CI = 0.30-1.16).

Besides incidence, prognosis is also a modifier of breast cancer mortality. Differences in prognosis could result from differences in treatment between Nijmegen and Arnhem. In Nijmegen, 30% of the patients were diagnosed and treated at the University hospital, while the remainder were patients at the other Nijmegen hospital. At the latter hospital, a "Diagnostic Mamma Team" has been established, consisting of radiologists, pathologists and surgeons from

the two hospitals. Once a week, all the patients are discussed. The goal of these weekly discussions is to reduce the number of invasive diagnostic procedures. Although the patients from the 2 cities were treated according to protocols, the monitoring of diagnostic procedure may have influenced the decision for treatment.

Table 6.3 *Number of diagnosed breast cancer patients and woman-years in Nijmegen and Arnhem in four specified periods and the incidence rate ratio (95% CI)*

Period	Nijmegen		Arnhem		Incidence rate ratio (95% CI)
	Diagnosed patients	Woman-years	Diagnosed patients	Woman-years	
1975-1976	38	14378	50	14317	0.76 (0.50-1.15)
1977-1980	84	25545	71	25425	1.18 (0.86-1.62)
1981-1985	61	24918	83	25665	0.76 (0.54-1.05)
1986-1990	43	16379	53	17484	0.87 (0.58-1.29)
1975-1990	226	81220	257	82891	0.90* (0.75-1.07)

* *directly weighted pooled estimate*[12,13]

A difference may have existed in the extent of misclassification of the cause of death. The procedures followed and the criteria used to ascertain the cause of death were identical for the Nijmegen and Arnhem patients. However, the physicians who made the classification were not blinded for city. Although unlikely, this may have led to differential misclassification. It is also possible that the information available in Nijmegen was more extensive than in Arnhem, for instance due to the "Diagnostic Mamma Team". An indication that this may have been the case was the fact that 4 Nijmegen patients had been classified as "death from other cause with metastases of breast cancer", whereas no Arnhem patients had been classified as such. This category was only used during the last 3 years. Previously, deaths had been classified as either "due to breast cancer" or "due to other causes".

Several case-referent studies have been conducted in Nijmegen. In women aged 67 years or older at entry, breast cancer mortality after 6 years of follow-up for those screened at least once was 19% lower (RR = 0.81, 95% CI 0.23-2.75) than in those who had never been screened.[14] In the study reported in 1994, the follow-up period was twelve years.[5] In women aged 65 years and

older who had been invited for screening at least twice, breast cancer mortality in those who had participated in the most recent screening was 42% lower than in those who had rejected it (RR = 0.58, 95% CI 0.24-1.41). In those aged 65-74, the reduction in breast cancer mortality was 66% (RR = 0.34, 95% CI 0.12-0.97). Our most recent study on women aged 65 years and older after 17 years of follow-up showed that breast cancer mortality was 44% lower (RR = 0.56, 95% CI = 0.28-1.13) in women who had been screened regularly (*i.e.* after the two most recent invitations) than in women who had not been screened in the past 10 years.[6] In women aged 65-74 years the reduction in breast cancer mortality was 55% (RR = 0.45, 95% CI 0.20-1.02). In these three case-referent studies, contrast was made between women who were screened and those who were not. The design of the present study was quite different, because contrast was made between the invited Nijmegen population, regardless of their actual screening history, and the uninvited Arnhem population. The most important reason for this design was to avoid bias due to self-selection. However, the price to be paid was a loss of contrast, because less than 50% of the invited population participated in at least one screening round.

The Swedish two-county trial is the only other project with a long follow-up that included women aged 70 years and older. In that randomized study, the participation rate was 86% in women aged 65-69 and 77% in women aged 70-74 years. Women of over 74 years were excluded from all the analyses, because of the low participation rate of approximately 50%. After 14 years, the ratio of the cumulative risk (*i.e.* number of deaths to the number of women enrolled) in the women aged 65-74 years at entry was 0.68 (95% CI = 0.51-0.89), which is much larger than in the Nijmegen invited population (cumulative rate ratio = 0.80). However, after the participation rate had been accounted for, the results compared very well.

The results of the present study, although in themselves inconclusive because of the wide confidence intervals, show a reduction in breast cancer mortality in women who were older than 65 years at entry to the screening programme. After 10 years, the reduction in breast cancer mortality may be as large as 40%.

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Chapter 7

Discussion and conclusions

Review of the evidence

Many reviews have addressed the effect of mammographic screening in women aged 50 to 70 years. The reduction in breast cancer mortality is reported to be approximately 30%.[1-5] In the late 1980s and early 1990s, no evidence of an effect was evident in older women,[2,6,7] because the number of elderly women included in the studies was too small. The goal of this thesis was to assess whether screening women aged 65 years and older has an effect on disease stage and breast cancer mortality.

As expected on the basis of the review of the literature, mammographic screening of elderly women showed promising early results. In the Nijmegen project, breast cancer detection rates increased with increasing age but the tumours were being detected at a much more favourable stage, particularly in elderly women. The incidence of ductal carcinoma in situ (DCIS) was relatively small. The participation rates, however, were very low.

In the non-randomized Nijmegen screening project, the effect of screening on breast cancer mortality was initially assessed using the case-referent method. In screened women aged 65 years and older, after 14 and 19 years of follow-up, breast cancer mortality was 42% and 45% lower than in the unscreened women, respectively. Women were assigned to the "screened" group if they had participated in the programme in the relevant period, i.e. just before breast cancer had been diagnosed in the cases who died from breast cancer. The observed effect was somewhat stronger in women aged 65-74 years at the most recent invitation, whereas it was absent in women of over 74, probably due to the small number of women screened and to self-selection bias. Later on, these results were verified using the "intention-to-treat" analysis in which breast cancer mortality in the invited Nijmegen population of women of over 65 at their first invitation was compared to that in the uninvited Arnhem population. In the period 10 to 15 years after the start of the screening programme, breast cancer mortality in Nijmegen was 40% lower than in Arnhem.

Only one other screening project, the Swedish two-county trial, has included women aged 70 years and older.[8] The analysis after 14 years of follow-up also showed a reduction in mortality due to screening. In women aged 65-74 years at entry, the ratio of the cumulative risk of death from breast cancer was 0.68 (95% CI = 0.51-0.89). In women aged 65-69 years, it was 0.58 (95% CI = 0.39-0.86) and in women aged 70-74 years, it was 0.78 (95% CI = 0.53-1.20). The smaller effect of screening in the older age category could be

explained by a lower participation rate (77% compared to 86% in those aged 65-69) and the smaller number of screenings that were offered (2 versus 4 in the younger women).[9] The measure of effect in this study, the cumulative risk of dying from breast cancer, may not have been appropriate, because the mean follow-up in the invited population was 13.8 years, whereas it was 10.6 years in the control population.[8] Calculation of the cumulative mortality *rate* ratio, which takes into account the difference in population time, produces 0.53 (95% CI = 0.40-0.69) in women aged 65-74 years at entry, which indicates a stronger effect. If the participation rate of 80% is accounted for,[5] the ratio of cumulative breast cancer mortality rates in the participants may be as small as 0.41. This estimate compares very well with that in Nijmegen after 19 years of follow-up. In women aged 65-74 years at the index invitation, the mortality rate ratio was 0.45 (95% CI = 0.20-1.02).

Randomized controlled trial

The paradigm for studying the effectiveness of screening has been the randomized controlled trial.[10-12] Bias due to self-selection is prevented by the random assignment of the study population to a group that is invited for screening and a group that is not, and analysis of the data according to the randomization groups, which will only differ in underlying breast cancer mortality due to chance. However, the experimental design has some problems of its own. A large study population and long follow-up time are required. Furthermore, participation will not be 100%, which dilutes the effect of screening on breast cancer mortality. In addition, women in the control population may be screened outside the study programme, which has been called "contamination" of the control population.

In the Malmö trial, the breast cancer mortality risk ratio was 0.96 (95% CI = 0.68-1.35) after 8 years of follow-up, whereas in a case-referent analysis the rate ratio was 0.42 (95% CI = 0.22-0.78).[10] The authors argued that the results of the case-referent design were biased due to self-selection. However, the relative risk estimate must have been biased also, because only 74% of the invited population actually participated and as many as 25% of the reference population had a mammogram outside the screening programme.[10,13]

It will be extremely difficult to assess of the effect of screening in women aged 75 years and older. A randomized trial would be inefficient because the participation rates may be as low as 50%. It has been argued that because of

the low participation rates, screening will not further reduce breast cancer mortality in the general population. This is probably true, but an important question remains, Would women of older than 75 years who want to be screened, benefit from it? By not setting an upper age limit in the Dutch national screening programme insight could be obtained into the effect of screening after age 74 and early outcomes at least could be studied in a larger study population. In addition, a case-referent study could be set up nested within this screening programme. However, control of bias due to self-selection would be difficult. Determinants of the incidence of breast cancer, i.e. risk factors for the disease, and determinants of the prognosis, i.e. the presence of prognostic comorbid conditions,[14] would need to be measured, but it will be almost impossible to measure these confounding factors accurately in the non-participants.

Gain in life expectancy

In this thesis, the effect of screening on breast cancer mortality was studied. A 50% reduction in breast cancer mortality in screened women does not mean that death is prevented in 50% of the women. Death can only be postponed and may eventually be due to other causes than breast cancer. It can be argued that the gain in life expectancy is a more appropriate outcome. In elderly women, with a relatively short life expectancy, a 50% reduction in breast cancer mortality in screened women may give only a marginal increase in life expectancy.

Table 7.1 shows the hazard rate (proportion of women who will die in the next year) and the life expectancy for women at specific ages. An increasing hazard rate and a decreasing proportion of deaths attributed to breast cancer, indicate that the number of life years gained by participating in the screening will not be large in elderly women. However, the quality of life will be increased in patients who will not suffer from metastasized breast cancer. Preventing metastasized breast cancer may be a more appropriate goal of breast cancer screening in elderly women than preventing death from the disease. The outcome to be studied would then be the incidence of metastasized breast cancer instead of mortality from breast cancer.

Table 7.1 *Life tables for women in the Netherlands (1994)*

Age in years	Hazard rate*	Years expected to live
70.5	0.018	14.8
75.5	0.032	11.2
80.5	0.054	8.1
85.5	0.102	5.6
90.5	0.175	3.8
95.5	0.290	2.6

Modified from the CBS
* *proportion of deaths within the next year*

Future research

Several issues for future research can be formulated. First, the quality of other screening modalities, e.g. palpation, should be studied. Breast self-examination is unlikely to form an alternative for mass screening.[15] Regular physical breast examinations are not yet known to be an effective way of reducing breast cancer mortality,[16] although in elderly women, the biological features that simplify the interpretation of mammography, i.e. the decreased proportion of parenchymal tissue and the increased proportion of fat, may also facilitate physical examination. Nevertheless, tumours detected by physical examination are generally larger than those detected by mammography. In a mixed group of symptomatic and asymptomatic breast cancer patients, only 18% of the mammographically detectable tumours of ≤ 10 mm could be detected by palpation by an experienced surgeon, whereas 74% of the tumours of 11-20 mm and 96% of those of >20 mm were palpable.[17] Only 19% of the in situ cancers were palpable. In elderly women, it is likely that a large proportion of very small cancers or in situ cancers would never become clinically relevant if undetected by mammographic screening. This means that the lower detectability of these small tumours by physical examination may be an advantage.

In the Canadian trial on women aged 50-59 years, after 7 years of follow-up the risk of dying from breast cancer in those who had been invited for annual mammography and physical examination was the same as that in the women who had only been invited for annual physical examination (RR = 0.97, 95%

CI = 0.62-1.52).[18] The poor quality of the mammography technique has been suggested as the cause for the disappointing results.[19] Another explanation may be that physical examination alone is just as effective as mammography plus physical examination for reducing mortality from breast cancer.[20] After 10 or 15 years of follow-up, this study should give clearer results on whether there is a reduction in mortality due to mammography in addition to physical examination. A study on the effect of screening with physical examination in women of older than 70 years, could be carried out within the Dutch national programme. Preferably, a comparison should be made with mammography screening.

A further issue is whether the interval between screening examinations can be extended in women older than 70 years. An analysis of the incidence of breast cancer in relation to the time since the last screening in women who have reached the upper age limit, could be helpful. Finally, the extent of over-diagnosis with mammographic screening should be studied, especially in the very elderly. If a large proportion of older screen-detected patients with a fairly indolent tumour are over-diagnosed and treated, then an upper age-limit should be set for breast cancer screening. As indicated previously, screening with physical examination instead of mammography may reduce the risk of overdiagnosis.

Concluding remarks

The findings in this thesis do not support the policy of the Dutch national breast screening programme to exclude women from screening after they have reached 70 years of age. A significant reduction in breast cancer mortality has been shown up to the age of 75, but there is no evidence that the reduction also extends to older women, because the number of elderly participants is too small and strong bias exists. It is possible, however, that women who *choose* to continue to participate may benefit up to the age of 85 years. First, these women have an increased risk of breast cancer compared to those who decide not to continue, and second, they have a longer than general life expectancy. Preferrably, women should be offered the opportunity to enroll for re-screening at the last planned screening examination, between 68-69 years of age. who show interest in being re-invited invited.

The research questions formulated for older women could be addressed in the national screening programme. For this purpose, different screening

strategies could be followed at different screening centres, for example biennial one-view mammography, or triennial one-view mammography, or biennial physical breast examination. In this way, the remaining questions may be resolved within 10 years.

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Summary

Regular mammographic screening of women aged 50 to 70 years reduces breast cancer mortality. In older women, there is lack of evidence of such an effect. The goal of this thesis was to estimate whether including women of 65 years and older in a screening programme affects disease stage and breast cancer mortality. The setting was the Nijmegen screening project for breast cancer, which was started in 1975 for approximately 23,000 women aged 35-65 years. Since 1977, nearly 7,700 older women have also been invited for biennial screening with one-view mammography.

The thesis starts with a review of the literature regarding epidemiological and biological factors that may influence the detection of breast cancer. In elderly women who do not undergo screening, breast cancer is diagnosed at a relatively late stage. In addition, a large proportion of older patients with advanced stage disease do not receive optimal therapy. The decreased proportion of glandular tissue in the breasts of older women facilitates the detection of breast cancer by mammography. On the other hand, cancer-free breasts can be identified more easily, because benign breast diseases are fairly uncommon in older women. The tumour growth rate decreases with advancing age. Evidence from several sufficiently long-standing screening projects which also included elderly women have indicated a mortality reduction up to the age of 75 years.

The capability of detecting breast cancer with one-view mammography was studied by reviewing the previous negative screening mammogram of 44 screen-detected patients and of 40 interval cancer patients. Thirteen per cent were classified as "screening error", 38% as "minimal sign present", 43% as "radiographically occult" and 6% as "radiographically occult at diagnosis". In this relatively small study, no difference in detectability was found between women aged 55-64 years and those 65-79. Future research may focus on a radiological analysis of "minimal sign" cases to find out whether the sensitivity can be improved without any significant decrease in the specificity. Further, computer-assisted reading of mammograms should be developed to help prevent screening errors and thus improve the sensitivity. A literature study was conducted to review the quality of one-view mammography compared to two-view mammography for initial screening. With two-view mammography, the detection rate was estimated to increase by 24%, while at the same time the rate of recall for additional mammography views was

estimated to decrease by 15%. It was concluded that two-view mammography should be used for the first screening.

In a study on age-specific early outcomes of the Nijmegen screening programme, decreasing rates of participation and increasing rates of breast cancer detection were found with increasing age. In women of over age 64 who had been screened regularly, the incidence of breast cancer was approximately 2 times higher than that in non-participant women. This may mean that the women who continue to participate are at an increased risk for breast cancer. In addition, survival rates in these women were higher than in those who dropped-out. Another important finding was that for all age categories, tumours detected at screening were smaller and less often associated with axillary lymph node metastases than tumours diagnosed clinically.

To determine whether screening after the age of 65 years affects breast cancer mortality, two case-referent studies and one non-randomized trial were performed. In the first case-referent study, with 14 years of follow-up from 1975 to December 1988, the study population consisted of women who were 65 years or older when they received their second invitation for screening. Thirty-three of these women died from breast cancer. For each of these cases, 5 population referents were selected, matched for age and the number of previous invitations. The analysis showed that breast cancer mortality in the women who had participated in the most recent screening was 42% lower than in those who had not. The 95% confidence interval (CI) of this reduction was 0.28-1.41. In the age category 65-74 years, the reduction was 66% (rate ratio (RR) = 0.34; 95% CI = 0.12-0.97), whereas in women older than 74 years, mortality increased.

In the second case-referent study, with an additional follow-up of 5 years, up to December 1993, the study population consisted of women who had been invited for screening at the age of 65 years or older. Eighty-two cases died from breast cancer; 410 referents were individually matched to the cases on age at invitation. In the women who had participated regularly (*i.e.*, in the 2 most recent screening rounds prior to diagnosis) breast cancer mortality was 44% lower (RR = 0.56; 95% CI = 0.28-1.13) than in the women who had not participated. In those aged 65-74 years, the reduction in breast cancer mortality was 55% (RR = 0.45; 95% CI = 0.20-1.02), whereas a 5% increase was found in women aged 75 years and older (RR = 1.05; 95% CI = 0.27-4.14).

An important limitation of case-referent studies is that mortality from breast cancer is studied in women who choose to be screened relative to those who

choose not to. These self-selected populations may differ with regard to the underlying risk of death from breast cancer. Several analyses showed that this bias had probably given an underestimation of the reduction in breast cancer mortality due to screening. In women aged 75 years and older, the bias may explain the increase in mortality in screened women. To verify the results of the case-referent studies, while avoiding bias due to self-selection, the Nijmegen programme was analysed according to the "intention to treat" principle used in clinical trials. Over the period 1978-1990, breast cancer mortality in the Nijmegen population, irrespective of participation in screening, was compared to that in the population of Arnhem, a neighbouring city without a screening programme. The analysis was restricted to women born between 1895 and 1909, who were 68-83 years old at their first invitation for screening. In Nijmegen, 40 patients had died of the disease by the end of 1990, compared to 51 Arnhem patients. The ratio of the cumulative breast cancer mortality rates was 0.80 (95% CI = 0.53-1.22). In the relevant observation period 1986-1990, the breast cancer mortality rate ratio was 0.53 (95% CI = 0.27-1.04), whereas it was 0.59 (95% CI = 0.30-1.16) after adjustment for the difference in incidence between the two populations. Restricting the bias due to self-selection in this way had a very high price. There was considerable loss of contrast between the study groups because only 46% of the Nijmegen population participated once or more in the screening. The result of this study, although in itself inconclusive, supports the findings of the case-referent studies.

A problem in each of the studies was misclassification of the cause of death, as the histological origin of suspected metastases had not always been verified. If misclassification of the outcome occurs with equal frequency in the contrasted populations, then the estimated mortality reduction will be smaller than the real reduction due to screening. Unfortunately, the existence of differential misclassification of the cause of death, specifically a larger number of deaths from other causes that were attributed to breast cancer in the unscreened population, cannot be excluded with certainty. If it was present, misclassification bias may have exaggerated the reduction in breast cancer mortality.

The overall conclusion is that mammographic screening after the age of 65 years, at least up to 75 years, can reduce breast cancer mortality. In participants, breast cancer mortality can be up to 45% lower. Owing to the self-selection of women at high risk and a longer than average life expectancy, screening may be beneficial up to the age of 85 years. However, the number

of life years gained in some of the screen-detected patients may only be marginal. In the elderly, increasing the quality of life by preventing life years lived with metastases of breast cancer may be a more appropriate goal of screening than a reduction in breast cancer mortality.

Several issues may be of interest for future research. The quality of regular physical breast examination as a screening method is of particular importance for elderly women. The number of years that a patient would have to live with the knowledge that she has breast cancer if it is diagnosed by physical examination is much lower than with mammographic screening. It is unknown whether and to what extent screening with physical breast examination can reduce breast cancer mortality. Another issue is whether longer intervals between screening examinations can be used for older women. Furthermore, the extent of overdiagnosis with mammographic screening should be studied.

Samenvatting

Resultaten van diverse onderzoeken hebben uitgewezen dat de sterfte aan borstkanker kan worden gereduceerd door vrouwen van 50 tot 70 jaar periodiek te screenen met mammografie. Onder de gescreende vrouwen kan de sterfte aan borstkanker met 45% worden teruggedrongen. Het effect van screening op hogere leeftijd was onbekend. Het doel van de in dit proefschrift beschreven onderzoeken was het bestuderen van het effect van mammografische screening van vrouwen van 65 jaar en ouder op het stadium van borstkanker bij diagnose en op de sterfte aan borstkanker. De onderzoeken werden uitgevoerd binnen het kader van het Nijmeegse proefbevolkingsonderzoek naar borstkanker dat in 1975 van start ging. Circa 23000 vrouwen in de leeftijd van 35 tot 65 jaar werden eenmaal per twee jaar uitgenodigd een mammogram te laten maken. Sedert 1977 werden ook ongeveer 7700 vrouwen ouder dan 65 jaar uitgenodigd deel te nemen.

In Hoofdstuk 2 is een wordt een literatuurstudie weergegeven naar de epidemiologische en biologische factoren die invloed kunnen hebben op de detectie van borstkanker. Voor oudere vrouwen die geen screening ondergaan, blijkt borstkanker doorgaans in een relatief vergevorderd stadium te worden gediagnostiseerd. Bovendien krijgen oudere patiënten met gemetastaseerde borstkanker vaker dan jongere patiënten minder zware therapie. Doordat de borsten van oudere vrouwen naar verhouding minder klierweefsel en meer vetweefsel bevatten, kan borstkanker relatief gemakkelijk worden opgespoord met behulp van mammografie. Bovendien komen goedaardige borstaandoeningen minder voor, waardoor de afwezigheid van borstkanker gemakkelijker kan worden vastgesteld. De groeisnelheid van borstkanker is lager op oudere leeftijd. Resultaten van een aantal screeningsprojecten met voldoende lange follow-up in verband met de lage groeisnelheid waarin ook ouderen tot de onderzoekspopulatie behoorden, wijzen in de richting van een reductie in de borstkankersterfte door screening tot aan de leeftijd van 75 jaar.

In Hoofdstuk 3 is de kwaliteit van mammografie met één opname per borst voor het opsporen van borstkanker bestudeerd door de voorafgaande negatieve screeningsmammogrammen van 44 patiënten met een bij screening ontdekt carcinoom en 40 patiënten met een intervalcarcinoom (ontdekt in het screeningsinterval na een negatief screeningsmammogram) opnieuw te beoordelen. Bij 13% van de patiënten bleken op het voorafgaande mammogram zeer sterke aanwijzingen voor borstkanker aanwezig te zijn ("fout bij screening"). Bij

38% van de patiënten was "een minimaal teken" zichtbaar dat slechts met kennis van de precieze localisatie in verband kon worden gebracht met de gediagnostiseerde borstkanker. Op 43% van de voorafgaande mammogrammen was geen enkel teken van borstkanker zichtbaar ("radiologisch occult"), terwijl in 6% van de gevallen noch het eerdere mammogram, noch het mammogram bij diagnose enig teken van kanker toonde ("radiologisch occult bij diagnose"). In dit onderzoek werd geen verschil in detectievermogen gevonden tussen de diverse leeftijdscategorieën. Nader onderzoek gericht op een grondige analyse van de groep met "minimale tekenen" werd aanbevolen om vast te stellen of de sensitiviteit van de mammografie kan worden verhoogd zonder een belangrijke verlaging van de specificiteit. Tevens werd de ontwikkeling aanbevolen van het gecomputeriseerd lezen van mammogrammen ter ondersteuning van de beoordeling door de radioloog, bij het detecteren van kanker.

Bovendien staat in Hoofdstuk 3 een literatuuronderzoek beschreven naar de kwaliteit van mammografie met één opname per borst bij eerste screening in vergelijking met mammografie met twee opnames per borst. Door de tweede opname zou het detectiecijfer kunnen worden verhoogd met circa 24%, terwijl tegelijkertijd het percentage gescreenden zonder borstkanker bij wie aanvullend mammografisch onderzoek zou moeten worden verricht, zou afnemen. Geconcludeerd werd dat bij eerste screening twee mammografische opnames per borst dienen te worden gemaakt. Of een tweede mammografische opname ook bij vervolgscreening kwaliteitsbevorderendwerkt, is nog onbekend.

Een onderzoek naar vroege uitkomsten van het screeningsprogramma wordt weergegeven in Hoofdstuk 4. Op hogere leeftijd was de deelnamegraad lager en het detectiecijfer van borstkanker hoger. In de groep regelmatige participanten (d.w.z. tenminste tweemaal achtereenvolgens gescreend) ouder dan 64 jaar was de incidentie van borstkanker circa tweemaal zo hoog als onder nonparticipanten van dezelfde leeftijd. Dit zou kunnen betekenen dat participanten die blijven deelnemen een verhoogd risico op borstkanker hebben. Bovendien was de overleving voor deze vrouwen langer dan voor participanten die ophielden deel te nemen. Een andere belangrijke bevinding was dat in alle leeftijdscategorieën de bij screening ontdekte tumoren kleiner waren en minder vaak uitzaaiingen naar de okselklieren vertoonden dan klinisch gediagnostiseerde tumoren.

Om het effect van screening na de leeftijd van 65 jaar op de sterfte aan borstkanker te onderzoeken, werden twee patiënt-controle onderzoeken (Hoofdstuk 5) en een vergelijking van populaties (Hoofdstuk 6) uitgevoerd. In het eerste patiënt-controle onderzoek, met 14 jaar follow-up van 1975 tot en

met december 1988, bestond de onderzoekspopulatie uit vrouwen die tenminste 65 jaar waren toen zij hun tweede uitnodiging ontvingen voor deelname aan de screening. Drieëndertig van deze vrouwen bleken te zijn overleden aan borstkanker en vormden de patiëntengroep. Bij elke patiënt werden 5 controles gezocht met identieke leeftijd bij de laatste uitnodiging voor de diagnose van borstkanker in de patiënt en met een gelijk aantal voorafgaande uitnodigingen. De resultaten lieten een reductie in de sterfte aan borstkanker zien van 42% voor de groep vrouwen die aan de meest recente uitnodiging gehoor hadden gegeven, vergeleken met de vrouwen die niet recent waren gescreend (rate ratio (RR) = 0,58; 95% betrouwbaarheidsinterval (BI) = 0,24-1,41). In de leeftijdscategorie 65-74 jaar was de reductie 66% (RR = 0,34; 95% BI = 0,12-0,97), terwijl voor vrouwen ouder dan 74 jaar een toename in de borstkankersterfte werd gezien.

Het tweede patiënt-controle onderzoek omvatte 5 extra jaren follow-up, nu tot en met december 1993. De onderzoekspopulatie bestond uit vrouwen die waren uitgenodigd voor deelname toen ze minstens 65 jaar oud waren. Tweeëntachtig patiënten waren aan borstkanker overleden. Bij elke patiënt werden 5 controles geselecteerd met identieke leeftijd bij de laatste uitnodiging voor de diagnose van borstkanker in de patiënt. Onder de vrouwen die regelmatig hadden deelgenomen (d.w.z. tenminste aan de twee meest recente screeningen) bleek de sterfte aan borstkanker 44% lager te zijn (RR = 0,56; 95% BI = 0,28-1,13) dan onder de vrouwen die in de afgelopen 10 jaar niet waren gescreend. In de leeftijdscategorie 65-74 jaar was de reductie 55% (RR = 0,45; 95% BI = 0,20-1,02), maar in de leeftijd 75 jaar en ouder werd een toename van 5% gevonden (RR = 1,05; 95% BI = 0,27-4,14).

Een belangrijke beperking van patiënt-controle onderzoeken is de mogelijkheid dat de resultaten vertekend zijn door zelfselectie. De groepen die worden vergeleken zijn namelijk de deelneemsters en niet-deelneemsters. De uitgenodigde vrouwen hebben zelf verkozen wel of niet aan het screeningsonderzoek deel te nemen. De aldus zelfgeselecteerde populaties kunnen verschillen ten aanzien van het onderliggende risico op sterfte aan borstkanker. Diverse analyses toonden aan dat de resultaten inderdaad waren vertekend. Indien echter voor deze vertekening gecorrigeerd had kunnen worden, zou de reductie in borstkankersterfte nog groter zijn geweest. Voor vrouwen van 75 jaar en ouder kon de vertekening de toename in borstkankersterfte onder de gescreenden verklaren.

De resultaten van de patiënt-controle onderzoeken werden geverifieerd in een studie volgens het in gerandomiseerde trials naar het effect van medische

interventie veel gebruikte "intention-to-treat" principe om vertekening door zelfselectie te voorkomen (Hoofdstuk 6). De sterfte aan borstkanker in de populaties van Nijmegen en Arnhem werd vergeleken over de periode 1978-1990. Voor Nijmeegse vrouwen werd buiten beschouwing gelaten of ze daadwerkelijk aan de screening hadden deelgenomen. In Arnhem was in deze periode geen screeningsprogramma. In de analyses werden alleen vrouwen beschouwd geboren in de jaren 1895-1909, die 68-83 jaar waren bij de eerste uitnodiging voor deelname aan de screening in Nijmegen. In de studieperiode bleken 40 Nijmeegse en 51 Arnhemse patiënten ten gevolge van borstkanker te zijn overleden. De reductie in de cumulatieve borstkankersterfte in de Nijmeegse populatie was 20% (cumulatieve RR = 0,80; 95% BI = 0,53-1,22). In de relevante observatie periode 1986-1990 was de reductie 47% (RR = 0,53; 95% BI = 0,27-1,04). Na correctie voor een verschil in incidentie tussen de populaties was de reductie 41% (RR = 0,59; 95% BI 0,30-1,16. In deze studie bleek dat het vermijden van de vertekening door zelfselectie ten koste ging van het contrast tussen de te vergelijken populaties, daar slechts 46% van de Nijmeegse vrouwen tenminste eenmaal had deelgenomen aan de screening. Deze resultaten wijzen in dezelfde richting als die van de beide patiënt-controle onderzoeken.

Een complicatie in elk van de onderzoeken was misclassificatie van de doodsoorzaak, daar het histologische origine van verdachte metastasen niet altijd werd geverifieerd. Bij een gelijke mate van misclassificatie in de te contrasteren populaties zal de reductie in borstkankersterfte in de studie worden onderschat; het werkelijke effect van screening zal groter zijn. Niet kon met zekerheid worden uitgesloten dat het percentage borstankerpatiënten overleden aan een andere oorzaak doch geclassificeerd als overleden aan borstkanker, groter was geweest in de non-participanten. Als dit daadwerkelijk het geval is geweest, kan de reductie in borstkankersterfte zijn overschat.

De eindconclusie (Hoofdstuk 7) is dat mammografische screening na leeftijd 65 jaar en tenminste tot aan 75 jaar, de sterfte aan borstkanker kan reduceren. Onder de participanten kan deze reductie zelfs 45% bedragen. Omdat ten gevolge van zelfselectie vrouwen blijven deelnemen die een relatief groot risico op borstkanker en een betrekkelijk lange levensverwachting hebben, zou screening zelfs op leeftijd 85 jaar nog een gunstig effect kunnen hebben. Echter, het aantal gewonnen levensjaren zou voor sommige patiënten met een bij screening ontdekte borstkanker slechts marginaal kunnen zijn. Op hogere leeftijd zou de toename in de kwaliteit van leven door het voorkomen van gemetastaseerde borstkanker een belangrijkere doelstelling van screening

kunnen zijn dan reductie in de sterfte aan borstkanker.

In Hoofdstuk 7 worden tevens aanbevelingen gedaan voor aanvullend onderzoek. Periodiek lichamelijk borstonderzoek (palpatie) als screeningmethode zou met name van belang kunnen zijn voor oudere vrouwen, omdat door de relatief geringe aanwezigheid van klierweefsel detectie van borstkanker met deze methode beter zou kunnen zijn. Onbekend is echter of, en zo ja in welke mate, screening middels palpatie de sterfte aan borstkanker kan reduceren. Een andere vraag is of voor oudere vrouwen een interval tussen de screeningsonderzoeken langer dan 2 jaar zou kunnen worden gebruikt. Tenslotte zou de mate van overdiagnostiek met mammografische screening kunnen worden onderzocht.

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Curriculum Vitae

Op 16 februari 1961 in Arcen werd ik, Jos van Dijck, geboren.

In 1979 behaalde ik het VWO-B diploma aan het Sint Thomascollege te Venlo. Aansluitend startte ik met de 2-jarige opleiding tot radiodiagnostisch laborante in het Sint Radboud Ziekenhuis te Nijmegen, waar ik na het behalen van het diploma in 1981 nog 4 jaar als gediplomeerd laborante werkzaam was.

In 1985 begon ik met de studie Biomedische Gezondheidswetenschappen aan de Katholieke Universiteit Nijmegen (KUN). Als afstudeerrichting koos ik epidemiologie, met als afstudeerstages een onderzoek van 5 maanden naar het vóórkomen van spierkrampen in Nederland en een onderzoek van 5 maanden naar de groeisnelheid van borstkanker. Na het behalen van het doctoraalexamen in 1989 werd ik aangesteld als junior epidemioloog bij de afdeling Epidemiologie van de KUN. Mijn functie bestond voor 50% uit onderwijstaken, met name voor het curriculum Biomedische Gezondheidswetenschappen, en voor 50% uit onderzoektaken ten behoeve van het Nijmeegse proefbevolkingsonderzoek naar borstkanker.

Na twee jaar verschoven de onderzoektaken in de richting van het Landelijk Referentiecentrum voor het Bevolkingsonderzoek naar Borstkanker. Onderwijstaken werden toegespitst op het doceren van de epidemiologie van borstkanker binnen de opleidingen van radiodiagnostisch laboranten, radiologen en pathologen tot screeningsfunctionaris. De onderzoektaken werden gestructureerd tot het voorliggende promotie-onderzoek.

Postdoctoraal onderwijs epidemiologie bestond uit het wekelijks "epidemiologie-refereren" bij de afdeling Epidemiologie, en cursussen van de professoren Miettinen, Rothman en Weiss.

Ik ben getrouwd met André te Boekhorst. Samen hebben wij drie dochters, Mieke, Ellen en Susan.

Stellingen

behorend bij het proefschrift

The efficacy of mammographic screening for breast cancer in elderly women

1. Vrouwen dienen ook ná het bereiken van de leeftijd van 70 jaar de mogelijkheid te krijgen aan het landelijk bevolkingsonderzoek naar borstkanker deel te nemen, aangezien periodieke mammografische screening van oudere vrouwen leidt tot een vermindering van de borstkankersterfte (*dit proefschrift*).

2. De lage deelnamegraad van vrouwen van 70 jaar en ouder is eerder een argument vóór dan tegen inclusie van deze leeftijdscategorie bij het landelijke bevolkingsonderzoek naar borstkanker, daar degenen die blijven deelnemen een verhoogde kans op borstkanker hebben (*dit proefschrift*).

3. Bij vrouwen die voor het eerst deelnemen aan het bevolkingsonderzoek naar borstkanker dient het screeningsonderzoek te bestaan uit twee opnames per borst (*dit proefschrift*).

4. De waarde van twee opnames per borst bij vervolgscreening is nog niet aangetoond, ook niet bij vrouwen met een dicht borstparenchym patroon.

5. Agressieve screening, waarbij de nadruk op de sensitiviteit en minder op de specificiteit ligt, verdient in het geval van borstkanker geen voorkeur.

6. Zelfselectie-bias is een vorm van confounding bias.

7. De grote precisie van een onderzoeksresultaat is weinig zeggend indien de validiteit ervan niet vaststaat.

8. Ouderschap dient niet alleen gericht te zijn op de beïnvloeding van de groei en ontwikkeling van kinderen, maar tevens op de groei en ontwikkeling van de ouders (*Naar Thomas Gordon, Luisteren naar kinderen, 1979*).

9. De aarde is slechts één land waarvan wij allen burgers zijn (*Bahá'ullah*).

10. Het leven is als een legpuzzel zonder voorbeeld.

Jos van Dijck, 7 november 1996