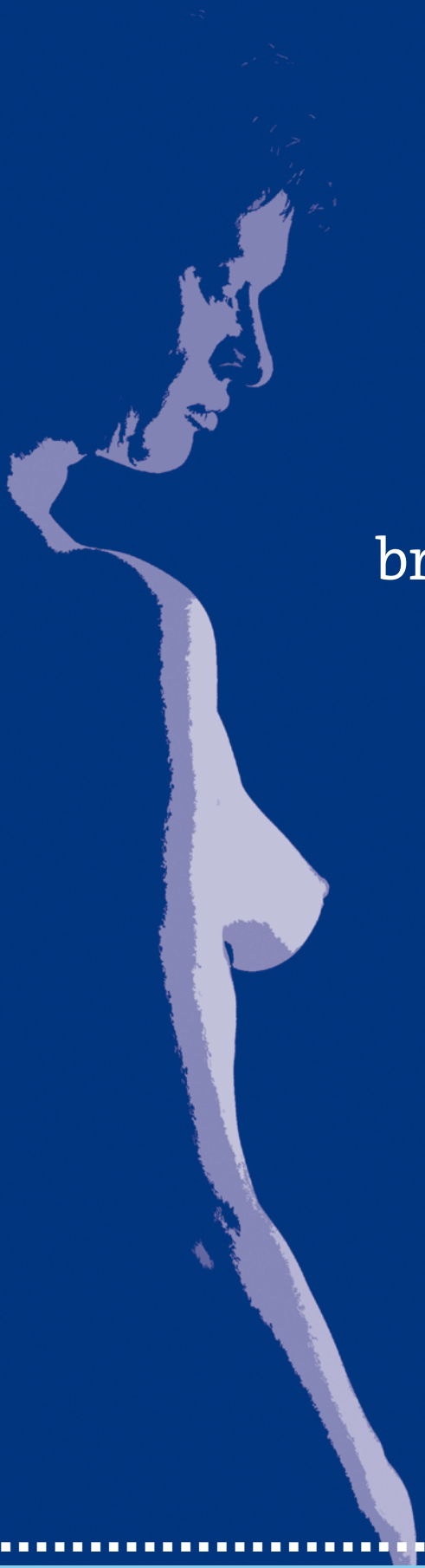

National evaluation of breast cancer screening in the Netherlands 1990-2007

LETB XII

National Evaluation Team for Breast cancer screening

Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker

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National evaluation of breast cancer screening in the Netherlands

1990 – 2007 (XII)

Twelfth evaluation report

National Evaluation Team for Breast cancer screening (NETB)
Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker (LETB)

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Translation of the Dutch report
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Table of contents

1

Introduction

The last detailed report from the National Evaluation Team for Breast cancer screening (NETB) on the Dutch breast cancer screening programme appeared in 2005. It presented the screening results up until the end of 2003 which, however, were incomplete for some regions. The same applies to the two brief interim reports that were released in 2006 and 2007. The new evaluation report adds four reporting years to the entire evaluation period, i.e. those from 2004-2007. The fact that this 12th report by the NETB is based on complete nationwide data on the screening activities of all nine screening regions is particularly good news. This is thanks to the additional efforts made by the two regions that had had a backlog of screened women's follow-up data for years, enabling the backlog to be eliminated by spring 2009. It also enabled the optimum analysis of 18 years of national population research, and the presentation of the results without qualification. Unfortunately, this does not apply to the data on interval cancers which, subsequent to 1999, are far from being fully available at national level.

Compared to previous detailed NETB reports, the primary results of the evaluation tables are presented here in less detail, a task made otherwise nearly impossible due to the increasing quantity and detail of evaluation data over the years. The advantage of the evaluation of the Dutch breast cancer screening programme is precisely the fact that the recent results can be seen relative to a longer period of time, allowing proper assessment of whether, and if so, which measures and policy changes from the past produced genuine results. Good examples are the optimisation study and the extension of the programme age limit to 75, both of which began around ten years ago. Without revealing any of the specific results further on in this report, it can already be said that this report clearly demonstrates the consequences thereof.

The main emphasis of this report therefore lies on the more detailed analyses of numerous aspects of the breast cancer screening programme. These were essentially also the most prominent activities by the members of the NETB in recent years, partly set in motion by the need for an optimum understanding of the advantages and disadvantages of breast cancer screening in order to provide balanced information to the target group. And not just advantages and disadvantages in general, but preferably specifically quantified advantages and disadvantages from the Dutch programme.

This report has special significance, now that the Dutch breast cancer screening programme is about to make the full switch to digital mammography. It can be viewed as a reference point for what has been achieved after nearly two decades of analogue screening, and sets the minimum benchmark for what digital mammography must achieve. This concerns not only the question of which method can detect more cancers, but also the continued decrease of breast cancer mortality, minimising the negative effects and keeping the costs to a minimum. We believe that this report shows that this is all possible – yet it is up to readers to judge for themselves.

Structure of this report

Chapter 2 presents the most significant national breast screening results from 2007 and the entire period from 1990 to 2007, such as attendance, refer-

rals, and detected breast cancers (screen-detected carcinomas) with tumour-specific features.

Chapter 3 goes into some of the Chapter 2 results in greater detail, taking into consideration various stages of the screening programme and specific aspects, such as the screening for women aged 70-75, and digital screening. This chapter often uses subsets of data, adjusted where necessary for differences in age distribution over the years, in order to allow optimal comparability of the annual results over a longer time period.

Chapter 4 describes the breast cancer incidence, breast cancer therapy and breast cancer mortality both within and outside of the programme target group. Various approaches are presented for how a reasonable case can be made for a link between the screening programme and (reduced) breast cancer mortality. Lastly, this chapter also discusses the question of whether the future mortality pattern among the female population will begin to change if fewer (or increasingly fewer) women die of breast cancer.

The MISCAN microsimulation model was recently significantly reviewed and modified according to the latest findings based on newly available data. *Chapter 5* reports on this matter, and also presents the initial predictions on the effects of the current screening programme for the decade to come.

The costs of the breast cancer screening programme have been thoroughly updated to the most recent year, as *Chapter 6* describes. A significant aspect here is the question of how the imminent full digitisation of the programme will affect the costs.

Chapter 7 discusses the results of the previous five chapters, weighing up the advantages and disadvantages of screening.

The *appendix* contains a list of the screening regions with an accompanying region code (Appendix 1), an overview with main results and regional comparison of some outcome parameters (Appendix 2), as well as a short description of the evaluation tables and evaluation concepts (Appendix 5) and of the breast cancer screening programme (Appendix 6). There are also various tables with overviews of annual data on attendance, screening examinations, screening results, interval cancers, breast cancer incidence and breast cancer therapy (Appendix 3 and 4).

2

National results 1990-2007

This chapter contains all of the results from the A and B-tables (attendance and screening results, respectively) that had been received from the nine screening regions by early May 2009. In addition to data on the 2007 reporting year, which for the most part had already been released in autumn 2008, updates from previous years are also included (greater completeness on follow-ups of referred women and the features of screen-detected carcinomas), as well as the elimination of the backlog that two regions had had for some years. Except for the interval cancers, this chapter is therefore based on complete data from the entire 1990-2007 period of the nation-wide breast cancer screening.

2.1 Target population

In 2007 there were 2.37 million women aged 50-75 living in the Netherlands, around half of whom were eligible to receive an invitation for screening in that same year. Even before the screening programme was extended to age 75, the target population had grown by 1-3% per year. The extension in 1998 represented a one-off increase in the target population of 25.6%. Since 1998, the annual target group for the has grown from 1.02 million to 1.18 million in 2007; an increase of almost 16%. Figure 2.1 illustrates the 'baby-boom effect': a peak in the number of women born in 1947 or later. In 2007, the number of women

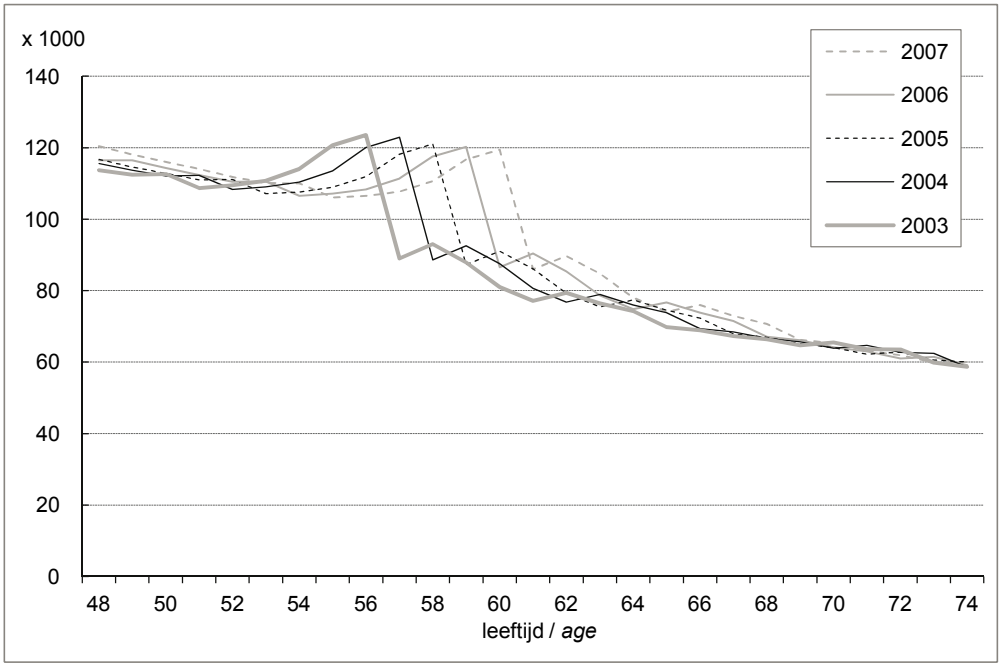


Figure 2.1
Age-specific target population 2003-2007

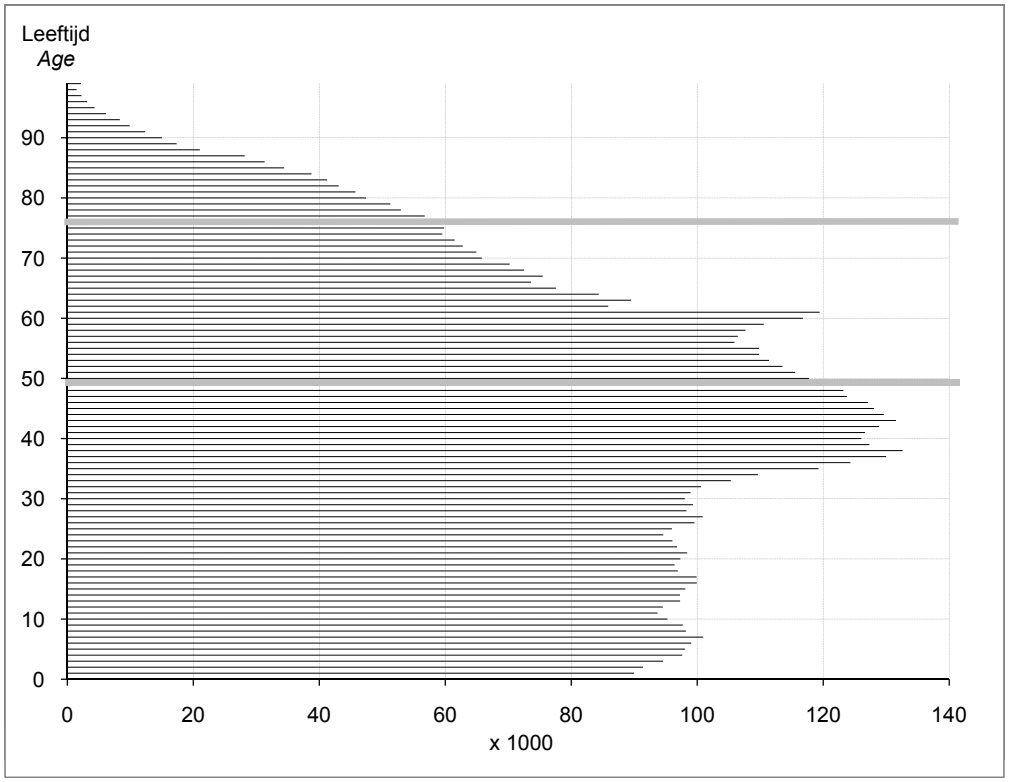


Figure 2.2
Female population in the Netherlands in 2008 (source: Statistics Netherlands)

aged between 49 and 60 was therefore around 50% greater than the number of women aged 60-70. Figure 2.2 shows the female population of the Netherlands in early 2008, from which it can be derived that the screening programme will welcome some additional years of population boom over the coming decade, resulting in a further increase in the target population in the ten years to come. After that, the target population will shrink by around 10% within a few years.

2.2 Invitations and attendance

Definitive non-participation

Not all women in the target population are actually invited to take part in the screening programme. Despite the fact that women who are known to have breast cancer are no longer invited (whether the cancer was detected by the study or not), the number of 'definitive non-participants' in the target population has remained constant since 2004 at

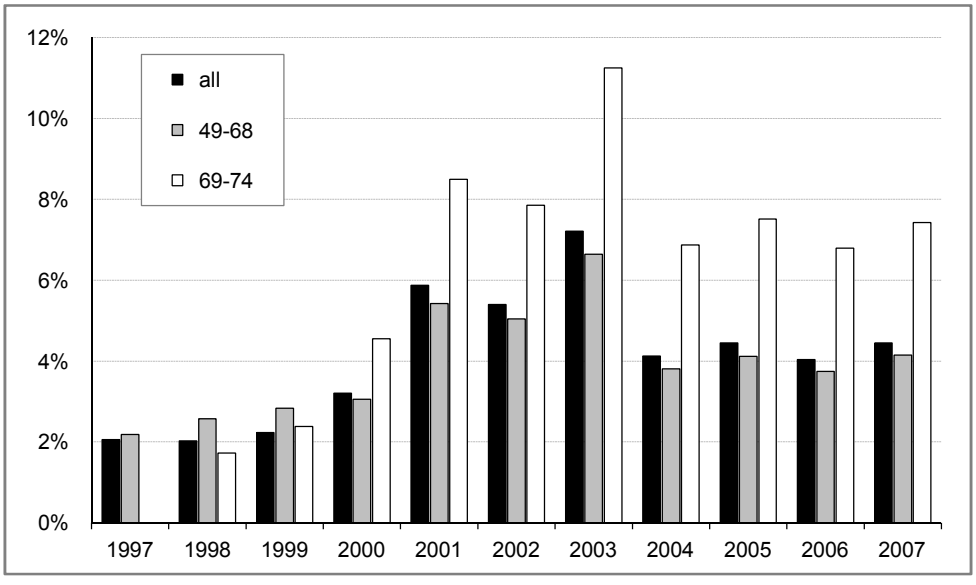


Figure 2.3
Percentage of definite non-participation in the total targeted age group 50-75, and for ages 50-69 and 70-75 years, 1997-2007

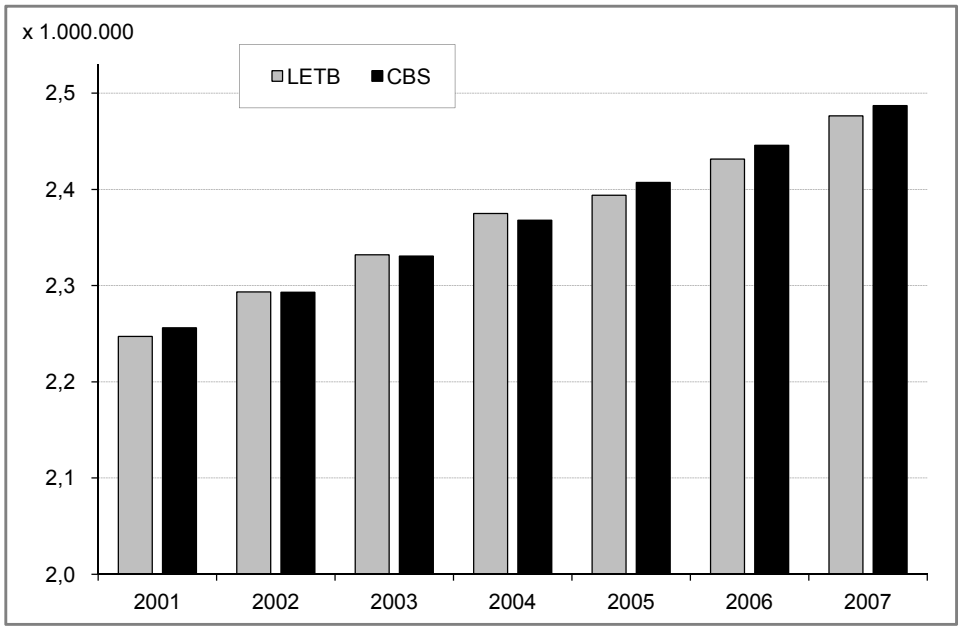


Figure 2.4
Target population as reported by the screening organisations (LETB) and according to Statistics Netherlands (CBS), 2001-2007

around 4-4.5% (figure 2.3). This is surprising, given the increasing numbers of women with a screen-detected carcinoma or interval cancer. This could mean that there are fewer other reasons for not wishing to be invited anymore, or that more women who become symptom-free after treatment for breast cancer once again join the screening programme. Because this cannot be recorded by all screening regions, no distinction can be made between non-participation due to a screening/interval carcinoma and non-participation of women by their own choice. However, definitive non-participation does increase with age, to approximately 8% around age 73.
It is unclear why the number of definitive non-participants in 2001-2003 was considerably higher than in the periods before and after (figure 2.3). Prior to 2002, the data on the target population and the underlying reasons for ceasing invitation were incomplete (5-7 of all 9 regions), which could explain the divergent percentages in recent years. In 2002 and 2003 the data was complete at a national level, yet the high percentages of definitive non-participation remain difficult to explain. Partly because of this situation, the target population as reported by the nine screening regions was compared to the population data from Statistics Netherlands (CBS). Figure 2.4 shows that there is hardly any difference between the two data sources, and that the relatively high proportion of definitive non-participants in 2002 and 2003 is at least not attributable to selection of the target population.

Invitations and attendance

In 2007, the number of women invited to take part in the screening programme exceeded 1.1 million for the first time. After a small drop in the number of invitations in 2006 (0.6% fewer than in 2005), the number grew again by 2.3% in 2007. The percentage initial screening examination invitations was 11.2%; the attendance rate among these (mostly young) new participants was 79.0% (table 2.1). 82.8% of the nearly 1 million women invited for a subsequent examination took part. A total of precisely 10% of the women invited received a reminder invitation, resulting in 1.5% of the total attendance percentage of 82.4% in 2007. More reminders were sent out for

Table 2.1 Numbers of women invited and attending in 2007, and attendance rate (%)

	Oorspronkelijke uitnodiging *Initial invitation*		**Herinneringsuitnodiging** *Reminder invitation*		**Totaal** *Total*	
	N	**Opkomst (%)** *Attendance (%)*	**N**	**Opkomst (%)** *Attendance (%)*	**N**	**Opkomst (%)** *Attendance (%)*
1e uitnodiging *1st invitation*	123.946	76,8%	17.450 14,1%	2,3%	97.974	79,0%
Uitnodiging vervolgscreening *Invitation subsequent screening*	984.217	81,4%	93.848 9,5%	1,4%	814.705	82,8%
Totaal *Total*	1.108.163	80,9%	111.298 10,0%	1,5%	912.679	82,4%

Figure 2.5
Number of invited and screened women,, and attendance rate (%) by year (1990-1997: 50-69 years; 1998-2007: 50-75 years)

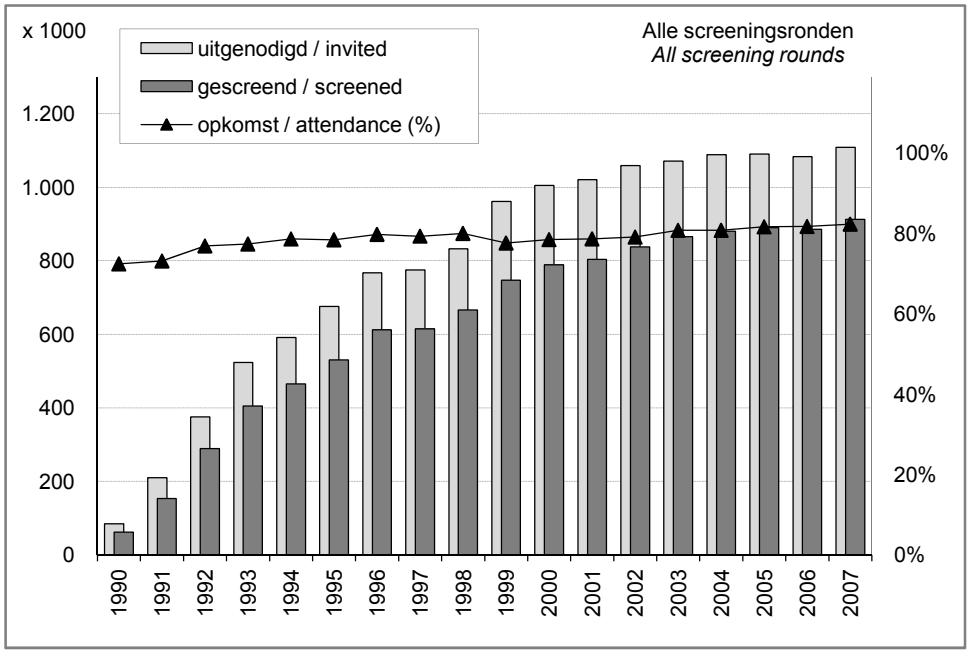


Figure 2.6
Age-specific attendance rates (%) by year, 1990-2007

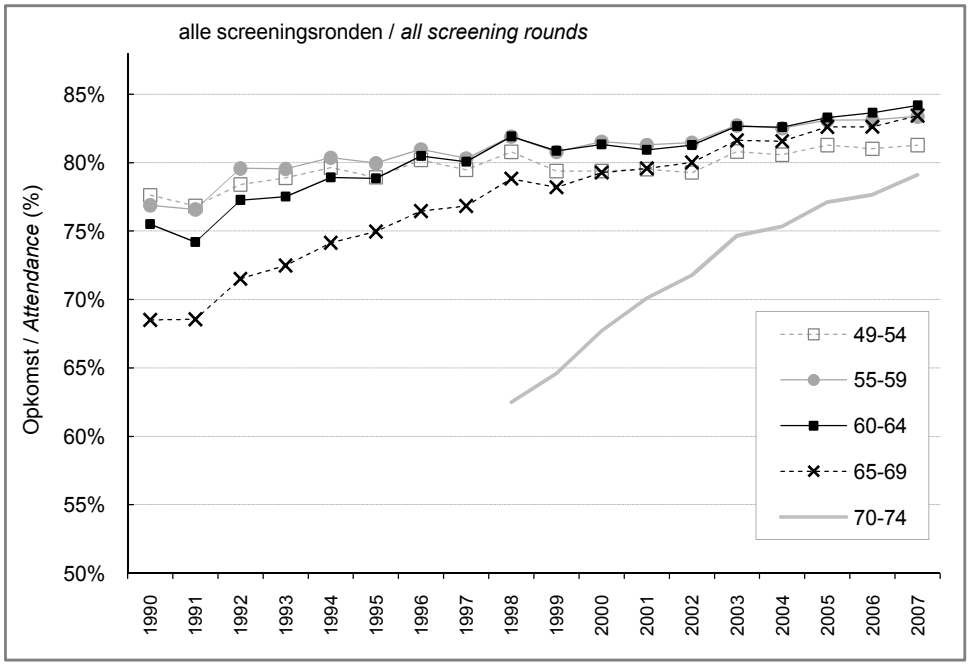
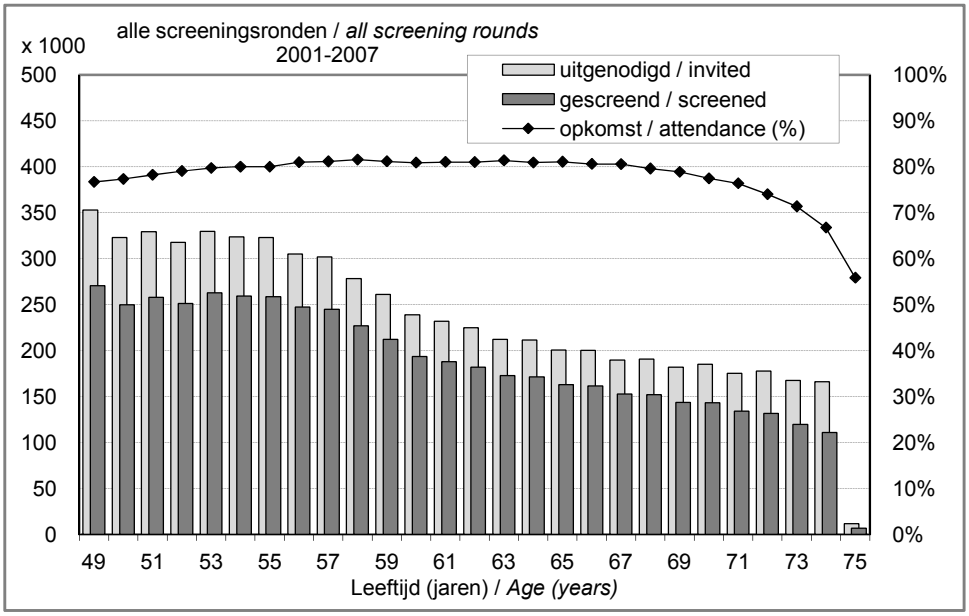


Figure 2.7
Number of invited and screened women, and attendance rate by single age year, during 2001-2007



initial invitations (14.1%), with a larger proportion of resulting participation (2.3%).
Over 14 million invitations for a screening examination were sent to more than 3 million women between 1990 and 2007. Attendance across this entire period was 79.7%. During the implementation of the screening programme for women aged 50-69, the attendance percentage increased from 72.5% in 1990 to 80.1% in 1997 (figure 2.5).
The extension of the screening programme to include women up to age 75 in 1999 caused total attendance to drop to 77.7%, however, afterwards it continued to grow to 82.4% in 2007. The increase in attendance is visible in all age groups, but is most pronounced among those aged 70-74, and secondly among women aged 65-69 (figure 2.6). In 2007, the attendance of the oldest age group spanning five years differs from the younger age groups by only 2-5%. Yet attendance does start to drop sharply from the age of 72, reaching less than 70% at the age of 74 (figure 2.7).

All of the trends described here apply to invitations for both initial and subsequent examinations, but in general they are more pronounced among the latter. After extension of the study to age 75 was complete in 2001, an average of around 1000 women per year aged 70-75 received an initial screening invitation, to which approximately half responded. We suspect that this mostly has to do with migrant or repatriated women who may not be so familiar with population studies in general or breast cancer screening in particular, and who therefore did not respond in great numbers.

Of the women who took part in the previous screening round and received an invitation for a subsequent round, 93.8% again took part in the programme in 2007. In 1992, this 'loyalty' to the programme was less than 90%. Figure 2.8 shows that in recent years, for every ten women invited to take part in two consecutive screening rounds, eight women attend both times, one woman attends one of the two rounds, and one women attends neither round. This ratio is slightly lower among both young new participants and women aged 70 or over. Just over 30% of women who did not attend a previous round do attend a subsequent round of the screening programme.

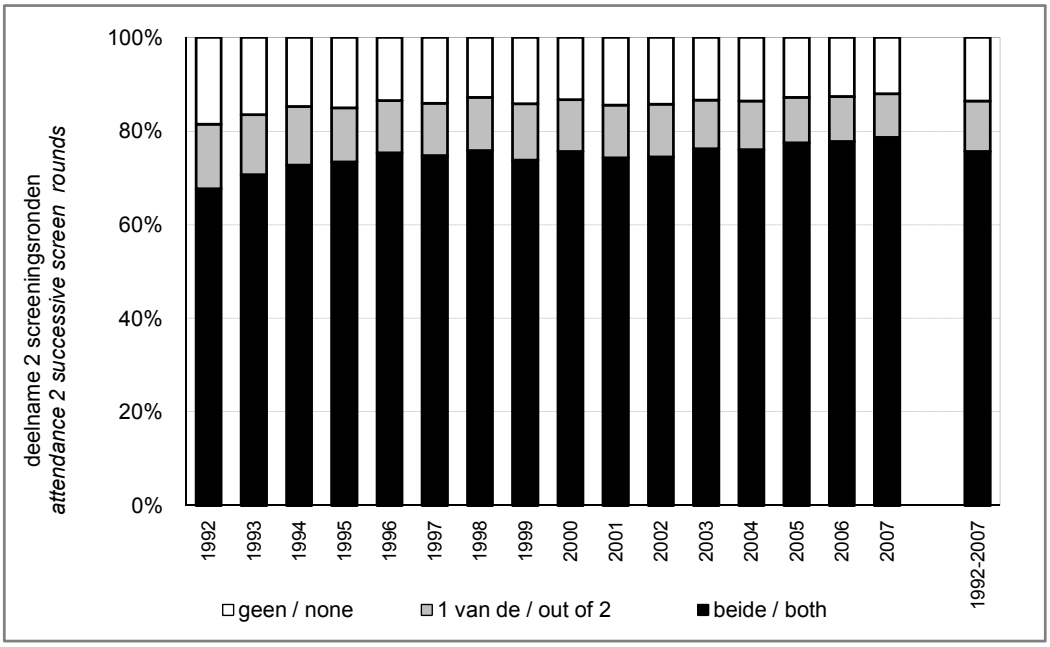


Figure 2.8 Percent distribution of (non-)participation in two successive screening rounds by year, 1992-2007

2.3 Screening examinations

In 2007 911,547 screening examinations were carried out. Following a small 0.7% drop in 2006 compared to 2005, the number of screening examinations once again grew by 3%, exceeding nine hundred thousand for the first time. At 12%, the proportion of initial screening examinations was the lowest ever, and the percentage of subsequent screening examinations carried out 2.5 or more years since the previous examination ('long-interval') also reached its lowest (4.0%) since the extension of the programme in 1998. As a result, the number of regular subsequent examinations within 2.5 years was higher than ever, at 84%. However, these percentages have remained reasonably constant since 2002 (figure 2.9). Over the whole period since 1990, slightly less than one-quarter have been initial screening examinations (23.2%) and nearly three-quarters regular subsequent examinations (72.3%), the remaining 4.5% being subsequent examinations with a long screening interval (appendix 3.2).

Digital screening examinations were also carried out in 2004 as part of the screening programme for the first time, forming 1.1% of all examinations. This proportion increased to 7.4% in 2007. The digital examinations included a greater proportion of initial screens (14.0%) and long-interval screens (4.8%) than analogue examinations.

Invitation and screening intervals

For pragmatic reasons, regular subsequent examinations were originally defined as subsequent screens that take place within 2.5 years of the previous examination. Although this may seem like an extremely large margin with a formal screening interval of 2 years, it is almost impossible to exactly guarantee this interval for large groups of women, even if they receive individual invitations. In such a case, women would need to be given an examination date precisely two years later, and preferably not be allowed to reschedule the appointment. Moreover, screens should only be performed at permanent examination locations. In practice however, the Dutch screening programme invites women at group (postcode) level, and the timing of the majority of invitations is determined by the period in which the mobile examination unit can be positioned in the relevant town/city. Women are also able to postpone the examination date that they are offered; an estimated 30% of women do this. Lastly, it is also possible for women who move to another town/city or even a different region to end up in a completely different screening schedule.

The formal screening interval therefore depends primarily on the invitation time, which in turn relies on effective scheduling. In an ideal situation, examination units are placed within a certain postcode area at precise two-year intervals. According to the guidelines, women in the same group (i.e. a certain postcode area) ought to receive an invitation every 24 ± 2 months. In the past, this was monitored by recording the starting date of new screening rounds for each municipality. Due to the disappearance, amalgamation and redistribution of Dutch municipalities (whose number decreased from 749 in 1990 to 443 in 2007), this is no longer a satisfactory instrument. Since 2001, eight of the nine regions have used a new table to report the numbers of invitations per 2-month period, and all regions since 2004. This is

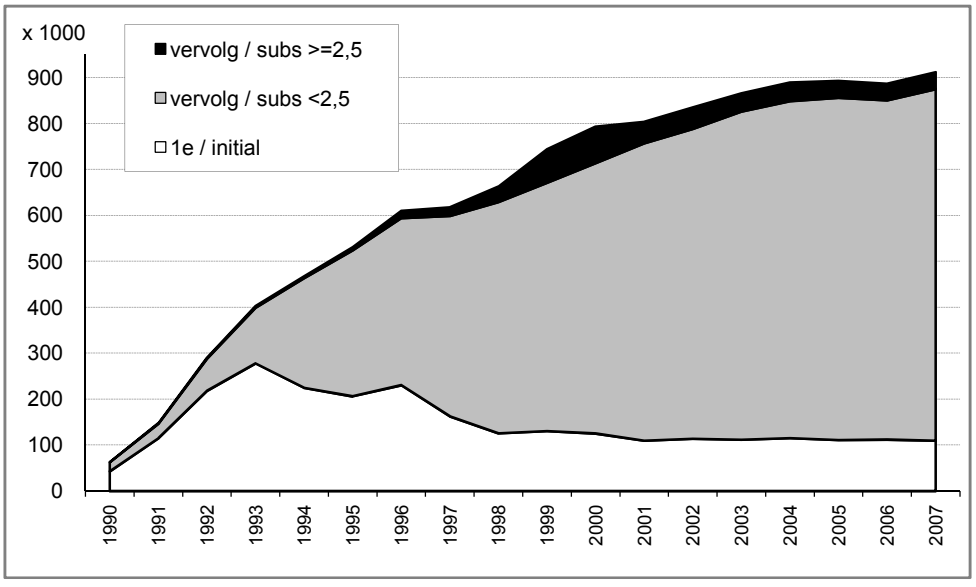


Figure 2.9 Number of intial screens, regular subsequent screens within 2.5 years, and subsequent screens >=2.5 years by year, 1990-2007

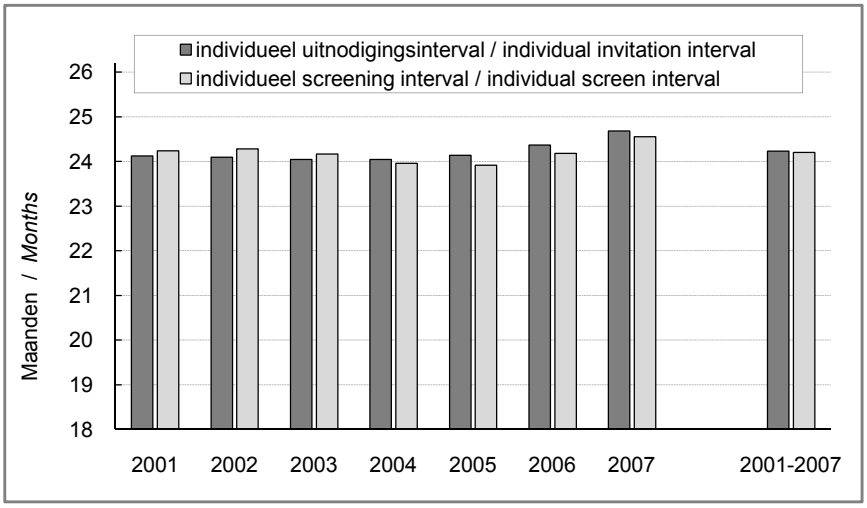


Figure 2.10
Length of the mean individual invitation and screening interval in months, 2001-2007

used as a basis for calculating the average individual invitation interval that can be related to the average individual screening interval. Figure 2.10 shows that the mean individual invitation and screening intervals are around the 24-24.5-month mark, and are roughly the same. However, it is surprising that in some years the average invitation interval is longer than the average screening interval. One would sooner expect the opposite, since rescheduling an appointment would probably make it take place later rather than sooner, yet no concrete information is available on this matter. This 'strange proportion' can probably also be attributed to various methods for calculating the invitation and screening interval, which are not produced in exactly the same way (i.e. either at 2-month or 3-month intervals).

Over the last year, the average individual screening interval for regular subsequent screens varied between 23.9 and 24.7 months. Although this seems like a limited distribution, figure 2.11 shows that the differences arise through considerable annual variations in interval distribution within this group. For example, in 2000 around 80% of all examinations took place within 24 ± 3 months, whereas this has been the case for more than 90% of all examinations since 2004. The only year in which approximately the same number of examinations took place before and after the two-year interval is 2005. A longer mean screening interval may be associated with a higher breast cancer detection rate, which would then be incorrectly attributed to increased screening performance in the screening programme.

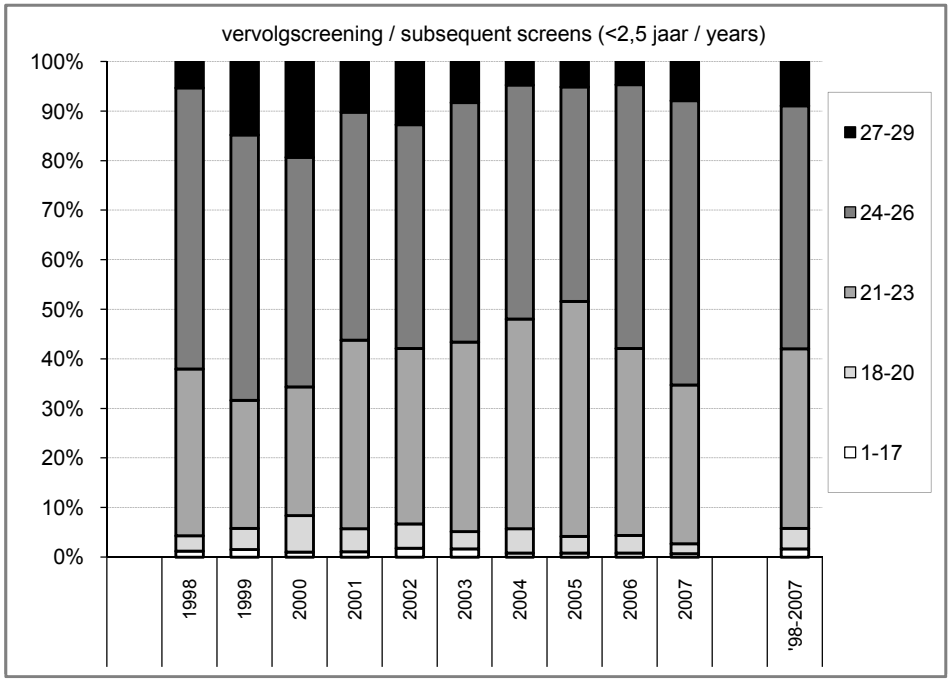


Figure 2.11
Percent distribution of the length of the mean individual screening interval by year, 1998-2007

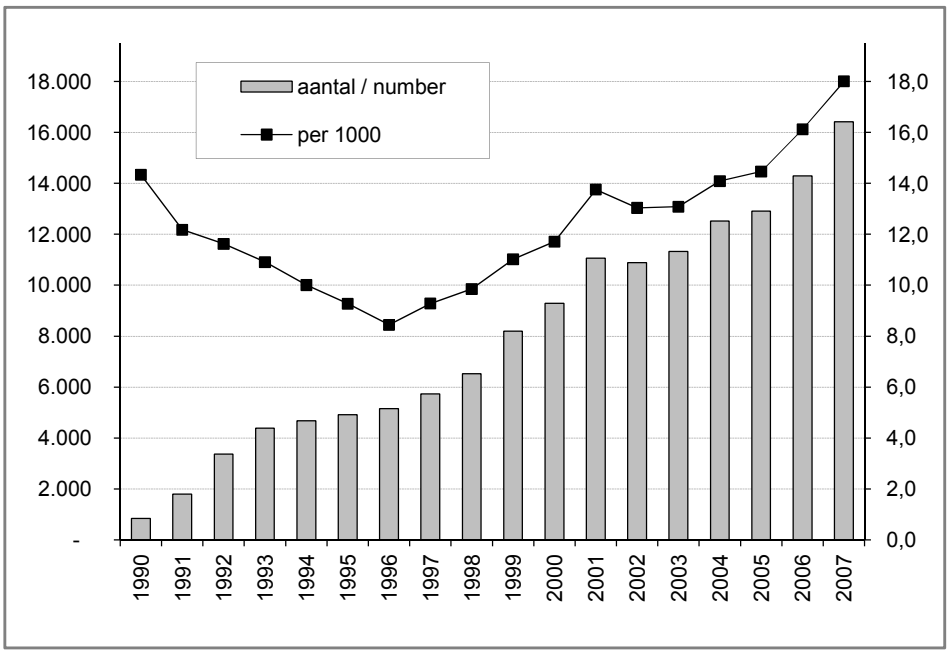


Figure 2.12
Number of referral recommendations and crude referral rate per 1000 by year, 1990-2007

2.4 Referrals

The number of referrals for further examination was 16,414 in 2007, amounting to 18 women per 1000 screened. The referral rate has more than doubled since 1996, the year in which the referral rate was at its lowest (8.4 per 1000, figure 2.12). The drop in referrals in the first half of the 1990s was partially due to the shift in what were originally mainly initial screening examinations to increasing numbers of subsequent examinations, and partially due to an actual drop in the referral rate for both initial and subsequent screens. This also led to a lower detection rate among subsequent screens (see Chapter 3). Referrals started increasing in 1996 and seemed to stabilise at around 13 per 1000 in 2002-2003, but started rising again in 2004.

In order to gain an accurate understanding of the trends in the referral rate over a longer period, the referral rate was age-adjusted and limited to the 49-54 age group for initial screenings. Figure 2.13 indicates that the referral rate shows the same pattern for initial screens as for regular subsequent screens. However, the referral rate increased more rapidly for initial examinations, and in 2007 was three times higher than in 1996, whereas the rate doubled in regular subsequent examinations over the same period. The increase in the referral rate among both initial and subsequent screens in all nine regions can be seen to be the same as the trend in the national average.

The rise in the referral rate occurs in all age groups. The referral rate generally increases as age increases

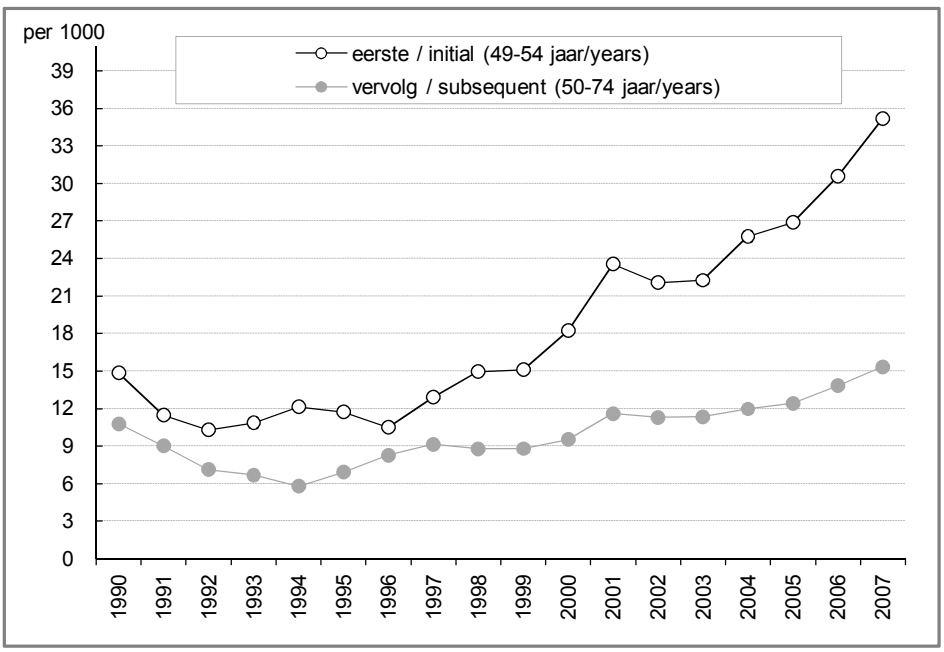


Figure 2.13
Age-adjusted referral rate per 1000, for initial screens in women aged 49-54 years, and b. regular subsequent screens in women aged 50-74 years, 1990-2007

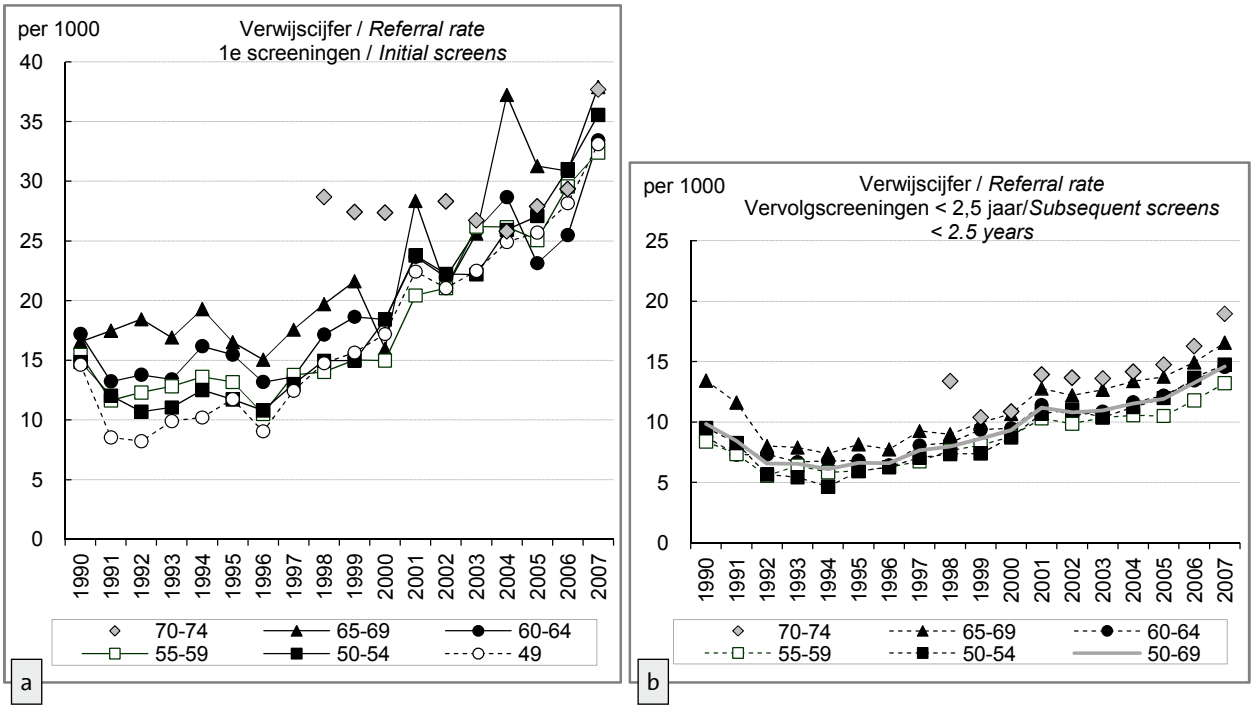


Figure 2.14 Age-specific referral rates per 1000, 1990-2007, for a. initial, and b. regular subsequent screen examinations

(figure 2.14a and 2.14b), yet this relationship is not as pronounced for initial screens (figure 2.14a). This is mainly due to the relatively small number of women aged 55 and over who were screened for the first time after 1997, producing unpredictable, fluctuating age-specific patterns from this age onwards.

2.5 Detection rates and predictive value of referrals

Follow-up of screen-positive women

Between 1990 and 2007, nearly 145,000 women (1.27%) were referred for additional diagnostic assessment in hospital due to a suspected abnormality in their mammogram. The results of the further diagnosis are known for 98.1% of these referrals. The follow-up information of referred women has been over 95% complete since 1991, despite the fact that in several years, not all regions reached this percentage (figure 2.15). However, every year there was at least one region with 100% complete follow-up. The high national average of over 95% complete follow-up on suspicious screening results allows for reliable conclusions on the performance of the screening programme. Periodical (e.g. annual) monitoring of such a programme depends on the promptness and completeness of the availability of the relevant data at

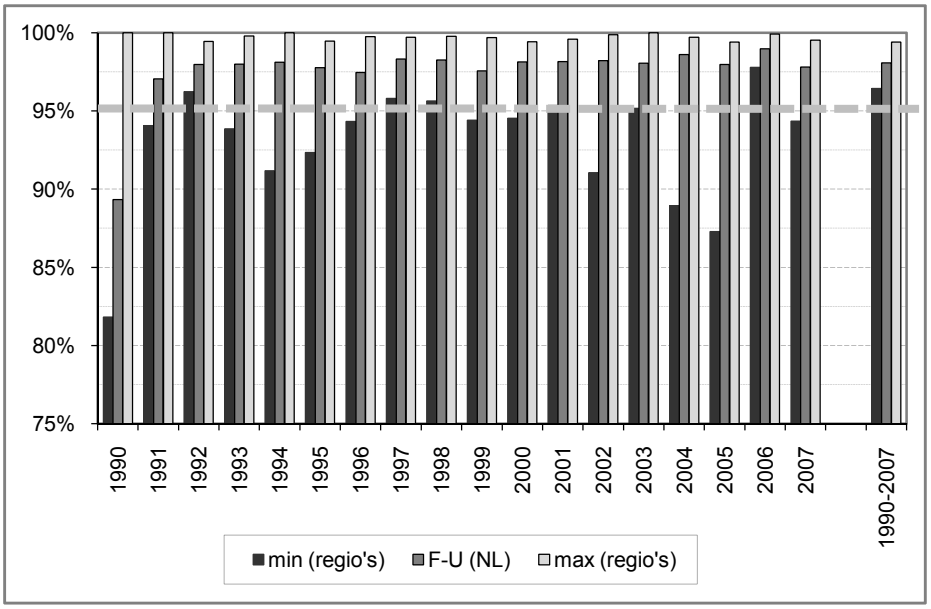


Figure 2.15
Annual percentage of complete follow-up (F-U) of referral recommendations in the Netherlands, and the regional minimum (min) and maximum (max) percentage of complete follow-up, 1990-2007

Table 2.2 Average number and percentage of all referral advices per year without a final diagnosis, period 2002-2007

Reden geen einddiagnose ***Reason for missing final diagnosis***	**Gemiddeld per jaar (2002-2007)** ***Annual mean (2002-2007)***	
	N	**%**
overleden vóór einddiagnose *death before final diagnosis*	5,0	0,04%
vertrokken *moving to another place*	6,3	0,05%
cliënt ziet af van nader onderzoek *diagnostic assessment not desired*	14,8	0,11%
ingevuld bezwaarschrijft *no permission for follow-up*	1,8	0,01%
onvolledige follow-up *incomplete follow-up*	12,5	0,10%
niet verwezen of verder onderzocht *not referred or no diagnostic assessment*	12,3	0,09%
geen reden / onbekend *no reason / unknown*	20,3	0,16%
Totaal / *Total*	73,2	0,56%

a certain point in time. Waiting for 100% complete follow-up data would take too long to make monitoring effective.
Moreover, 100% is not feasible in practice. For example, over 7,000 women (0.62‰ of all examinations) have submitted objections to having their data recorded and/or shared with a GP, hospital or cancer registry. If any of these women have been given a referral, the ultimate diagnosis remains unknown. Also, some women who received a referral were never fully diagnosed, because they either died before the diagnosis was complete, moved away, decided against further examination or were not referred on by their GP. On average, this group has formed 0.56% of referred women since 2002 (table 2.2).

Detection rate

The total rate of detection in 2007 was 5.5 breast cancers per 1000 women screened. Initial screening examinations detected 5.9 cancers per 1000 women screened, and regular subsequent screens 5.2 (9.4 in subsequent screenings with an interval greater than or equal to 2.5 years). This makes the detection rate for initial examinations almost as high as in the period from 1990-1995, in which it varied between 6.0 and 6.9 per 1000 due to the large proportion of women aged 55 and over who were screened for the first time. From 1996-2006, the rate generally did not exceed 5.5 per 1000, with the exception of the extension of the screening programme up to age 75 in 1991-2001, when it was 5.9-6.1 per 1000. Up to 1998, regular subsequent screenings showed a detection rate of fewer than 4.0 per 1000 (3.2-3.9), from 1999 until 2005 between 4.0 and 5.0 per 1000 (4.0-4.7), and since 2006, 5.0 per 1000 or higher. However, due to the changing age distribution of the screened population over the years, it is difficult to judge whether recent years have indeed witnessed increased sensitivity of the screening programme based on raw figures. Age-specific data (figures 2.16a and 2.16b) clearly show that detection rates increased in all age groups, particularly among subsequent screens.

In figures 2.17a and 2.17b, the detection rates are limited to the age groups that qualified for screening across the entire length of the study from 1990-2007 (49-54 for initial screens and 50-69 for regular subsequent screens) and corrected for variances in the age distribution. Since the start of this millennium, both types of screening examination clearly show a higher rate of detection than in the period prior to 2000.

Positive predictive value of referral

The considerable rise in referral figures with a proportionally far smaller increase in the detection rate is reflected in the calculations of the positive predictive value of the referral rate. The 43% predictive value of initial screening examinations in 1990 dropped to 17% in 2007, and the 56% value of subsequent regular examinations in 1992 dropped to 34% in 2007. This means that now, five out of every six women with a suspected abnormality from their initial screen are given a false positive result, as well as two out of every three who are referred from a regular subsequent examination.

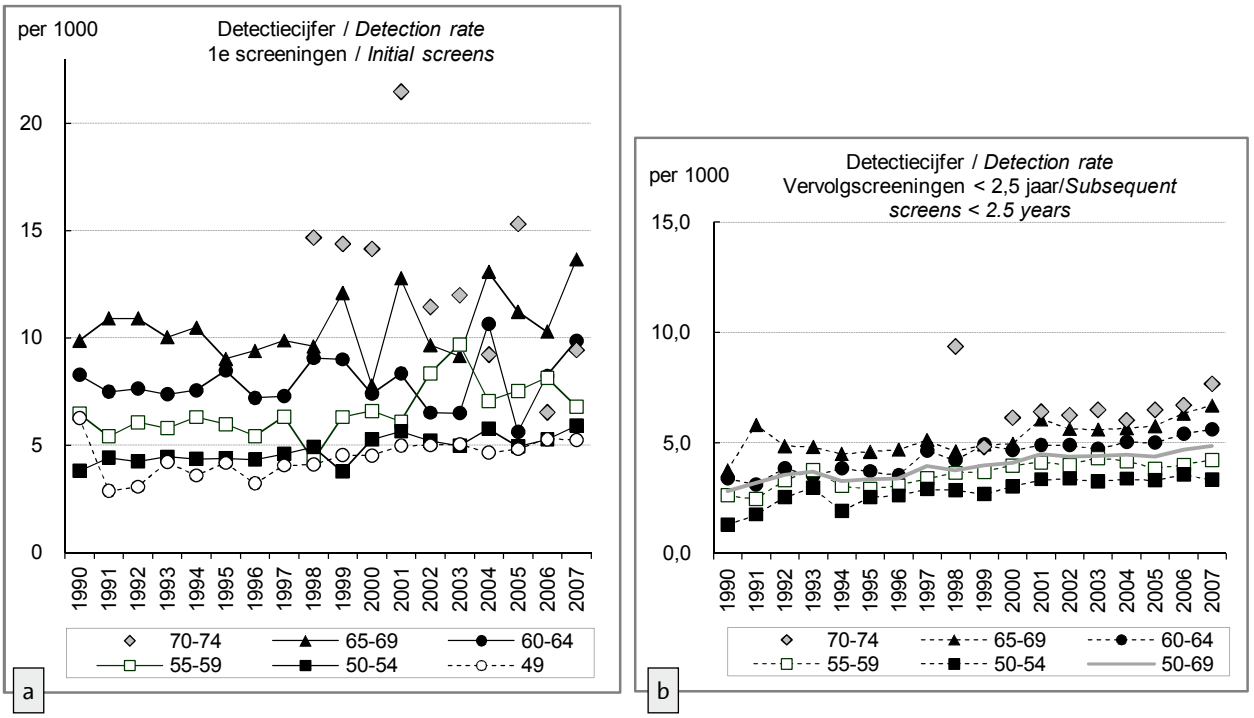


Figure 2.16 Age-specific breast cancer detection rate per 1000, 1990-2007, for a. initial, and b. regular subsequent screen examinations

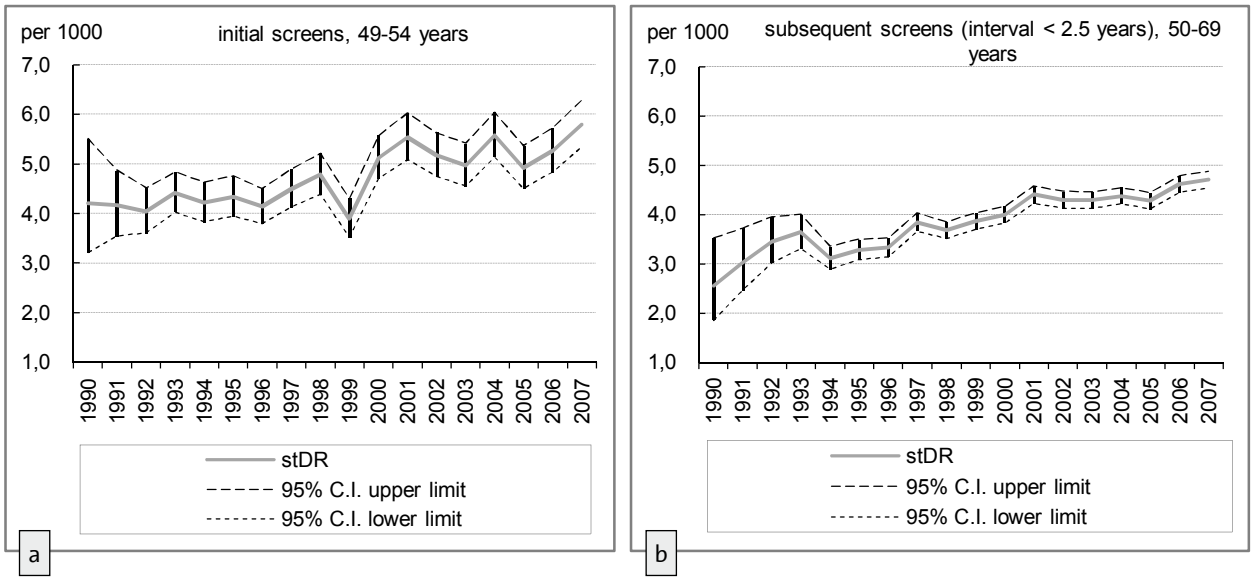


Figure 2.17 Age-adjusted breast cancer (invasive and in-situ; stDR) detection rate per 1000, 1990-2007, for a. initial screens in women aged 49-54 years, and b. regular subsequent screens in women aged 50-69 years

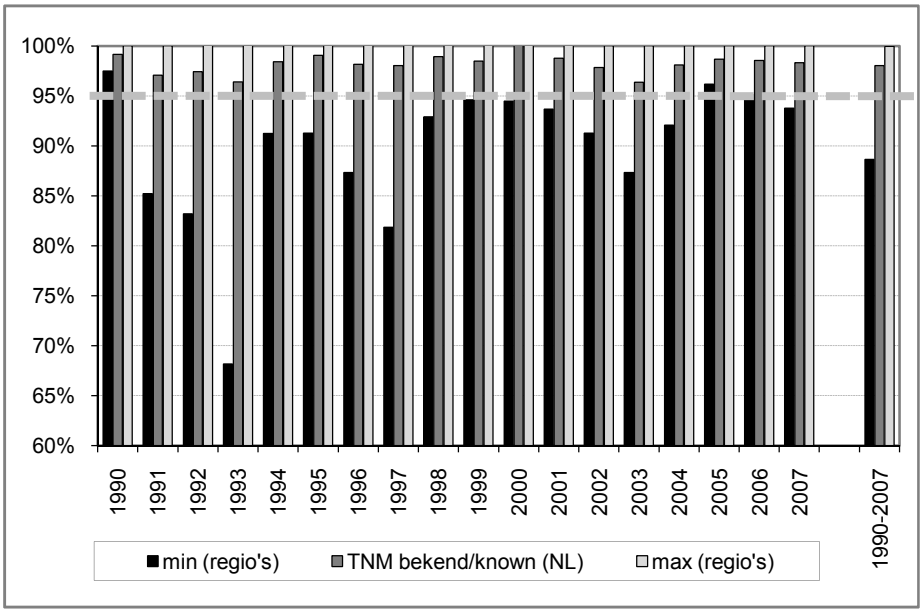


Figure 2.18
Annual percentage of complete TNM-classification of screen-detected breast cancers: national mean and regional minimum (min) and maximum (max), 1990-2007

2.6 Screen-detected carcinomas

Completeness of TNM status

Since 1990, a total of 56,254 women have been diagnosed with breast cancer as the result of a screening examination (screen-detected carcinoma). This figure is based on the previous annual reports by screening regions, but will be somewhat higher in reality due to follow-up data yet to be submitted. Of all screen-detected carcinomas, a nation-wide average of 98% have been classified according to tumour size, lymph node involvement and distant metastasis (the TNM-classification). Although this percentage has been above 95% every year since 1990, there were sometimes considerable regional differences (figure 2.18). Several years showed one region that was only able to establish less than 90% of the TNM classification of screen-detected carcinomas. Across the entire 1990-2007 period, the TNM-data from 8 of the 9 regions was over 95% complete, with one region reaching almost 100% (99.95%); the 9th region reached 88.6%.

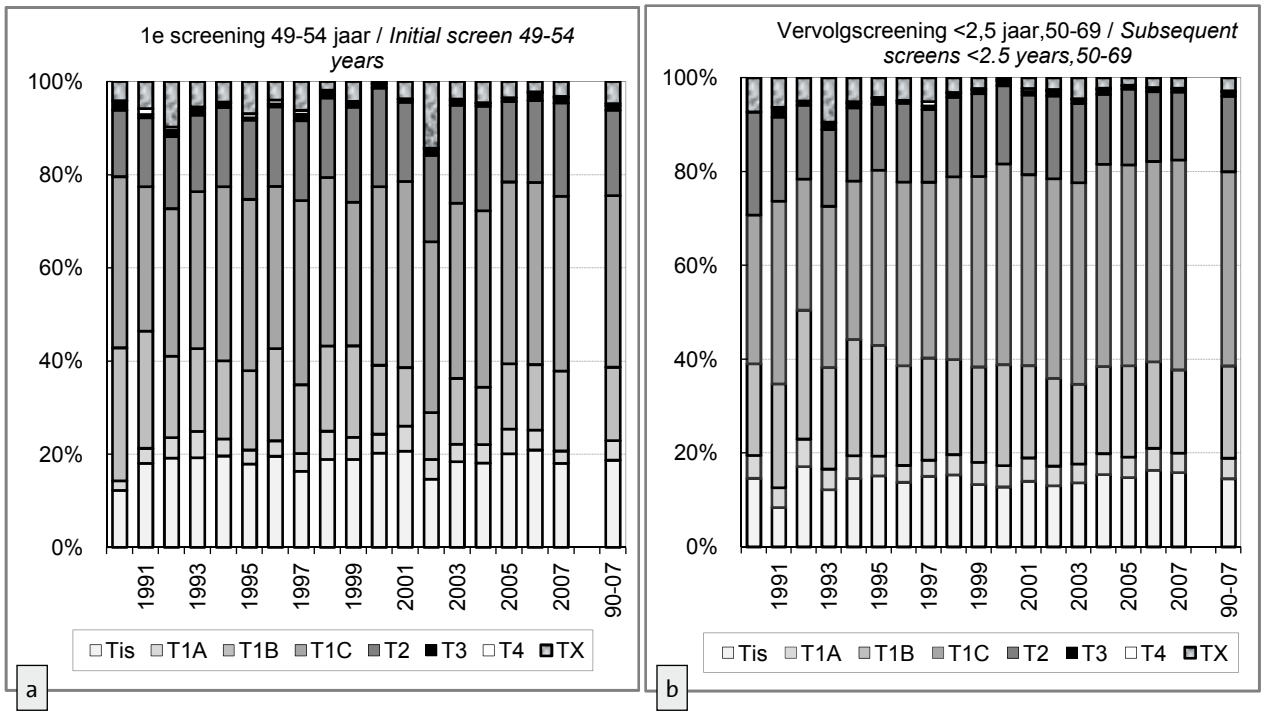


Figure 2.19 Percent tumour size distribution of breast cancers detected a. at initial screens in women aged 49-54 years, and b. at regular subsequent screens in women aged 50-69 years, 1990-2007

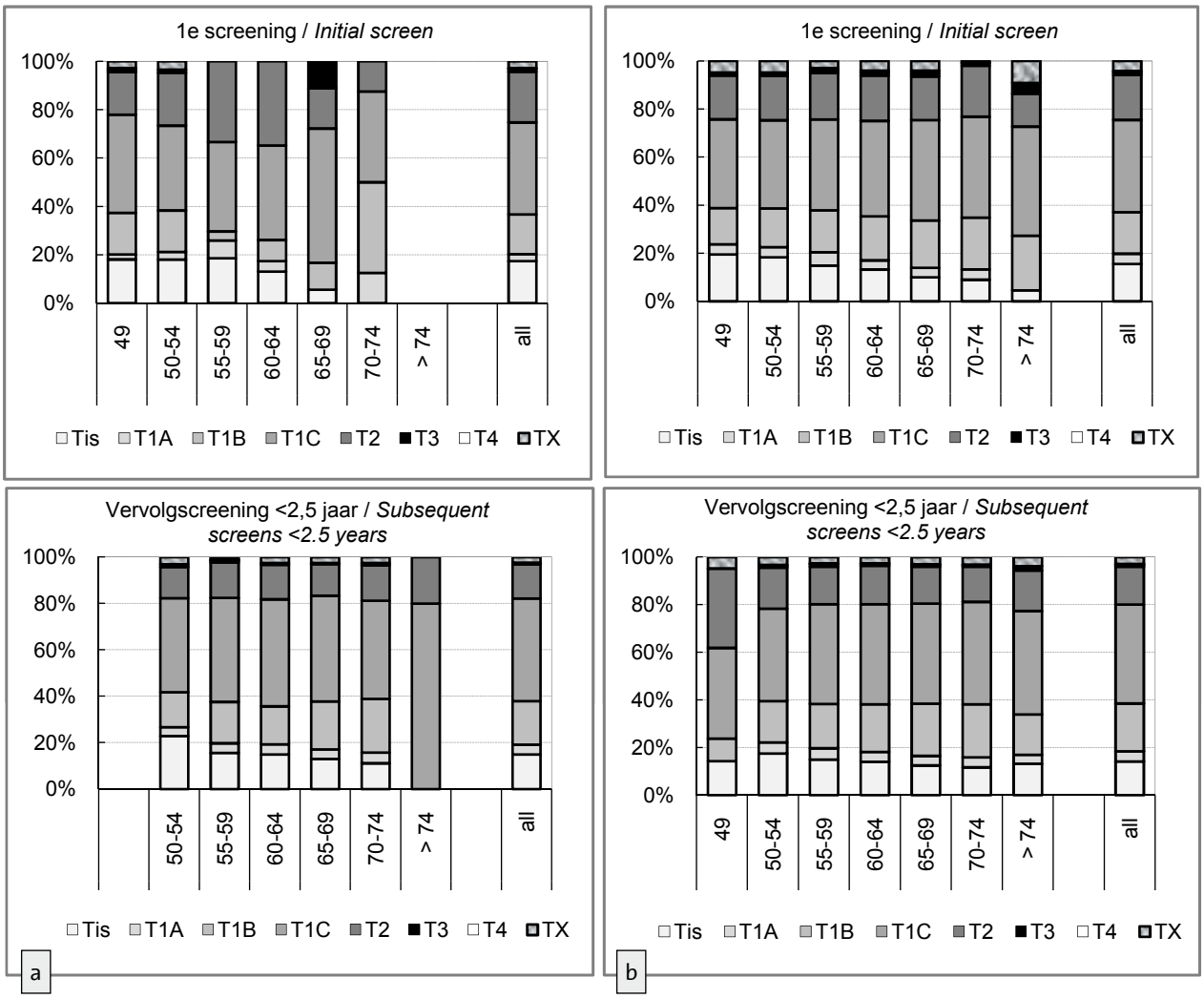


Figure 2.20 Percent tumour size distribution of screen-detected invasive breast cancers at initial and regular subsequent screens, by 5-year age group: a. 2007, and b. total period 1990-2007

Tumour size of screen-detected carcinomas

Of the 4,999 breast cancers detected by screening in 2007, 15.1% were ductal carcinomas in situ (DCIS), and 65.8% invasive carcinomas with a diameter of 2 cm or less. These percentages are slightly higher than those taken across the entire period of the screening programme (DCIS in 1990-2007: 14.4%; T1: 64.3%). Comparing the age-corrected annual tumour size distributions of initial and subsequent examinations, initial screenings (49-54 years) showed slightly more DCIS and invasive T2 tumours (21-50mm diameter) whereas regular subsequent examinations (women aged 50-69) showed more invasive T1b (6-10 mm) and T1c (11-20 mm) tumours (figures 2.19a and 2.19b). The number of T1c tumours detected by subsequent screens increased over the years up to over 40% to the cost of a reduction in the number of T1b tumours.

Lymph node status of screen-detected carcinomas

Of the invasive breast cancers detected by screening in 2007, 72.8% were found to have no tumour cells that had spread to the lymph nodes. This percentage was lower (69.2%) across the entire 1990-2007 period, almost certainly as the result of the higher proportion of invasive carcinomas with unknown lymph node status up to 2001 (Nx; 3.7% across 1990-2007 vs. 1.4% in 2007). Slightly more than one-quarter of the invasive tumours were node positive (N+), and metastases were also found in other tissues (M1) in around 0.5% of cases. A relatively higher proportion of node-positive breast cancers (approx. 30%) were discovered after initial screening examinations than after subsequent screens (figures 2.21a and 2.21b).

In the late 1990s, the sentinel node procedure became part of the routine pathological diagnosis for suspected breast cancer, and since 2001, has been recorded separately as part of the evaluation of the screening programme. Figures 2.21 show quite elegantly how within just a few years, the majority of all node-negative breast cancer diagnoses were based on the sentinel node procedure; since 2006 this figure has applied to two-thirds of all node-negative results. The sentinel node procedure also resulted in

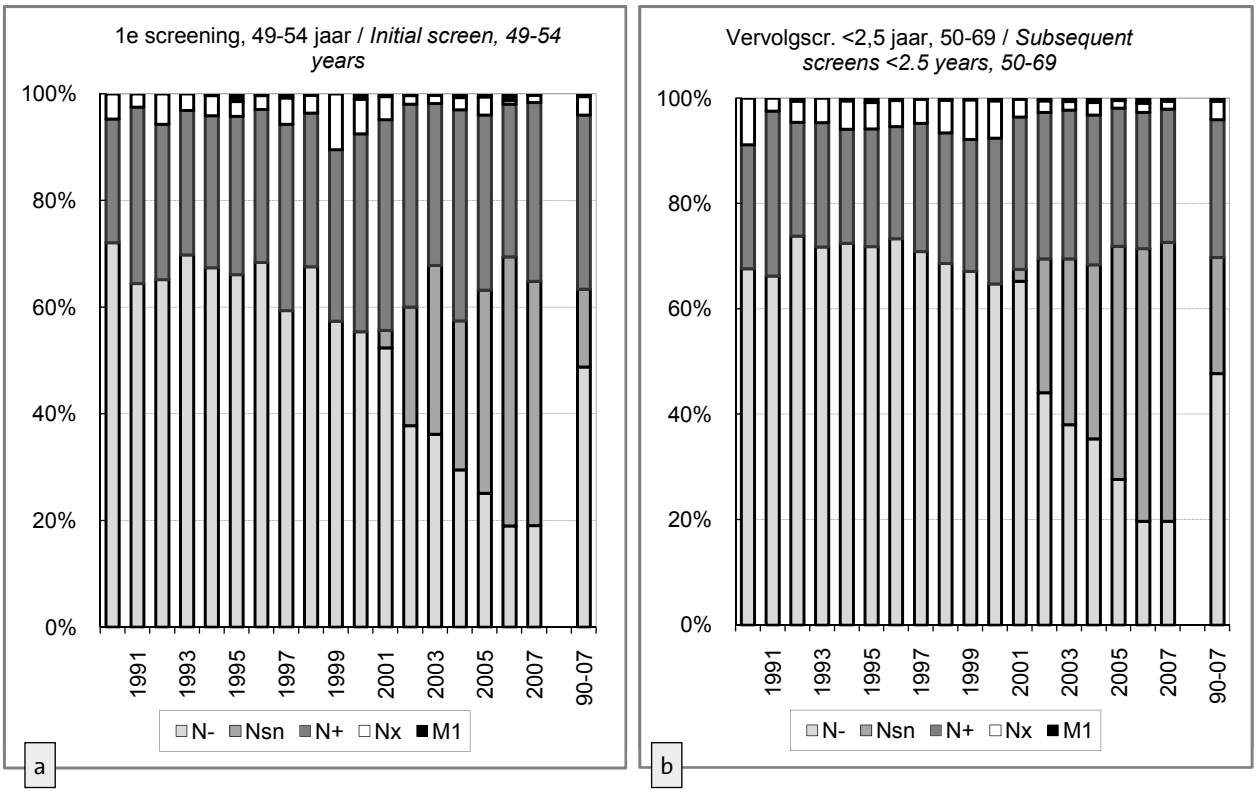


Figure 2.21 Percent distribution of lymph node status (Nsn = negative sentinel node) and distant metastases of invasive screen-detected breast cancers a. at initial screens in women aged 49-54 years, and b. at regular subsequent screens in women aged 50-69 years, 1990-2007

a decrease in the number of cases with an unknown lymph-node status (Nx). Previously, a negative lymph-node status could only be assigned once a minimum of six lymph nodes had been examined. The sentinel node procedure caused this classification rule to be altered, since the procedure usually identifies and examines fewer than six lymph nodes.

3

Screening performance

The screening results based on the total number of screening examinations do not provide the most accurate indication of screening performance. Screening performance depends on factors such as the age of the screened women, the screening method (analogue or digital), the type of examination (initial or subsequent) and the length of the screening interval, the technical quality of the mammography and the experience and expertise of the screening radiologists and the radiographers. Since the very start of the screening programme, a standard distinction has been made in the evaluation between initial and regular subsequent screens, and subsequent screens with an interval greater than 2.5 years. Since 2004, separate data sets have been kept for digital screening examinations.

Because the age distribution of the women invited and screened in recent years no longer corresponds to the distribution at the outset of the screening programme, the raw figures cannot be compared across a longer period as they are. This chapter therefore limits the trend analyses across the entire 1990-2007 period to those age groups that were invited or screened in all years of the screening programme. For initial screening examinations this concerns the young, new participants in the screening programme (49 and 50-54). Standard correction for differences in age distribution was also applied to the groups examined.

3.1 Stages of the screening programme

The Dutch breast cancer screening programme can be divided into four stages, in which the aforementioned factors have varying levels of influence and partly affected the screening results.

- **1989/90-1997**
  Implementation of the screening programme for women aged 50-69 – This stage witnessed a shift from what at first were mostly initial examinations to ultimately around 85% subsequent examinations. With a few exceptions, initial screening examinations involved only young, new participants aged around 50. Because the breast cancer detection is lower for both subsequent screens and among younger women, the total detection rate gradually decreased during this stage.

- **1998-2001**
  Extension of the screening programme to include women aged 70-75 – The detection rate once again increased during this stage, due to the large influx of older women. Another significant factor in this stage was that a large number of the older women had a subsequent screening after an interval of 4-6 years, because they had not been invited to the previous 1 or 2 screening rounds due to their age (>69). The average individual screening interval also increased during this time due to capacity problems resulting from the 25% increase in the target population. After a longer screening interval, more breast cancers enter a preclinical detectable stage, more of which will therefore be detected by screening.

- **2002-2004**
  Following full implementation for women aged 50-75 – This was the first period of the screening programme that exhibited a steady-state situation, with a stable ratio between initial and subsequent

screens. The average individual screening interval also decreased again somewhat during this stage.

- **2005 onwards**
  Start of the transition to digital screening – Three units had actually already commenced digital screening in the second half of 2004, yet the number of women examined remained very small. In 2006 and 2007, another two screening units converted to digital screening.

3.2 Breast cancer screening among women aged 70-75

In 1998, immediately following the implementation of the screening programme among women aged 50-69, work began on extending the study to include groups up to age 75. This meant expanding the target group by around 300,000 women, around half of whom were annually eligible for a screening examination. The inclusion of this new target group took until late 2001. In terms of invitation, screening and referral policy, no distinction was made between the original target group (50-69) and the new, older target group.
During the first ten years of this '70+ screening', more than 1.6 million invitations were sent to women aged 70-75 (table 3.1). At 73.3%, attendance over the entire 1998-2007 period was significantly lower than for women aged under 70 (81.4%). However, attendance among the group of older women did increase, from 63% in 1998 to 79% in 2007 (figure 3.1; see also figure 2.6). This rise in attendance can be fully explained by the attendance following invitations for a subsequent examination. Attendance at initial screening examinations ranged from 50-60%. These were small numbers of women (around 1000 in 2007) and mostly immigrants, who are possibly less familiar with the screening programme.
Over the ten years of 70+ screening, a total of 1,205,019 women aged 70 or over were examined. Initial screening examinations were considerably underrepresented at 3.8% (15.8% among women aged 50-69), whereas at 14.1%, the number of subsequent examinations with an interval greater than 2.5 years was much higher than for the younger age group (4.2%) (table 3.1). Both initial and subsequent long-interval examinations produced high referral and detection rates. However, after weighting the results according to the varying composition of examination types, the weighted results parameters proved to be hardly any different to the raw data shown in table 3.1.

Compared to the younger women, the referral rates, biopsy figures, detection rates and positive predictive values of both referrals and biopsies were significantly higher among women aged between 70 and 75 (table 3.1). The percentage of screen-detected carcinomas in situ was significantly lower (11.4% vs. 15.2%) and the proportion of invasive tumours 6-10 mm in size (T1b) significantly higher (21.9% vs. 18.1%). The proportion of node-positive tumours among invasive carcinomas was clearly smaller, and that of node-negative tumours clearly larger.

Ten years later, we can conclude that the integration of the new 70-75 target group into the screening programme went practically without a hitch. Attendance was greater than we had dared to hope for, and the detection rate, the positive predictive value of the

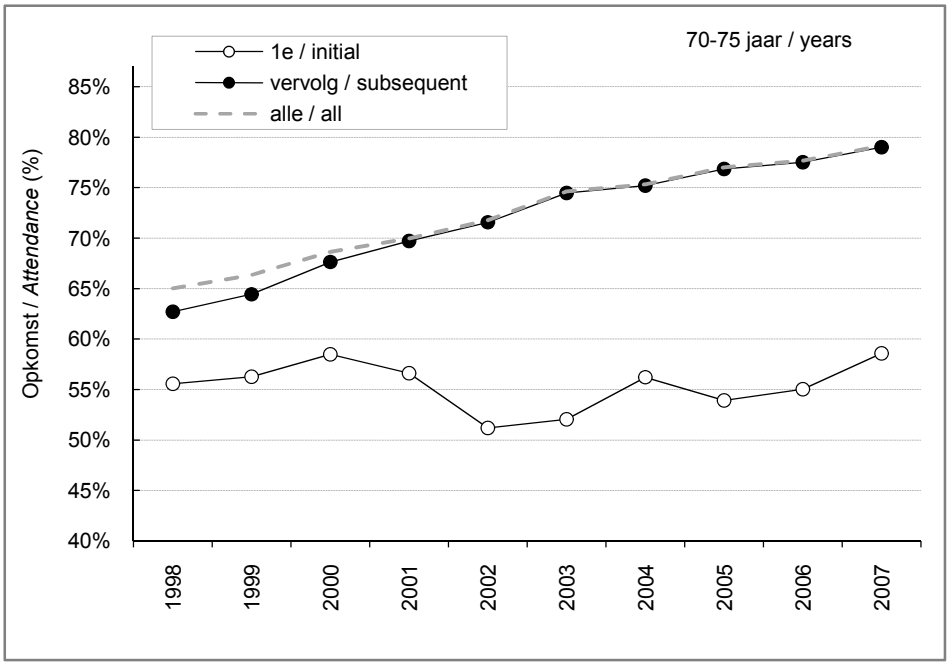


Figure 3.1
Annual attendance rates (%) women aged 70-75 years following initial, subsequent and all invitations, 1998-2007

Table 3.1 Screen results 1998-2007 of women aged 50-69 and 70-75 years (based on evaluation ages 49-68 and 69-74 years, respectively)

	50-69		70-75	
Uitnodigingen (N) *Invitations (N)*	8.692.080		1.611.291	
Opkomst (%) *Attendance (%)*		81,4%		73,3%
Opkomsttrouw (%) *Reattendance (%)*		93,5%		88,4%
	N	% of/*or* per 1000	N	% of/*or* per 1000
Screeningsonderzoeken *Screen examinations*	7.077.972		1.205.019	
- eerste screeningsonderzoeken - *initial screens*		15,8%		3,8%
- reguliere vervolgscreeningen (< 2,5 jaar) - *regular subsequent screens (< 2.5 years)*		80,0%		82,0%
- vervolgscreeningen > 2,5 jaar - *subsequent screens after > 2.5 years*		4,2%		14,1%
Verwijsadviezen *Referral recommendations*	93.917	13,27	19.507	16,19
Volledigheid follow-up na verwijzing *Follow-up screen-positives*		98,2%		98,1%
(Naald-) Biopsieën *(Needle) Biopsies*	47.623	6,73	11.412	9,47
Door screening ontdekte borstkanker *Screen-detected breast cancers*	32.260	4,56	9.029	7,49
Positief voorspellende waarde verwijsadvies *Positive predictive value referral recommendation*		34,3%		46,3%
Positief voorspellende waarde biopsie *Positive predictive value at biopsy*		67,7%		79,1%
Screeningscarcinomen *Screen-detected breast cancers*				
- DCIS	4.918	15,2%	1.028	11,4%
- T1a (invasive 0-5 mm)	1.413	4,4%	374	4,1%
- T1b (invasive 6-10 mm)	5.825	18,1%	1.982	21,9%
- T1c (invasive 11-20 mm)	13.416	41,6%	3.862	42,8%
- T2 (invasive 21-50 mm)	5.479	17,0%	1.451	16,1%
- T3 (invasive >50 mm)	283	0,9%	63	0,7%
- T4 (invasive)	96	0,3%	36	0,4%
- Tx	830	2,6%	234	2,6%
Invasieve borstkankers *Invasive cancers*	27.342		8.001	
- lymfklierpositief N+ - *lymph node positive N+*	7.600	27,8%	1.726	21,6%
- lymfkliernegatief N- - *lymph node negative N-*	11.341	41,5%	3.637	45,5%
- schildwachtklieren (SNB) negatief - *sentinel node (SNB) negative*	6.885	25,2%	2.144	26,8%
- lymfklierstatus onbekend Nx - *lymph node status unknown Nx*	875	3,2%	311	3,9%
- metastasen op afstand M1 - *distant metastases M1*	138	0,5%	44	0,5%
- onbekend - *unknown*	503	1,8%	139	1,7%

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referral rate and the stages of screen-detected carcinomas were more positive than those of women aged under 70. The fact that on average the breast cancers detected allowed a better prognosis could be an indication of what is called the 'length-time bias'. Due to average slower tumour growth as age increases, the tumours remain in a preclinical detectable stage for longer, making them easier to identify by screening. In general, these tumours are less aggressive and are probably less likely to cause death. In some cases screening therefore advances the diagnosis without improving the chances of survival for the woman in question. In extreme cases, such cancers would never even be detected during the woman's lifetime, resulting in overdetection and overtreatment.

3.3 Digital screening

In 2004, three digital screening units commenced operation in Utrecht, Dordrecht and Heerenveen. They were established as pilot programmes, in order to gather some initial experience with digital mammography in a day-to-day screening context, and to answer a variety of practical questions. A separate evaluation of these three pilot screening units, in which the first year of digital screening was compared to the previous year's analogue screening, showed that production had decreased by 30% and that referrals during the first four months had increased by a factor of 2-3. The detection rate was slightly higher but not significantly so, particularly for carcinomas in situ (Fracheboud & de Koning, 2007). Partially based on these results, the Dutch National Expert and Training Centre for Breast Cancer Screening (NETCB) and the National Institute for Public Health and the Environment (RIVM) developed a short-cycle monitor in order to steer the transition to a fully-digitised screening programme in the right direction. The results of the digital screening examinations were also separately evaluated. The years 2006 and 2007 saw the conversion of a fourth and fifth unit to digital screening. Over the course of 2008, nation-wide digitisation of the screening programme was intensified. The aim is to have all units exclusively using digital screening by mid-2010.

From 2004-2007, five screening units in four regions conducted a total of 155,548 digital screening examinations as part of the screening programme, 55,601 of which took place in 2007 (7.4% of all examinations conducted in 2007) (table 3.2). Compared to the over 3.5 million analogue screening examinations within the same period, the number of initial examinations and long-interval subsequent screens (≥ 2.5 years) are slightly overrepresented. Comparing the digital examinations to the 715,809 analogue examinations that were assessed during the same period by the same reading units reveals 50% increase in the referral rate and a 22% increase in the total detection rate. Of all detected breast cancers, 45% were carcinomas in situ or small invasive carcinomas not larger than 10 mm, compared to 37% from analogue examinations.

Further analysis of the digital screens shows that over the years, the increase in the digital referral rate compared to that of the analogue examinations decreased from 133% in 2004 to 44% in 2007, partly due to the specific training created by the NETCB for screening radiologists as a result of the 2004 peak in referrals. The detection rates of both invasive carcinomas and carcinomas in situ (16% and 64% respectively) were also significantly higher. With the exception of the referral rate, these findings can be fully attributed to the results of the regular subsequent screens, and in turn mostly to the Drechtsteden pilot region, which conducted by far the largest number of digital examinations. Initial screens of new participants aged 49 and 50 showed a non-significant rise in the total detection rate, fully attributable to increased detection of carcinomas in situ. It seems plausible that this last aspect will attain statistical significance with larger numbers of screens. This is supported by the fact that the breast cancer detection rate of all digital examinations was significantly higher in 2007, the year in which most digital examinations were conducted.

3.4 Screening performance per stage of the programme

Previous NETB reports had already indicated that there were relatively large differences in screening performance between the regions. With the exception of two regions, several groups of radiologists (the 'reading units') are involved in assessing the screening mammograms. For this reason, collection of assessment data per reading unit began in the early 2000s. However, until 2005 this data was not of sufficient quality to be able to report on at a detailed level.

In order to assess performance most effectively, data on interval cancer is required. However, this data is not available nationally subsequent to 1994 (8 of the 9 regions), and only from some regions between 2002 and 2004. The national programme sensitivity and specificity can therefore not be reliably determined for the most recent years. Tracing interval cancers is a complex matter which requires linking screening data with data from the cancer registry. Due to the regional cancer registers converting to a national system in 2005 (which took much longer

Table 3.2 Results of digital and screen-film examinations from 5 reading units during 2004-2007 compared with the national total during the same period

	Netherlands		**5 beoordelingseenheden / 5 reading units**					
	Alle onderzoeken *All screen examinations*		Alle onderzoeken *All screen examinations*		Analoge onderzoeken *Film-screens*		Digitale onderzoeken *Digital screens*	
opkomstpercentage *attendance rate*		81,7%		81,2%		--		--
screeningonderzoeken *screening examinations*	3.578.701		871.357		715.809		155.548	
- eerste / *initial* (N / %)	448.468	12,5%	110.836	12,7%	89.049	12,4%	21.787	14,0%
- regulier vervolg / *regular subsequent* (< 2,5 jaar/*years*) (N / %)	2.981.794	83,3%	719.795	82,6%	593.473	82,9%	126.322	81,2%
- vervolg / *subsequent* >= 2,5 jaar/*years* (N / %)	148.439	4,1%	40.726	4,7%	33.287	4,7%	7.439	4,8%
aandeel digitaal / *proportion digital screens*		4,3%		17,9%		--		--
gemiddelde leeftijd (jaar) / *mean age (years)*	60,11		60,05		60,09		59,87	
verwijsadviezen / *referral recommendations* (N / per 1000)	56.136	15,7	14.803	17,0	11.080	15,5	3.723	23,9
screeningscarcinomen / *screen detected carcinomas* (N / per 1000)	18.331	5,1	4.517	5,2	3.564	5,0	953	6,1
pvw verwijsadvies / *ppv referral recommendation*		32,7%		30,5%		32,2%		25,6%
DCIS (N / %)	2.717	14,8%	747	16,5%	548	15,4%	199	20,9%
T1a + T1b (N / %)	4.122	22,5%	1.036	22,9%	806	22,6%	230	24,1%
T1c (N / %)	7.879	43,0%	1.848	40,9%	1.487	41,7%	361	37,9%
T2 + T3 (N / %)	3.118	17,0%	768	17,0%	621	17,4%	147	15,4%
Tx / not classified (N / %)	495	2,7%	118	2,6%	102	2,9%	16	1,7%
N0 (incl. negative sentinel nodes) (N / %)	10.865	69,6%	2.618	69,4%	2.085	69,1%	533	70,7%
N+ (N / %)	4.042	25,9%	977	25,9%	785	26,0%	192	25,5%
Nx (N / %)	277	1,8%	84	2,2%	66	2,2%	18	2,4%
M1 (N / %)	94	0,6%	19	0,5%	18	0,6%	1	0,1%
unknown	336	2,2%	72	1,9%	62	2,1%	10	1,3%

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than expected), the data of women screened after 2000 was no longer linked in a number of regions. The aim is to eliminate the backlog over the course of 2009, linking data at a national level for all screening examinations up to the end of 2004.

Referral and detection rates

In 1996, the total referral rate was 8.4 per 1000 women screened, and the total detection rate 4.2 per 1000, both lower than ever before. Especially for regular subsequent screens, the detection rate from those years remained far lower than expected at 3.2-3.4 per 1000, which was attributed to the extremely low referral rate of 6.1-6.6 per 1000. Screening radiologists were then encouraged to make more referrals, first by the Dutch National Expert and Training Centre for Breast Cancer Screening (NETCB) and later as a result of the optimisation study. After 1996, the referral rate rose continuously until it had tripled for initial screenings and almost doubled for subsequent screenings ten years later (see figure 2.13). The initial effect hereof was on detection rates (of both invasive tumours and carcinomas in situ) during the 75+ extension phase, which increased by 13% and 16% respectively (standardised values) (table 3.3). During the period from 2005-2007, the non-digital (i.e. analogue) detection rate from initial screening examinations was 24% higher, and from regular subsequent screenings 31% higher than the average during the implementation stage from 1990-1997. Digital examinations showed a 43%/49% higher detection rate, yet this was also accompanied by a referral rate that was 3/1.5 times higher.

Referral and detection rates rose over time in all nine screening regions, among both initial and regular/long-interval subsequent screens. However, significant differences can be perceived between the

Table 3.3 Age-adjusted referral recommendation and breast cancer (invasive and in-situ) detection rate per 1000 during different periods of the breast cancer screening programme (initial screens: 49-54 years; regular subsequent screens: 50-69 years)

Periode ***Period***		**1e / *initial* screening (49-54 jaar / *years*)**			**vervolg- / *subsequent* scr. (50-69 jaar / *years*)**[1]		
	Verwijscijfer / *Referral rate*	Onderzoeken (N)	per 1000	+ / -	*Screens* (N)	per 1000	+ / -
1990-1997	Implementatie 50-69 jaar *Implementation 50-69 years*	665.907	11,5	--	1.570.930	6,8	--
1998-2001	Implementatie 70-75 jaar *Implementation 70-75 years*	404.486	17,9	+55%	2.125.915	9,3	+36%
2002-2004[2]	Steady state 50-75 jaar *Steady state 50-75 years*	307.078	23,2	+101%	1.810.899	11,1	+62%
2005-2007	Conventionele (analoge) screening *Film-screen mammography*	286.258	30,0	+160%	1.900.602	13,3	+95%
2005-2007	Digitale screeningsonderzoeken *Digital screening examinations*	18.137	45,6	+295%	29.545	18,2	+166%
	Detectiecijfer / *Detection rate*	Borstkankers (N)	per 1000	+ / -	*Cancers* (N)	per 1000	+ / -
1990-1997	Implementatie 50-69 jaar *Implementation 50-69 years*	2.786	4,3	--	5.537	3,4	--
1998-2001	Implementatie 70-75 jaar *Implementation 70-75 years*	1.915	4,8	+13%	8.668	4,0	+16%
2002-2004[2]	Steady state 50-75 jaar *Steady state 50-75 years*	1.567	5,2	+22%	7.955	4,3	+25%
2005-2007	Conventionele (analoge) screening *Film-screen mammography*	1.486	5,3	+24%	8.771	4,5	+31%
2005-2007	Digitale screeningsonderzoeken *Digital screening examinations*	111	6,1	+43%	152	5,1	+49%

+ / - = verandering t.o.v. 1990-1997
change compared with 1990-1997

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[1] Reguliere vervolgscreeningen (< 2,5 jaar interval)
Regular subsequent screen examinations (< 2.5 years interval)

[2] Excl. digitale onderz. 2004: 1.609 (0,6%) 1e en 7.849 (0,5%) vervolgscr.
Excl. digital screens 2004: 1,609 (0.6%) initial and 7,849 (0.5%) subsequent

regions. In 2007 for example, partially due to the influence of digital screening, the standardised referral rate for initial screens varied between 21.7 and 50.4 per 1000 women screened aged 49-54, and the standardised detection rate varied between 5.0 and 7.2 per 1000. The respective variation among subsequent screens was 10.8-21.4 per 1000 aged 50-69, and 4.2-5.6 per 1000.

The rise in the detection rate can primarily be attributed to increased detection of invasive tumours with a diameter of 11-20 mm (T1c) (figure 3.2c). In recent years there has also been a perceptible increase in DCIS and the smallest invasive tumours (T1a and T1b), possibly partly due to the growing number of digital screening tests (see also table 3.3).

Table 3.4 shows the changes in age-corrected referral and detection rates per region for regular subsequent screens across the four stages of the screening programme. Compared to the initial implementation stage from 1990-1997, there was an increase in referral and detection rates in all nine regions, albeit varying to a large extent. The rise in the referral rate over 2005-2007 varied from 45% (region B) to 147% (region E), and that of the detection rate from 9% (region B) to 61% (region D). The percentage changes are, of course, dependent on the situation at the outset: in the period from 1990-1997, region B had by far the highest detection rate (3.9 per 1000) and region D by far the lowest (2.9 per 1000). In the interests of nation-wide high quality, the strong rise in breast cancer detection in region D is of particu-

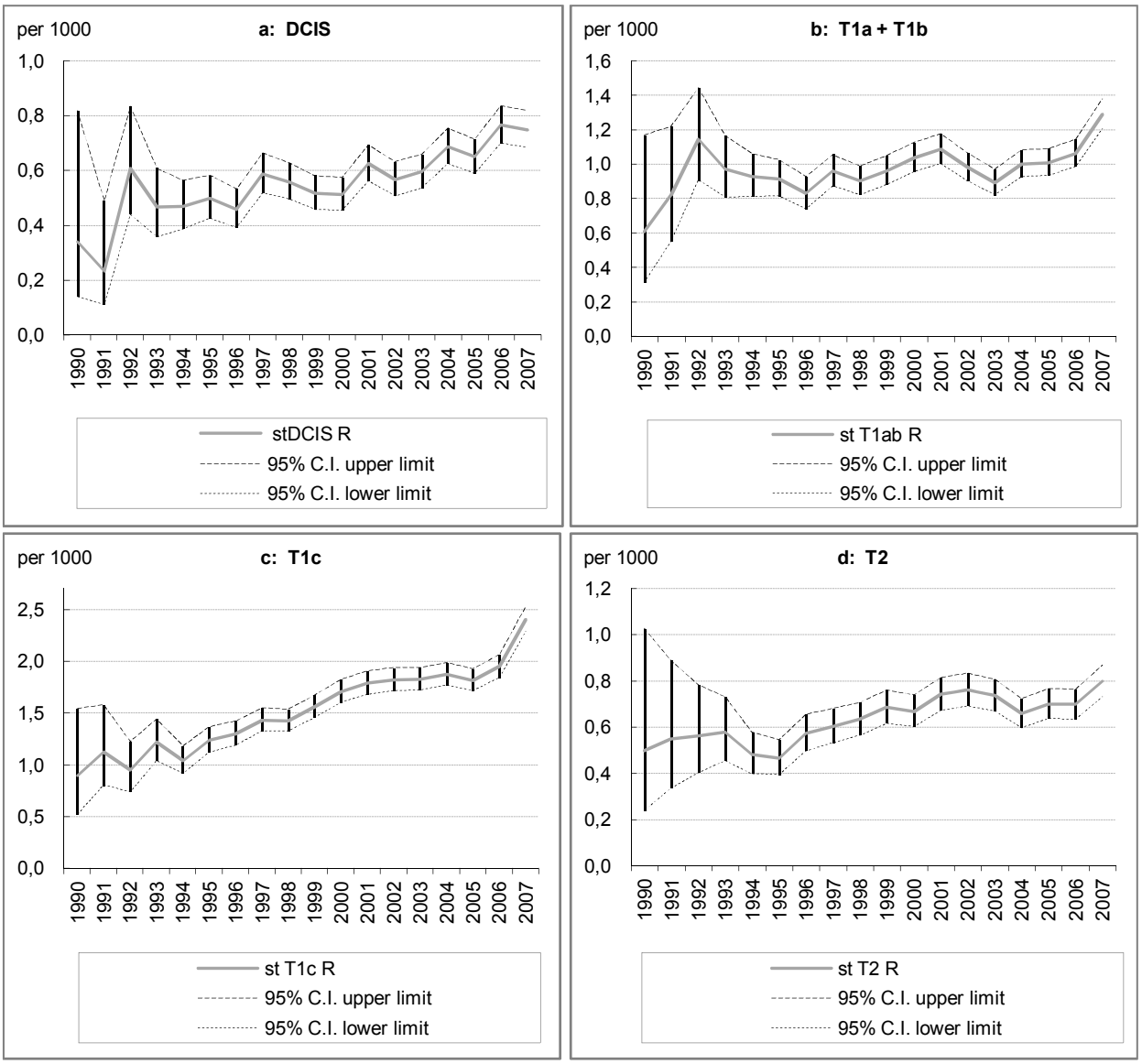

Figure 3.2 Age-adjusted breast cancer detection rate per 1000 with 95% confidence interval, regular subsequent screens 1990-2007 in women aged 50-69 years, for a. ductal carcinoma in situ (DCIS), b. invasive cancers T1a+T1b (<= 10 mm), c. invasive cancers T1c (11-20 mm), and d. invasive cancers T2 (21-50 mm)

Table 3.4 Regional age-adjusted referral recommendation and breast cancer (invasive and in-situ) detection rate pers 1000 during different periods of the breast cancer screening programme, regular subsequent screens 50-69 years

Periode / *Period*	vervolg / *subsequent* (50-69 jaar / *years*)[1]	A			B			C		
	Verwijscijfer / *Referral rate*	Screens (N)	per 1000	+ / -	Screens (N)	per 1000	+ / -	Screens (N)	per 1000	+ / -
1990-1997	Implementatie 50-69 jaar *Implementation 50-69 years*	127.807	7,0	--	214.050	7,8	--	192.722	7,0	--
1998-2001	Implementatie 70-75 jaar *Implementation 70-75 years*	143.320	11,2	+60%	167.242	8,0	+2%	342.067	9,8	+39%
2002-2004[2]	Steady state 50-75 jaar *Steady state 50-75 years*	122.133	10,9	+55%	144.781	10,2	+30%	283.839	11,8	+69%
2005-2007	Beginnende digitale screening *Start with digital screening*	121.961	13,0	+86%	156.151	11,3	+45%	292.127	14,3	+103%
	Detectiecijfer / *Detection rate*	Cancers (N)	per 1000	+ / -	Cancers (N)	per 1000	+ / -	Cancers (N)	per 1000	+ / -
1990-1997	Implementatie 50-69 jaar *Implementation 50-69 years*	453	3,5	--	856	3,9	--	652	3,2	--
1998-2001	Implementatie 70-75 jaar *Implementation 70-75 years*	588	4,1	+16%	729	4,3	+9%	1.303	3,8	+16%
2002-2004[2]	Steady state 50-75 jaar *Steady state 50-75 years*	434	3,6	+0%	663	4,5	+15%	1.285	4,4	+38%
2005-2007	Beginnende digitale screening *Start with digital screening*	533	4,4	+23%	682	4,3	+9%	1.306	4,4	+37%
		D			**E**			**F**		
	Verwijscijfer / *Referral rate*	Screens (N)	per 1000	+ / -	Screens (N)	per 1000	+ / -	Screens (N)	per 1000	+ / -
1990-1997	Implementatie 50-69 jaar *Implementation 50-69 years*	127.481	4,9	--	212.864	6,1	--	152.212	5,7	--
1998-2001	Implementatie 70-75 jaar *Implementation 70-75 years*	307.458	9,2	+88%	174.913	7,8	+28%	171.819	8,4	+45%
2002-2004[2]	Steady state 50-75 jaar *Steady state 50-75 years*	263.749	11,4	+132%	144.530	9,8	+61%	141.387	10,2	+78%
2005-2007	Beginnende digitale screening *Start with digital screening*	278.546	10,7	+119%	154.659	15,0	+147%	148.488	11,6	+102%

	Detectiecijfer / *Detection rate*	Cancers (N)	per 1000	+ / -	Cancers (N)	per 1000	+ / -	Cancers (N)	per 1000	+ / -
1990-1997	Implementatie 50-69 jaar *Implementation 50-69 years*	371	2,9	--	763	3,5	--	546	3,5	--
1998-2001	Implementatie 70-75 jaar *Implementation 70-75 years*	1.277	4,1	+42%	702	3,9	+12%	754	4,3	+21%
2002-2004[2]	Steady state 50-75 jaar *Steady state 50-75 years*	1.233	4,6	+60%	587	4,0	+14%	604	4,2	+19%
2005-2007	Beginnende digitale screening *Start with digital screening*	1.320	4,6	+61%	732	4,6	+33%	737	4,9	+38%
		G			**H**			**I**		
	Verwijscijfer / *Referral rate*	Screens (N)	per 1000	+ / -	Screens (N)	per 1000	+ / -	Screens (N)	per 1000	+ / -
1990-1997	Implementatie 50-69 jaar *Implementation 50-69 years*	155.367	7,9	--	159.171	7,1	--	229.256	7,3	--
1998-2001	Implementatie 70-75 jaar *Implementation 70-75 years*	204.671	9,1	+16%	273.591	10,6	+51%	340.834	9,0	+22%
2002-2004[2]	Steady state 50-75 jaar *Steady state 50-75 years*	191.958	9,6	+23%	232.062	13,0	+85%	293.384	11,4	+56%
2005-2007	Beginnende digitale screening *Start with digital screening*	205.254	14,5	+85%	259.756	16,4	+132%	313.205	12,8	+75%
	Detectiecijfer / *Detection rate*	Cancers (N)	per 1000	+ / -	Cancers (N)	per 1000	+ / -	Cancers (N)	per 1000	+ / -
1990-1997	Implementatie 50-69 jaar *Implementation 50-69 years*	577	3,6	--	548	3,4	--	771	3,3	--
1998-2001	Implementatie 70-75 jaar *Implementation 70-75 years*	889	4,3	+19%	1.084	3,9	+15%	1.342	3,8	+16%
2002-2004[2]	Steady state 50-75 jaar *Steady state 50-75 years*	841	4,3	+20%	1.083	4,6	+36%	1.268	4,2	+27%
2005-2007	Beginnende digitale screening *Start with digital screening*	1.035	5,0	+40%	1.243	4,7	+38%	1.335	4,2	+27%

+ / - = verandering t.o.v. 1990-1997
change compared with 1990-1997

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[1] Reguliere vervolgscreeningen (< 2,5 jaar interval)
Regular subsequent screen examinations (< 2.5 years interval)

[2] Excl. digitale onderz. 2004: 1.609 (0,6%) 1e en 7.849 (0,5%) vervolgscr.
Excl. digital screens 2004: 1,609 (0.6%) initial and 7,849 (0.5%) subsequent

lar importance. Between 2005 and 2007, the highest detection rate was 5.0 per 1000 (region G) and the lowest 4.2 per 1000 (region I).

Figure 3.3 indicates that a higher referral rate (the full length of the bars in the graph) does not automatically equate to a higher proportion of true-positive results (i.e. the detection rate). Although it is true that in 2007 region E had the most referrals after a regular subsequent screen and also detected the most breast cancers (figure 3.3c), this is actually an exception. Figure 3.4 shows the relationship between true-positive and false-positive results from regular subsequent screens according to the 27 reading units. As opposed to figure 3.3, this data is neither limited to a certain age group nor corrected for any differences in age distribution among the women screened. Yet it is expected that standardisation will not significantly alter the results, since by 2002 the women aged 70-75 in all regions had already been completely integrated into the screening programme. The bars marked 'D' refer to assessment centres that also used digital screening to some extent in 2004 or later. On average, the proportion of digital mammograms in the five reading units involved was 17.8%, meaning that any influence on the results due to digital screening will be barely visible. Nevertheless, it is striking that two of the five reading units are in the top three with true-positive results.

False-positive results

The considerable rise in referral rates with a proportionally far smaller increase in the detection rate over the years led to a drop in the predictive value of the referral rate. The 43% predictive value of initial screening examinations in 1990 dropped to 17% in 2007, and the 56% value of subsequent regular examinations in 1992 dropped to 34% in 2007. This means that now, five out of every six women with a suspected abnormality from their initial screen are given a false positive, as well as two out of every three who are referred from a regular subsequent examination.

Calculated from the total number of women screened, the likelihood of a false-positive result from a subsequent screening examination has tri-

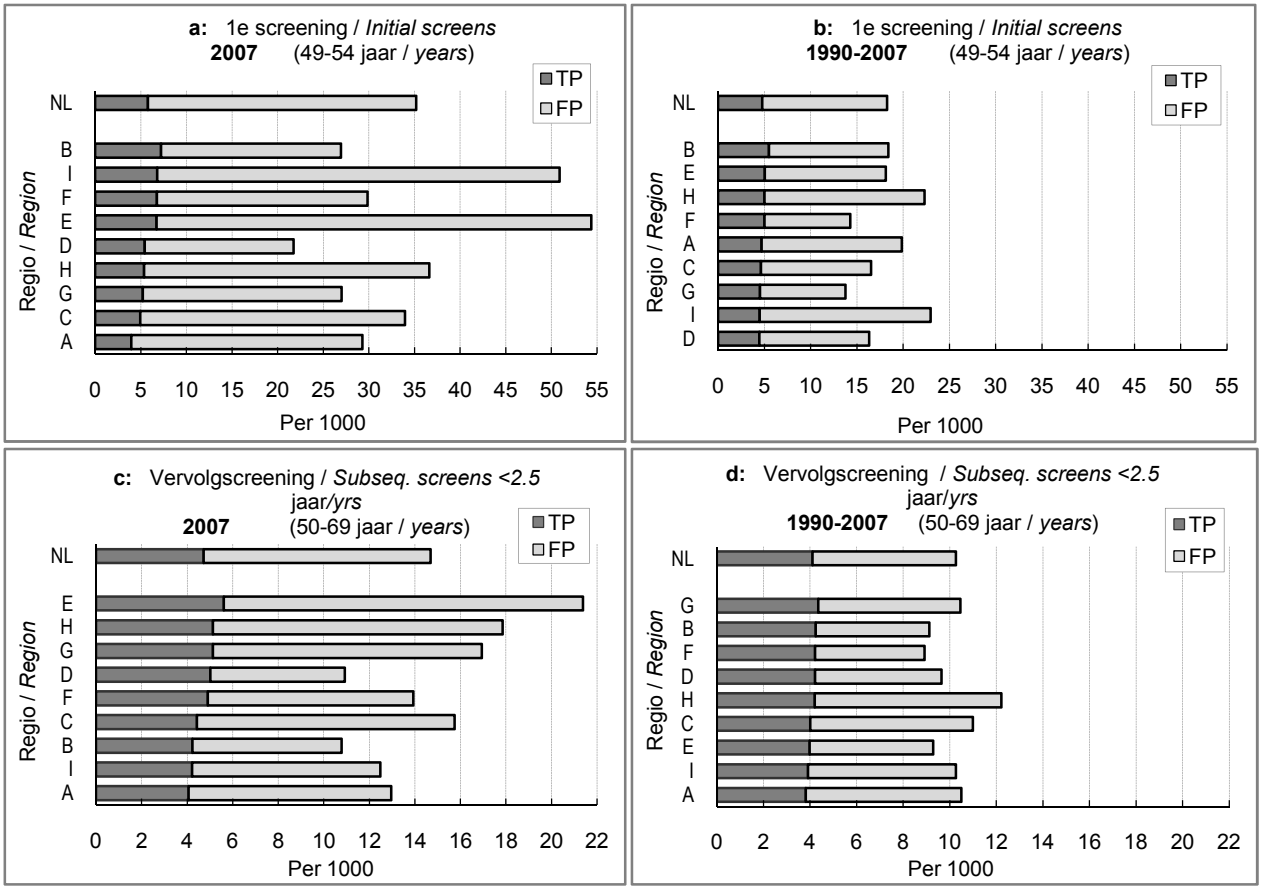


Figure 3.3 Regional age-adjusted true positive (TP) and false positive (FP) results per 1000 of a. initial screens 2007 (49-54 years), b. initial screens 1990-200 (49-54 years)7, c. regular subsequent screens 2007 (50-69 years), and d. regular subsequent screens 1990-2007 (50-69 years)

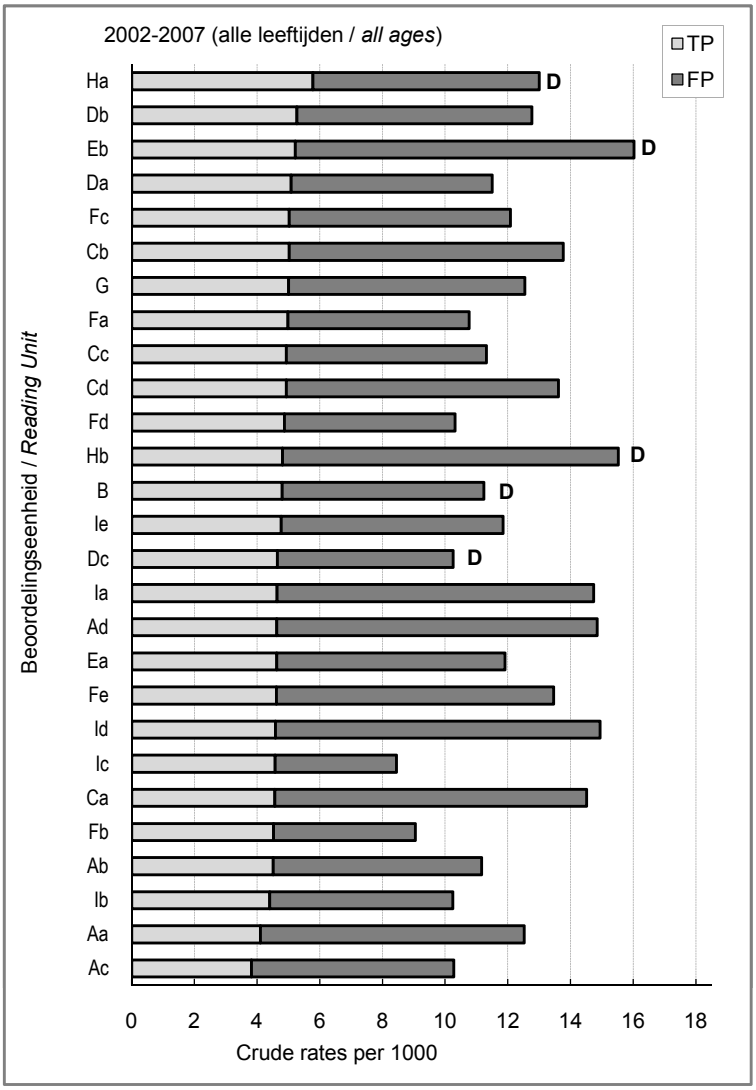


Figure 3.4
True-positive (TP) and false positive (FP) results per 1000 by reading unit, regular subsequent screens 2002-2007, all ages (D = reading units with also digital mammography during this period)

pled from 0.33% in the first half of the 1990s to 1.0% in 2007. Comparing these with international figures, the proportion of false-positives is still relatively low, yet the difference is no longer as large as it was in the 1990s. Referral rates from abroad of over 40 per 1000 women screened are common, which are accompanied by a high proportion of false-positive results. Over a longer period with regular participation in screening, women in other countries also therefore have a bigger chance of receiving at least one false-positive result. Table 3.5 shows that, based on previous referral and detection figures, women aged 51 and being screened for the first time in 1991 had a cumulative 5.1% chance of a false-positive result somewhere during their first nine screening rounds until the end of 2007. Assuming this situation remains unchanged after 2007, this likelihood would increase to 9.1% after 13 rounds, and for post-2007 digital screening even as high as 11.0%. This assumes that the likelihood of a false-positive result in each screening round is independent of the results of previous rounds. Furthermore, the calculation is based on 'historical' age-specific referral and detection rates up until the ninth round of screening in 2007 (i.e., rates that increase over the years) and on a constant rate of 0.99% per round thereafter. Assuming age-specific referral and detection rates in 2007, the cumulative likelihood of a false-positive result after 13 screening rounds would rise to 15.5%.

Interval cancers

Data is available for 77.7% of the 8.7 million screening tests conducted up to 2004 on whether interval cancer was discovered outside of the programme within the first two to three years following screening. A total of 16,866 interval cancers were reported, 13,654 of which were found within 24 months of screening. This amounts to 2.0 interval cancers per 1000 screened, or, relative to the nearly 13 million women years of follow-up time, 1.05 per 1000 women years. This last method of calculation is more precise, and prevents underestimation of the interval cancer frequency, because it takes into consideration women who could not be followed during the entire two-year screening interval, e.g. due to death or relocation, or who had another screen before the interval period had expired. At 1.08 and 1.04 per 1000 women years follow-up (for initial and regular subsequent screens respectively), the observed interval cancer frequency up to the end of 2004 was 5-10%

Table 3.5 Cumulative risk of a false positive screening result, based on observed (up to round 10) and estimated (from round 10 on) data

Screeningsronde (jaar) *Screening round (year)*	Kans op fout-positieve uitslag (FP) *Risk of false-positive result (FP)*			Leeftijd *Age*
	niet FP *not FP*	per ronde *per round*	cumulatief *cumulative*	
1 (1991)	99,24%	0,76%	0,76%	51
2 (1993)	98,99%	0,25%	1,01%	53
3 (1995)	98,69%	0,30%	1,31%	55
4 (1997)	98,35%	0,33%	1,65%	57
5 (1999)	97,91%	0,44%	2,09%	59
6 (2001)	97,26%	0,65%	2,74%	61
7 (2003)	96,65%	0,61%	3,35%	63
8 (2005)	95,85%	0,80%	4,15%	65
9 (2007)	94,86%	0,99%	5,14%	67
10 (2009)*	93,88%	0,99%	6,12%	69
11 (2011)*	92,89%	0,99%	7,11%	71
12 (2013)*	91,90%	0,99%	8,10%	73
13 (2015)*	90,92%	0,99%	9,08%	75

* bij ongewijzigde uitslagen na 2007 / *assuming the same results as in 2007* LETB/*NETB,* 2009

higher than the anticipated frequencies of 1.00 and 0.96 per 1000 women years (table 3.6). However, because nation-wide reporting on interval cancers is not complete, interpreting the trends is difficult. The average programme sensitivity up until 2004 was 71.0%, meaning that over two-thirds of all (latent) present breast cancers were detected by screening. The sensitivity of initial screening examinations among women aged 49-54 was 74.5%, and 67.7% for regular subsequent screenings among women aged 50-69, with 99.0% and 99.5% specificity respectively. This means that, up until 2004, 1% of women who received an initial examination and 0.5% of those who received a subsequent examination received a false-positive result.

According to the inspection reports of the Dutch National Expert and Training Centre for Breast Cancer Screening (NETCB), reviewing the screening mammograms that preceded the diagnosis of interval cancers revealed that over half of the interval cancers could not have been detected by screening (table 3.7). Leaving aside these interval cancers places the sensitivity of mammography at around 84%.
The frequency of interval cancer declines with age. Between 1990 and 2004, 1.15 interval cancers per 1000 women years follow-up were found in women aged around 50, and 0.94 per 1000 women years among women aged 70-74. At 80.1%, programme sensitivity among women aged 70+ was significantly higher than in the 50-69 age group, and the specificity slightly lower (99,17% versus 99,25%).

The rise in breast cancer detection since the end of the 1990s would lead one to expect the interval frequency to decrease over the same period. However, this is difficult to judge based on incomplete national data on interval cancers per calendar year, and the frequency sometimes rather seems to be increasing. The data has therefore been analysed in greater detail, per region and in two-year periods, in order to reduce the effects of random fluctuations in interval cancer frequencies through larger numbers. Figure 3.5 shows the provisional results of these analyses. The figure presents the age-corrected detection rates and the interval cancer frequencies in the first and second year after screening per region, as well as the Dutch average during the biennial periods of 1994-1995, 1996-1997, 1998-1999 and 2000-2001, with initial screens on the left (age 49-54) and regular subsequent screens on the right (50-69 years). A trend line (line of regression) was drawn through all three parameters. Because the results have been ordered according to the detection rate (light bar), the uppermost trend line drops in all figures. By contrast, the interval-cancer frequency bars (light and dark-grey) in the first and second year following screening display less-clear ordering according to their value, even though in the majority of periods the trend lines indicate a slightly rising trend when detection rates drop. In this way, the figures do provide some indication that screening regions with higher detection figures generally tend to have a lower interval cancer frequency. Yet it will not be possible to confirm this relationship until complete data on interval cancer frequency becomes available for the years following 2000.

Table 3.6 Numbers and rates (per 1000 woman years) of interval cancers, sensitivity and specificity, 1990-2004

	1990-1997	1998	1999	2000	2001	2002	2003	2004	1990-2004
Gegevens (N) regio's / *Data (N) regions*	8 à 9	*8*	*8*	*7*	*7*	*6*	*5*	*2*	
Intervalcarcinomen < 2 jaar na onderzoek *Interval cancers < 2 years since screen*	*5.522*	*1.201*	*1.398*	*1.455*	*1.304*	*1.264*	*934*	*576*	*13.654*
Vrouwjaren follow-up (x 1000) *Woman-years of follow-up (x 1000)*	*5.470*	*1.126*	*1.275*	*1.254*	*1.253*	*1.167*	*949*	*502*	*12.996*
Intervalcarcinomen per 1000 vrouwjaren *Interval cancers per 1000 woman-years*	*1,01*	*1,07*	*1,10*	*1,16*	*1,04*	*1,08*	*0,98*	*1,15*	*1,05*
1e screening / *Initial screen (49-54 years)*									
- Intervalcarcinomen per 1000 vrouwjaren *Interval cancers per 1000 woman-years*	*1,02*	*1,22*	*1,16*	*1,37*	*1,13*	*1,26*	*1,08*	*1,32*	*1,08*
- Programmasensitiviteit *Programme sensitivity*	*75,7%*	*70,0%*	*73,8%*	*69,6%*	*73,5%*	*70,4%*	*72,9%*	*69,5%*	*74,5%*
- Programmaspecificiteit *Programme specificity*	*99,3%*	*98,9%*	*98,8%*	*98,7%*	*98,0%*	*98,2%*	*98,2%*	*98,2%*	*99,0%*
Vervolgscreening / *Subsequent screen*									
- Intervalcarcinomen per 1000 vrouwjaren *Interval cancers per 1000 woman-years*	*1,00*	*1,02*	*1,09*	*1,15*	*1,02*	*1,05*	*0,97*	*1,12*	*1,04*
- Programmasensitiviteit *Programme sensitivity*	*64,6%*	*66,2%*	*66,1%*	*66,1%*	*71,0%*	*70,5%*	*71,8%*	*70,1%*	*67,7%*
- Programmaspecificiteit *Programme specificity*	*99,6%*	*99,5%*	*99,5%*	*99,4%*	*99,2%*	*99,3%*	*99,3%*	*99,3%*	*99,5%*

cursief = Landelijk nog niet volledige gegevens / *in italic = Data not yet complete* LETB/*NETB,* 2009

Table 3.7 Classification of interval cancers based on review of preceding screening mammograms

Review screeningsmammogram ***Review screening mammogram***	**2001-02**	**2003**	**2004**	**2005**
- geen (zichtbare) afwijking - *no (visible) lesion*	55,8%	55,5%	52,4%	52,4%
- niet-significante afwijking (minimal sign) - *non-significant lesion (minimal sign)*	23,2%	22,3%	26,0%	23,3%
- significante afwijking - *significant lesion*	21,0%	22,1%	21,6%	24,2%

Bron: Landelijk ReferentieCentrum voor bevolkingsonderzoek naar Borstkanker (LRCB)
Source: National Expert and Training Centre for Breast cancer screening (NETBC)

One reason for a possible rise in the interval cancer frequency despite an increase in breast cancer detection could be that the large-scale attention in society to breast cancer and the screening programme has made both women and doctors more alert. In such a case, women with symptoms would go to their GP earlier, who would then be more prepared to refer them for further diagnosis. This would lead to earlier and more frequent diagnosis of interval cancers, and therefore also to a smaller average tumour size among interval cancers. However, closer examination of the interval cancers according to tumour size and the length of time between diagnosis and screening cannot confirm this theory as yet.

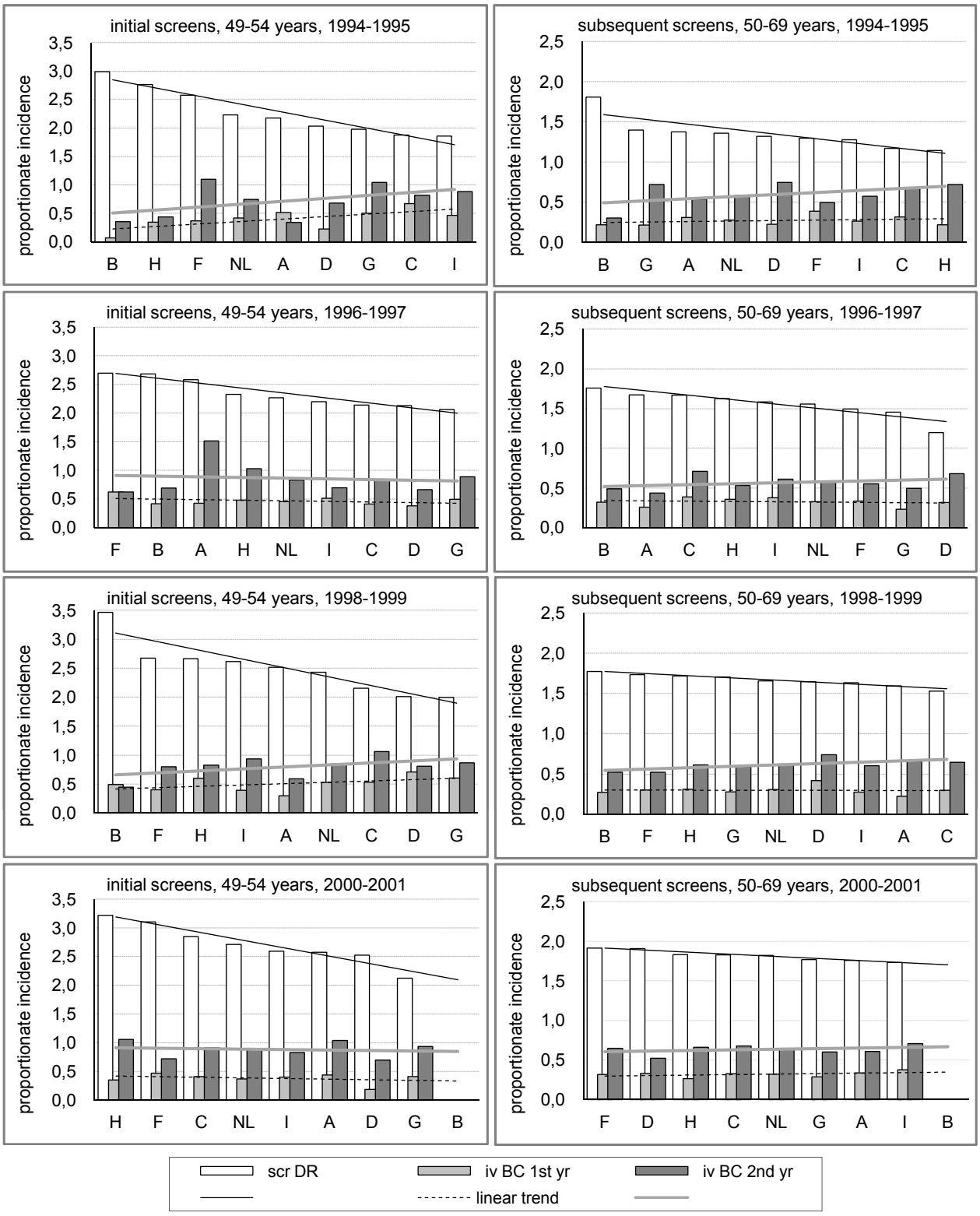


Figure 3.5 Regional age-adjusted screen-detected, first year interval and second year interval cancer rates per 1000 during successive 2-years periods 1994-2001, for initial screens in women aged 49-54 years (left) and regular subsequent screens in women aged 50-69 years (right)

4

Breast cancer incidence and mortality

This chapter examines various aspects concerning the breast cancer incidence and mortality. In addition to describing the progression of breast cancer incidence and mortality, one of the main questions concerns the extent to which the developments observed are related to the breast cancer screening programme, and how the (possible) contribution made can be more accurately estimated. Lastly, there is the question of what the consequences are of a successful breast cancer screening programme on the future pattern of mortality.

4.1 Breast cancer incidence and therapy

Data relating to the incidence and treatment of breast cancer is provided by the regional cancer registers in the form of C and D-tables. This is preceded by linking it with the data of women screened by the corresponding screening organisation, allowing both the incidence and the therapy in relation to possible participation in the screening programme to be examined. However, the integration of the individ-

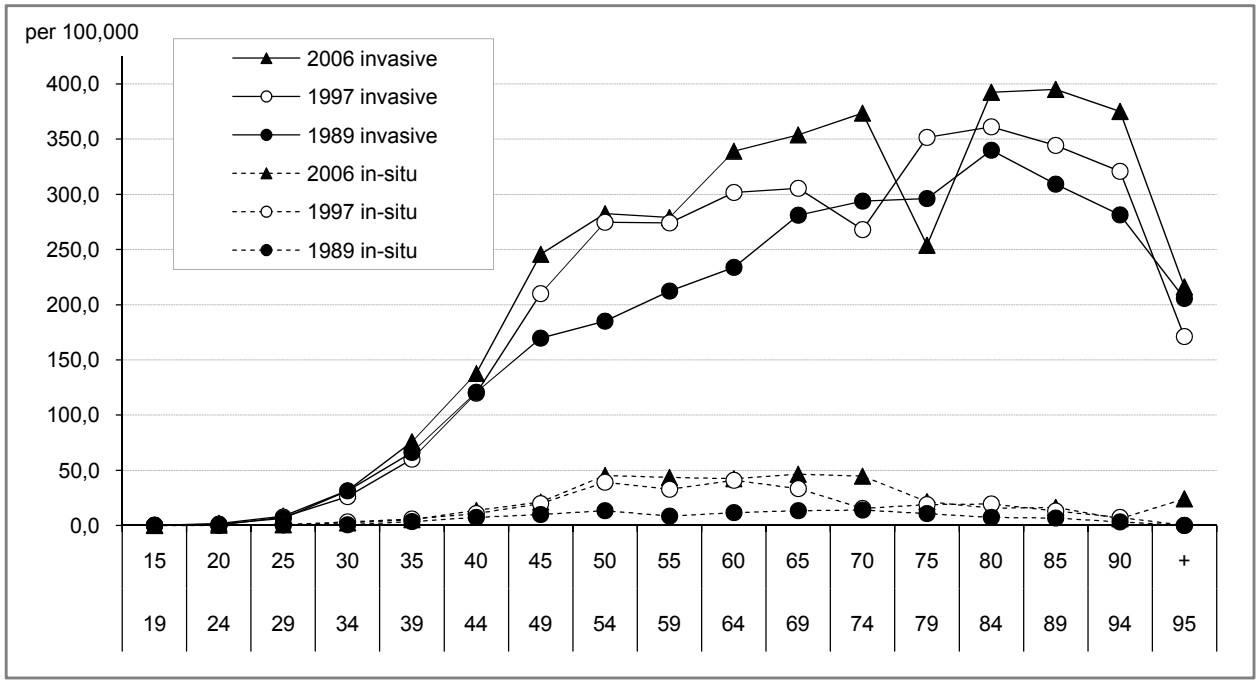


Figure 4.1 Age-specific invasive and in-situ breast cancer rates per 100,000 (ESR) in 1989, 1997 and 2006 (source: Netherlands Cancer Registry)

ual regional cancer registers to a national database has caused multi-year backlogs in the comparison of data, and in one of the regions no comparison has even taken place with the data of women screened after 2000 (see Chapter 3.4 on interval cancers). At the time of publication, data from the cancer register was complete at national level up to the end of 1999. For 2000 and 2001, data from seven of the nine regional cancer registers is available; for 2002, from four regions; for 2003, three; and for 2004, from one region. This impedes the interpretation of trends in incidence and treatment over recent years. For this reason, this section only covers a few aspects regarding the progression of breast cancer incidence and therapy.

Age-specific breast cancer incidence

Figure 4.1 is based on data from the Comprehensive Cancer Centres (www.ikcnet.nl) and shows the incidence of invasive and in situ mamma carcinomas per 5-year age group across three years: in 1989, prior to the implementation of the screening programme; in 1997, after full implementation for women aged 50-69 and prior to the extension of the up to age 75; and in 2006. In 1989 there was an almost linear increase in invasive breast cancer incidence up to the age of 84, whereas the incidence of carcinomas in situ was low and without any visible correlation to age. In 1997, the incidence in the screened population aged between 50 and 69 was considerably higher than in 1989, for both invasive and in-situ breast cancers. The incidence of invasive carcinomas then drops in the next 5-year age group of women aged 70-74 to a level somewhat below that in 1989, followed by a new incidence peak after the age of 75. In 2006, the first incidence peak has shifted to the 70-74 age group, and is followed by a sharp decrease in incidence among women aged 75-79. These drops indicate that some of the breast cancers that would normally be diagnosed in the relevant age groups have already been 'eliminated' by screening in previous years. A similar effect can be seen as early as 1997 among women aged 70-74, who up until that time had not been eligible for the screening programme.

Figure 4.2 shows the percentage difference in breast cancer incidence (invasive and in-situ together) between 1989 and 2006 for each 5-year age group, starting at 25. With the exception of the 75-79 age group, which shows a 12% decrease, incidence has risen in all age groups with a minimum increase of 7% (age 30-34) and a maximum increase of 40% (age 50-54). From age 35 upwards, the percentage difference is statistically significant for all age groups. The increase in the incidence rate among women aged 45-49 is particularly striking, which is higher in percentage terms than the increase in the 65-69 and 70-74 age groups. Depending on the screening schedule and their place of residence, some women

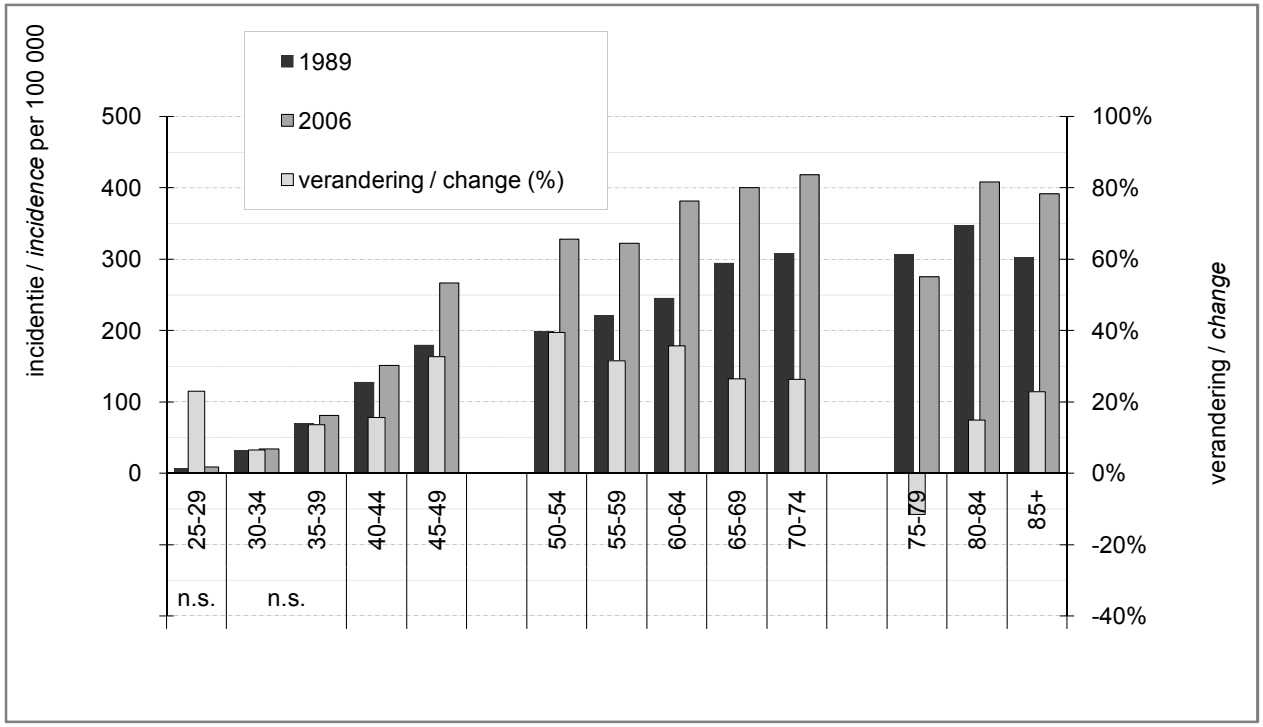


Figure 4.2 Age-specific breast cancer (invasive and in-situ) incidence per 100,000 (ESR) in 1989 and 2006, and percent change (source: Netherlands Cancer Registry). n.s. = not significant, otherwise difference significant

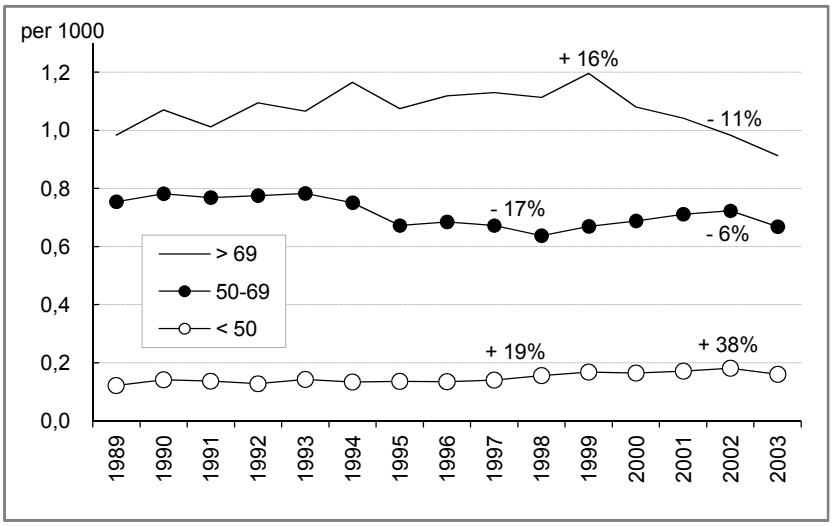


Figure 4.3
Age-adjusted advanced (T2+N+/M1) breast cancer rates per 1000 (ESR) by age category, 1989-2003 (7 regions without screening before 1990).
% : change compared to 1989.

receive screening invitations for the first time when they are only 49. In 2007, 40.2% of women aged 49 living in the Netherlands received a screening examination as part of the screening programme, or 7.7% of all women aged 45-49. In that same year, the percentage of women screened in the 5-year age groups from 50-69 was 38-39%, and 36.2% of women aged 70-74. The screening examinations therefore cannot fully explain the rise in incidence among women aged 45-49. It seems plausible that increased awareness of breast cancer would play a role in this age group, a time during which many women discover that the incidence of breast cancer in their environment is increasing, and possibly also know that they will soon become eligible for participation in the screening programme. The answer to the question of whether more 'opportunistic' mammograms also take place is not known, and would appear difficult to find. Among women who are still younger, the family genetic 'high-risk' screening has undoubtedly influenced the rise in incidence over the past two decades.

Advanced cancers

Several years ago in a separate study, the NETB analysed tumour-specific breast cancer trends in the 50-69 age group across the 1989-1997 implementation phase using supplementary data that had been obtained from the Netherlands Cancer Registry (Fracheboud et al., 2004). The study showed that the general rise in incidence was a consequence of the increased frequency (per 1000) of in-situ and small, lymph-node negative tumours. Advanced cancers, defined as invasive tumours with a diameter of more than 20 mm in combination with positive lymph nodes and/or distant metastases (T2+N+/M1), had also decreased significantly in frequency by 12.1%, and this decrease preceded the reduction in breast cancer mortality by 2-3 years.

A follow-up to this study, with a completely new data set extended up until the end of 2003, showed that in 1998 the frequency of advanced cancers among women aged 50-69 had declined by a further 17%, but increased again thereafter and in 2002 was only 6% lower than in 1989 (figure 4.3). The frequency among women aged 70+ rose by 16% from 1989 to 1999, and dropped sharply after that to reach a level 11% below that of 1989 in 2003. Hardly any change was observed up until 1998 among women aged under 50, yet from 1998 the frequency of advanced cancers started increasing rapidly, at its highest reaching an increase of 38% in 2002.

The trend in advanced breast cancer incidence seems reasonably justifiable among the oldest group of women, i.e. a gradual increase prior to the expansion of the screening programme to include women up to age 75, followed by a rapid drop once implementation had started. However, it is striking that the other two age groups show a sudden increase as of 1998. More detailed analyses indicate that this is probably related to the introduction of the sentinel node procedure in the second half of the 1990s. Because fewer nodes on average need to be examined during a sentinel node procedure than for an axillary lymph node dissection, the individual nodes are probably more closely analysed by the pathologist. In combination with more advanced laboratory examination of lymph nodes, this probably leads to more frequent discovery of micro or other metastases in the lymph nodes, and therefore to a greater number of node-positive mamma carcinoma (van der Heiden-van der Loo, 2006).

Primary treatment of breast cancer

Complete information on the primary treatment of breast cancers between 1990 and 1999 is available from seven of the regional cancer registers (two regions had no information on the type of surgical treatment during the initial years). In 1990 a total of 6,783 primary treatments of invasive and in-situ breast cancers were reported, and 9,442 in 1999. Per 100,000 female residents in the seven regions, the

number of primary treatments increased by 31.6% from 116.6 in 1990 to 153.4 in 1999 (see appendix 4.2).

Figure 4.4 shows the incidence of breast conservation surgery (BCS) and mastectomies (Mast) of invasive and in-situ breast cancers according to age group and year, as well as the figures per 100,000 women. The figure shows that the number of breast conservation surgeries in particular has increased, with a large increase in the early 1990s among women aged 50-69, and from 1998 among women aged over 70. This rise can be explained by the start (in 1990) and the extension (in 1998) of the nation-wide screening programme, which led to a major increase in the number of newly diagnosed small breast cancers. In 1999, 76.6% more breast conservation surgeries were carried out per 100,000 women than in 1990, and 5.6% more mastectomies.

The slight increase in the latter is completely attributable to the <50 age group, since after an initial increase, the number of mastectomies per 100,000 women aged both 50-69 and 70+ as of 1998 was lower than in 1990.

Data from the Dutch screening programme therefore does not confirm that mammography screening would lead to a greater number of mastectomies, as has been repeatedly suggested in recent years (Gøtzsche and Nielsen, 2006; Gøtzsche et al., 2009). After full national implementation of the screening programme among women aged 50-69, both the absolute number of mastectomies as well as the number of mastectomies per 100,000 women years is now lower than at the start of the study. The proposition regarding an increase in the number of mastectomies due to screening was based on Swedish breast cancer screening trials, which were conducted in a time and place in which mastectomies were still the predominant standard surgical treatment for breast cancer, and breast conservation surgery was only just beginning. In these screening trials, many women therefore underwent a mastectomy for breast cancers which, by today's standards, would be given standard consideration for breast conservation surgery.

Literature

Fracheboud J, SJ Otto, JAAM van Dijck, MJM Broeders, ALM Verbeek, HJ de Koning and National Evaluation Team for Breast cancer screening (NETB). Decreased rates of advanced breast cancers due to mammography screening in The Netherlands. Br J Cancer 2004; 91:861-867.

van der Heiden-van der Loo M, Bezemer PD, Hennipman A, Siesling S, van Diest PJ, Bongers V, Peeters PHM. Introduction of sentinel node biopsy and stage migration of breast cancer. EJSO 2006;32:710-4.

Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database Syst Rev 2006;(4):CD001877.

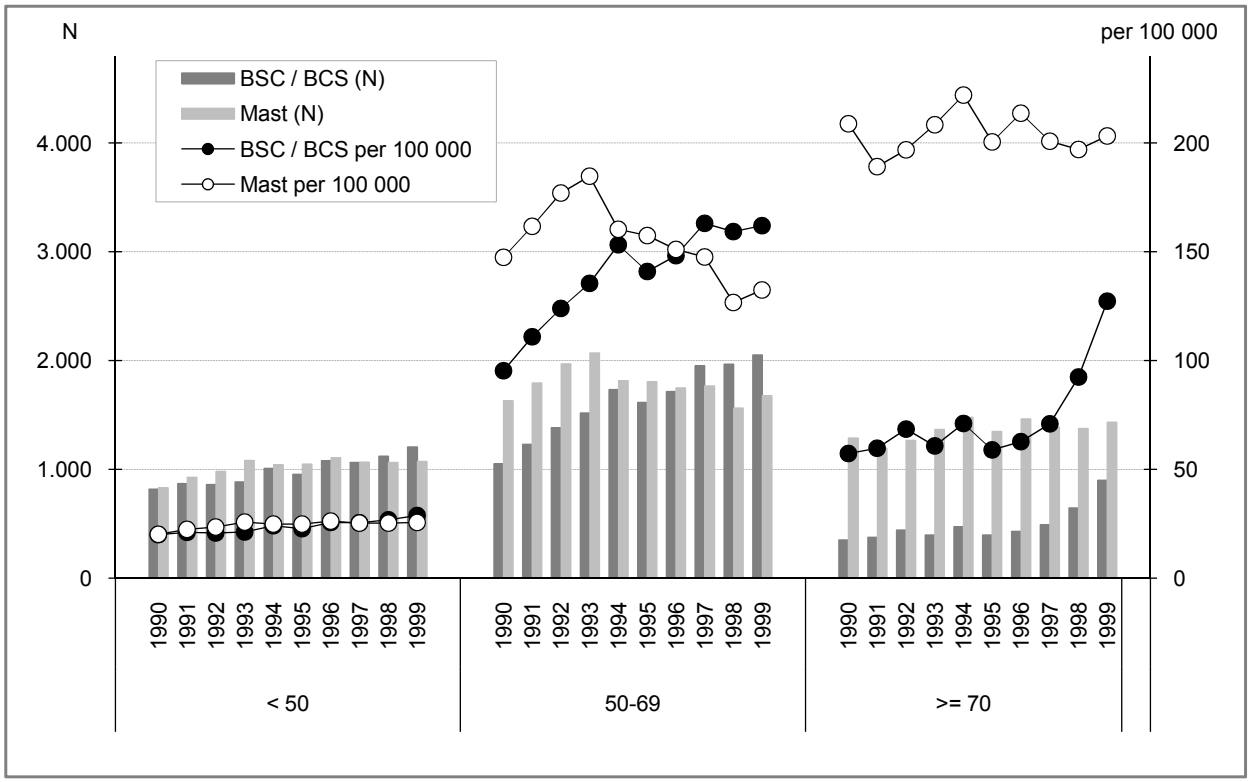


Figure 4.4 Numbers and rates per 100,000 woman-years of breast conserving surgery (BCS) and mastectomies (Mast) rates by age category, 7 regions 1990-1999

Gøtzsche PC, Hartling OJ, Nielsen M, Brodersen J, Jørgensen KJ. Breast screening: the facts—or maybe not. BMJ 2009;338:446-8(b86).

4.2 Trend in breast cancer mortality

In 1997, breast cancer mortality in the target group at that time showed a statistically significant decrease for the first time compared to the average in the three years (1986-1988) preceding the nation-wide screening programme (Otto et al., 2003). In the years after 1997, breast cancer mortality decreased further, albeit sometimes with considerable fluctuations. For example, mortality had decreased by 28.7% in 2007, but by 'only' 24.5% in 2008.

Table 4.1 shows the observed breast cancer mortality, the difference in the mortality rate and the percentage difference per year among women who were aged 55-74 at the time of death (source: Statistics Netherlands). Although the original target group was women aged 50-69, it is usual to evaluate breast cancer mortality once women are several years older (e.g. 5), since the effects of the screening programme are not immediately visible. This shift in time and age is also referred to as *lag-time*.

A problem with the interpretation of the trend in breast cancer mortality is the extension of the screening programme to age 75 in 1998. Figure 4.5a shows the observed breast cancer mortality rate compared to the anticipated rate that had been predicted in the past using model simulation (MISCAN), for situations both with and without a screening programme. These predictions were based on a screening programme for women aged 50-69, and therefore also provide the expected trend in breast cancer mortality among women aged over 69. The figure clearly shows that breast cancer mortality among women aged 75-79 after 2002 clearly dips below the expected rate (the bottom dotted line) in the situation with screening. The difference between the dotted line and the observed mortality rate is essentially the effect that can be attributed to the

Table 4.1 Age-adjusted breast cancer mortality rates (ESR) per 100,000 women aged 55-74 years from 1986/1988 until 2008

	Borstkankersterfte[1] ***Breast cancer mortality[1]*** **per 1000 (ESR)**	**Verschil** ***Rate difference***	**SD[2]**	**95% B.I.[3]** ***95% C.I.[3]***		**Verandering (%)** ***Change (%)***
1986-1988	105,2		3,2			
1989	102,9	-2,3	3,2	-8,6	4,0	-2,2%
1990	107,5	2,3	3,3	-4,1	8,7	2,2%
1991	105,0	-0,2	3,2	-6,6	6,1	-0,2%
1992	102,1	-3,2	3,2	-9,4	3,1	-3,0%
1993	101,1	-4,1	3,2	-10,3	2,1	-3,9%
1994	103,9	-1,3	3,2	-7,6	4,9	-1,3%
1995	100,2	-5,0	3,1	-11,1	1,2	-4,7%
1996	100,0	-5,2	3,1	-11,4	1,0	-4,9%
1997	98,2	-7,0	3,1	-13,1	-0,9	-6,7%
1998	92,1	-13,1	3,0	-19,0	-7,1	-12,4%
1999	97,8	-7,4	3,1	-13,4	-1,3	-7,0%
2000	89,7	-15,5	3,0	-21,4	-9,7	-14,8%
2001	85,3	-19,9	2,9	-25,6	-14,2	-18,9%
2002	85,7	-19,5	2,9	-25,1	-13,9	-18,5%
2003	82,1	-23,1	2,8	-28,6	-17,6	-22,0%
2004	78,3	-26,9	2,7	-32,2	-21,5	-25,5%
2005	78,0	-27,2	2,7	-32,5	-21,9	-25,9%
2006	80,5	-24,8	2,7	-30,1	-19,4	-23,5%
2007	75,0	-30,2	2,7	-35,4	-25,0	-28,7%
2008	79,4	-25,8	2,7	-31,0	-20,5	-24,5%

[1] Bron: CBS / *Source: Statistics Netherlands* LETB/*NETB,* 2009

[2] SD: standard deviatie / *SD: standard deviation*

[3] B.I.: betrouwbaarheidsinterval / *C.I.: confidence interval*

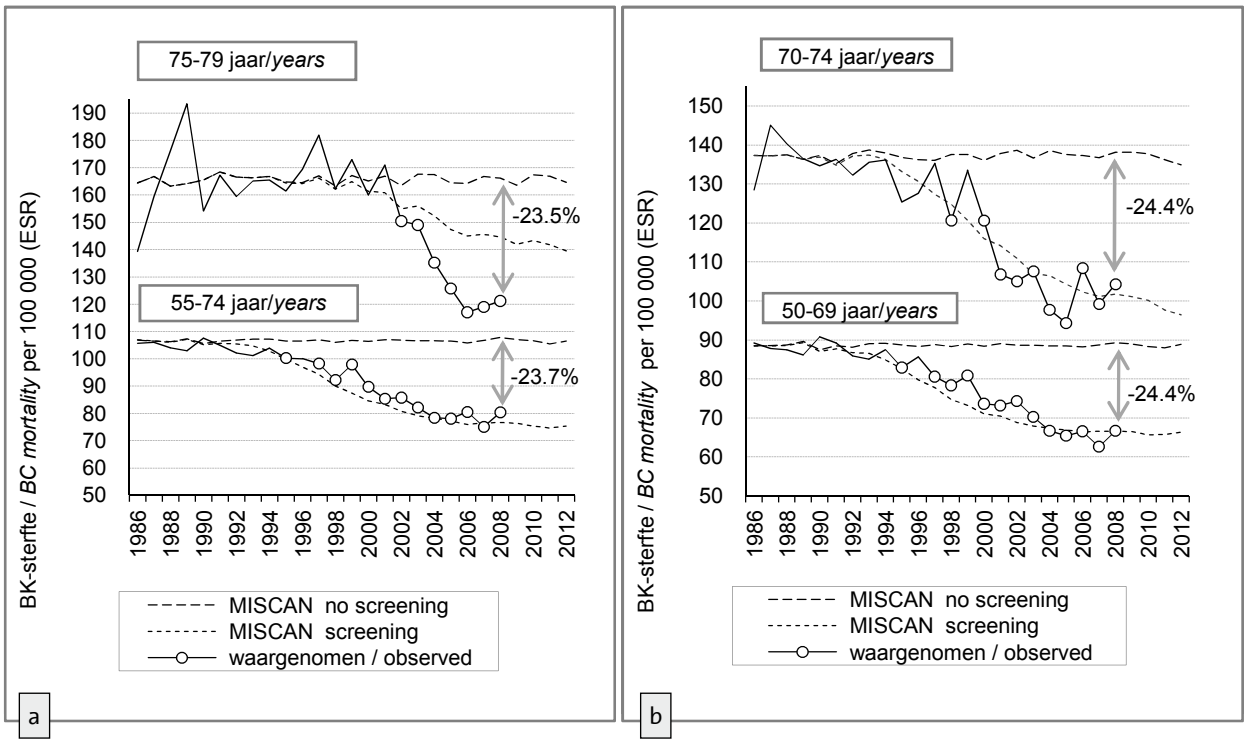


Figure 4.5 Age-adjusted breast cancer mortality (ESR per 100,000) as observed and predicted by MISCAN for the situation with screening and without screening, (a) women aged 55-74 and 75-79 years, (b) women aged 50-69 and 70-74 years (circle in observed line = significant difference)

screening examinations among older women. This is a consequence of extending the programme up to age 75. Among women aged 75-79, the long-term effects of breast cancer screening prior to the age of 70 (the dotted forecast line) are combined with the initial effects of screening from age 70 onwards. In 2008, breast cancer mortality among women aged 75-79 was 23.5% lower than the average in the years 1989-1988; around half of this decrease is the result of screening before the age of 70, and roughly half is the result of screening between age 70 and 75.
Figure 4.5b shows the same data as figure 4.5a, but for both the 50-69 and 70-74 age groups, i.e. without lag-time correction. The drop in breast cancer mortality reaches 24.4% in 2008 for both categories. The observed breast cancer mortality among women aged 70-74 corresponds to the anticipated rate in a situation involving a screening programme for women aged only 50-69. This means that the effect of the screening examinations given to these women from the age of 70 is not yet observable, and is better analysed in an age group that is five years older.

The fact that lag time plays less of a role in the group of women aged 50-69 is probably due to the large scope of this age group. Attendance among women aged 65 and over was relatively low during the implementation phase of the programme, and around 85% of women screened were aged under 65. If the positive effects of screening on breast cancer mortality appear within 5 years, then these last women will still fall within the 50-69 age group and the effects will therefore also manifest themselves in this category. However, after five years, most women in an age group with a five-year span are already part of the next age group, and then any effects within the original age group are only partially observable, if at all (results can be seen, however, from the screening examinations from the previous younger age groups).

It is regularly stated that a horizontal progression of breast cancer mortality in the absence of a screening programme would be unrealistic. After all, over the last two decades breast cancer mortality also dropped in the age groups that did not qualify for screening, as well as in countries where little or no screening takes place, primarily due to improved therapy and/or non-organised (opportunistic) mammography.
Supposing that breast cancer mortality would also drop somewhat without a screening programme, then the observed reduction in mortality would be overestimated. Yet we must keep in mind that breast cancer mortality among the target age group in the Netherlands showed a slight rise up until the late 1980s (Otto et al. 2003; Otten et al., 2008, see also section 4.3) and may have increased further without the influence of the above-mentioned factors.

This also indicates that the scope of the calculated mortality reduction is dependent on the reference point used for comparison (here, the average observed breast cancer rate between 1986 and 1988).

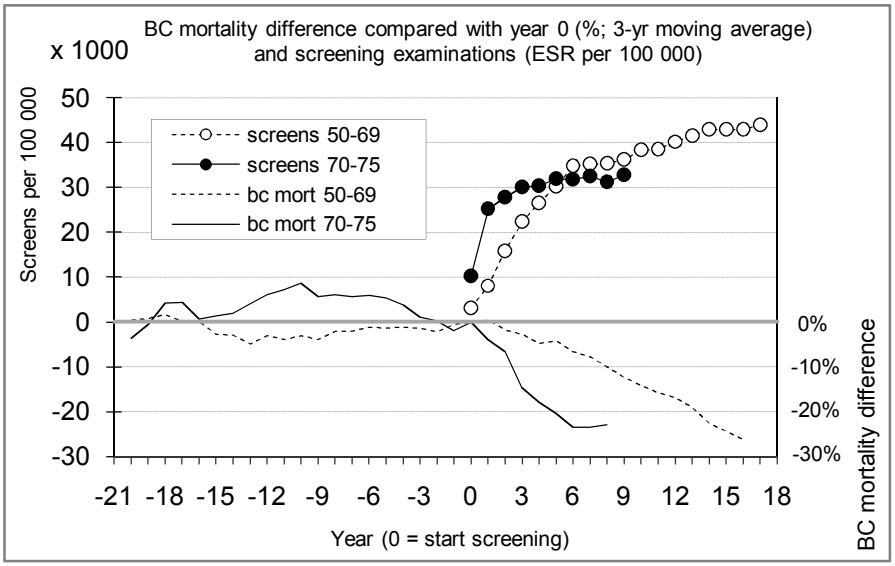


Figure 4.6
% Change of breast cancer mortality compared with first year of screening (year 0), and screen examinations per 100,000 women (age-agjusted 3-year moving averages)

If we were to choose a reference point further back in time, when breast cancer mortality was lower than in 1986-1988, the current observed drop in breast cancer mortality would be smaller. Various analyses of the long-term progression of breast cancer mortality clearly show that the start of the national screening programme caused a break in the trends among both women aged 50-69 and 70-75. For example, figure 4.6 shows that breast cancer mortality in the 20 years prior to either the initial year of screening in 1989 or the extension of the study in 1998 was less changeable than in the 5-15 years afterwards. Although it is true that breast cancer mortality dropped slightly among women aged 50-69 until 12 years before the programme commencing, after that it started climbing again. By contrast, breast cancer mortality among the older women first rose until around 10 years before these women became eligible for screening, and started dropping under the influence of screening examinations conducted prior to age 70. But from the first year of the screening programme (year 0 in the figure), both age categories display a sharp fall that within only a few years reaches a significantly lower level than in the previous 20 years. This drop is much more rapid among women aged 70-75 than in the 50-69 age group, due to both the aforementioned cumulative effect and also because the implementation took less time (around three-and-a-half years, instead of over seven), which is also reflected in the rapid increase in the number of screening examinations per 100,000 women.

MISCAN was recently updated, and used to simulate the actual development of the breast cancer screening programme including its extension to age 75. Chapter 5 describes the results and also presents the new forecasts for breast cancer mortality.

Literature

Otten JD, Broeders MJ, Fracheboud J, Otto SJ, de Koning HJ, Verbeek AL. Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975-2006. Int J Cancer 2008;123(8):1929-34.

Otto SJ, Fracheboud J, Looman CWN, Broeders MJM, Boer R, Hendriks JHL, Verbeek ALM, de Koning HJ and the National Evaluation Team for Breast cancer screening. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003;361:1411-1417.

4.3 The effects of the screening programme on breast cancer incidence and mortality in the Netherlands

This section is based on *Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality,* 1975-2006 (Otten JDM, Broeders MJM, Fracheboud J, Otto SJ, de Koning HJ, Verbeek ALM. Int.J.Cancer 2008;123:1929-34).

Introduction

The early detection and treatment of breast cancer is an important strategy for reducing mortality due to breast cancer. In addition to influencing mortality rates, the implementation of the breast cancer screening programme will also influence the incidence of breast cancer. Using data provided by Statistics Netherlands (breast cancer mortality from 1950 to 2006) and the Comprehensive Cancer Centres (breast cancer incidence 1975-2003), a trend study was conducted to research the effects of the implementation of the Dutch screening programme on incidence and mortality over the past three decades. Statistical computer programmes (join-point regression analy-

ses) can be used to determine whether there are any significant or other breaks in the trends, and if so, to calculate the moment in time when they take place.

Between 1975 and 2003, the number of women aged 35-84 with a newly diagnosed invasive breast cancer doubled, rising from 5,557 (180 per 100,000[1]) to 10,799 (238 per 100,000). The number of women with a non-invasive tumour actually tripled within the same period. In terms of mortality, the absolute number of deaths due to breast cancer increased from 2,256 to 2,742 between 1975 and 2006, yet the standardised[1] mortality rates per 100,000 women indicate a drop from 69.9 (1975) to 53.9 (2006).

Implementation of the screening programme

Since 1989, the Dutch breast cancer screening programme has offered women aged 50-69 a mammogram every two years. Building up the national screening network for this age group lasted until the end of 1997. In 1998 the upper age limit was raised to age 75; implementation for this age group lasted until 2001. All in all, the full implementation of the programme took over ten years. Table 4.2 contains a schematic for the implementation of the various age groups. To measure the effects on mortality, the age groups have been shifted up by 5 years. This is because any significant effect on breast cancer mortality cannot be expected until five years after the initial starting age of 50. The abbreviations 'Imp' for 'implementation' and 'Fc' for 'full capacity' relate to figures 4.7 and 4.8.

In this distribution (table 4.2), the ages of 49 and 69 constitute a 'contamination' problem. The 49-year-olds are invited for screens, but fall within the 'non-screening category' of women aged 35-49, and women aged 69 were generally not invited for their first screening examination until 1998, i.e. the start of the extension to include the 70-74 age group.

[1] Age-adjusted incidence/mortality according to the European standard population (ESR)

Incidence

Figure 4.7 shows the incidence among the various age groups. The youngest category (35-49) shows a turning point in 1989, i.e. from a consistent incidence to a slight increase. This rise is probably due to the screening of 49-year-olds in this group.

Four line segments can be identified in the 50-69 age group. After a slight (non-significant) rising trend between 1975 and 1989, incidence increased rapidly from 1989 until 1993. The period between 1993 and 1998 showed a slight (non-significant) drop, after which incidence rose again from 1998 until 2003. The strong rise in 1989 corresponds to the start of the screening programme. By 1993, 69% of the screening network was operational, after which the majority of women were therefore invited for a follow-up screen. At that point, the prevalence peak as a result of a large number of initial screening examinations had passed, after which the incidence again began to drop. The postponed invitations to women aged 69 most probably caused the rise after 1998 within this age group.

The 70-74 age group also shows four line segments: a slowly rising incidence from 1975-1992, followed by a (non-significant) decrease in the pre-screening period from 1992-1996, a large increase from 1996-1999, and ultimately a drop in incidence until 2003. A striking aspect is the drop in incidence during the pre-screening period prior to implementation (Imp2). This is a result of the screening in the previous 50-69 age group – the breast cancers otherwise prevalent among women aged 70-74 had already been detected by screening among the 50-69 age group. Upon implementation of screening among this group, it follows the same pattern as for the 50-69 age group; an initial increase, and a decrease at full capacity.

The same principle is also evident in the oldest age group (75-84). As a result of the detection of tumours among women aged 70-74, the incidence in the 75-84 age group decreased from 1999-2003.

Table 4.2 Implementation of the Dutch screening programme and the (different) age categories used for incidence and mortality rates

Leeftijdseffect incidentie *Age categories incidence*	Implementatie *Implementation screening* (Imp)	Volledige capaciteit *Full capacity* (Fc)	Leeftijdseffect sterfte *Age categories mortality*
35-49			35-44 en 45-54
50-69	1989 (Imp1)	1996 (Fc1)	55-64 en 65-74
70-74	1997 (Imp2)	2001 (Fc2)	75-84
75-84			

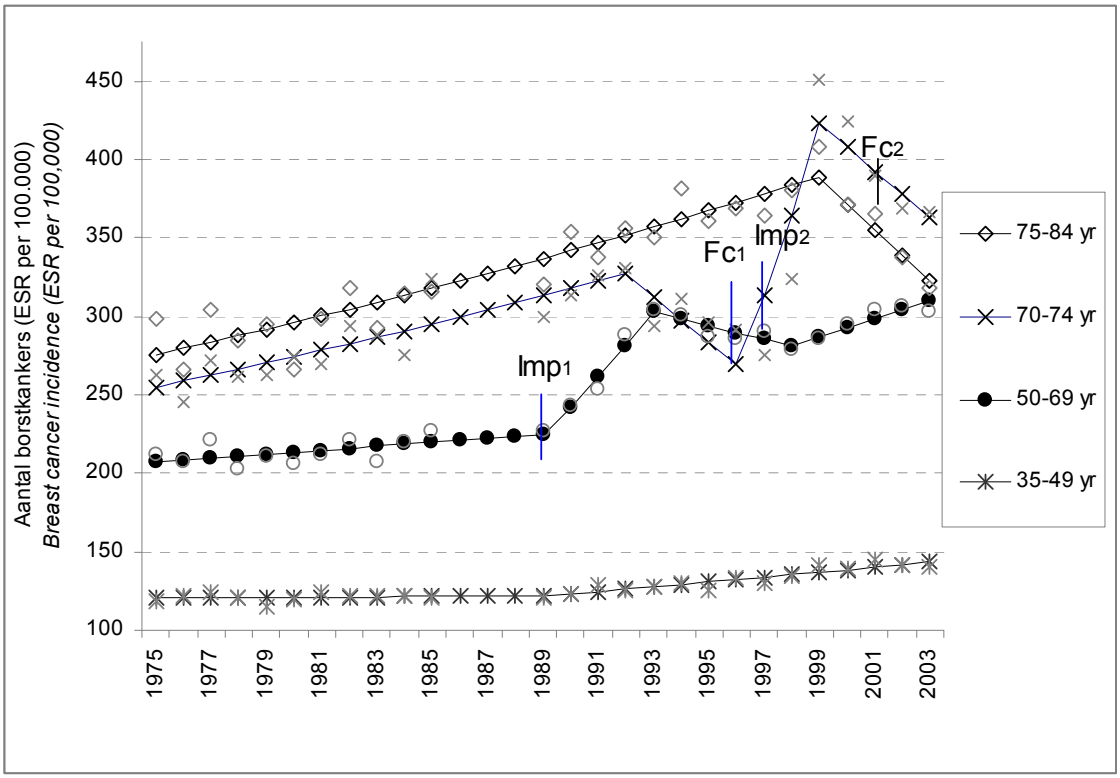


Figure 4.7 Age-adjusted (European standard population) invasive breast cancer incidence rates per 100,000 women aged 35-84 in the Netherlands. Incidence rates for the period 1987-1988 are incomplete.
Coverage population 50-69 years: Start implementation in 1989 (Imp1); percentage of targeted women annually invited: 11% (1990), 26% (1991), 48% (1992), 69% (1993), 77% (1994), 88% (1995) to full capacity in 1996 (Fc1)
Coverage population 70-74 years: Start implementation in 1997 (Imp2); percentage of targeted women annually invited: 26% (1998), 86% (1999), 91% (2000) to full capacity in 2001 (Fc2). Grey dots: observed incidence rates.

Breast cancer mortality

Figure 4.8 shows the mortality rates for various age categories, from age 35 up to and including age 84. Breast cancer mortality among women aged 44 and under remained stable until 1994, decreasing afterwards. Mortality increased between 1950 and 1971 in the 45-54 age group, and decreased from 1971-1980 and from 1992-2006. In the intervening period the mortality rate remained stable.

Breast cancer mortality decreased from 1994 among the age groups invited for screening (50-69 and 69-74), but increased slightly before that time. In the oldest group (75 and over), mortality remained stable until 2001, after which it, too, decreased significantly.

The drop in mortality is the most prominent among the age groups that took part in the screening programme (55-64, 65-74 and 75-84). Among these groups, breast cancer mortality seems to decrease around 5 years after the introduction of the screening programme.
The decrease in mortality is the result of screening in combination with therapy. For the youngest group, genetic counselling and the detection of high-risk families in the late 1990s may have also played a role.

The early decrease in breast cancer mortality in the 1970s among women aged 45-54 is very probably related to the application of adjuvant chemotherapy among pre-menopausal patients with positive axillary lymph nodes. The application of chemotherapy rose from 15% between 1975 and 1979 to 30% between 1980 and 1984. Adjuvant endocrine therapy (Tamoxifen) has been used among post-menopausal women with oestrogen-receptor-positive tumours and positive lymph nodes since the 1980s. Despite this application, breast cancer mortality rose among this age group (which was also the screening age group), and the drop in breast cancer mortality did not commence until the screening programme reached full capacity.

In summary

The introduction of the screening programme would seem to provide a significant and clear explanation of the rising incidence of breast cancer over the past three decades. Research into other explanations (such as changing risk factors) is currently underway. The drop in mortality is remarkable, very prominent among the target group of the screening programme and is observable from around five years after implementation of the screening programme commenced.

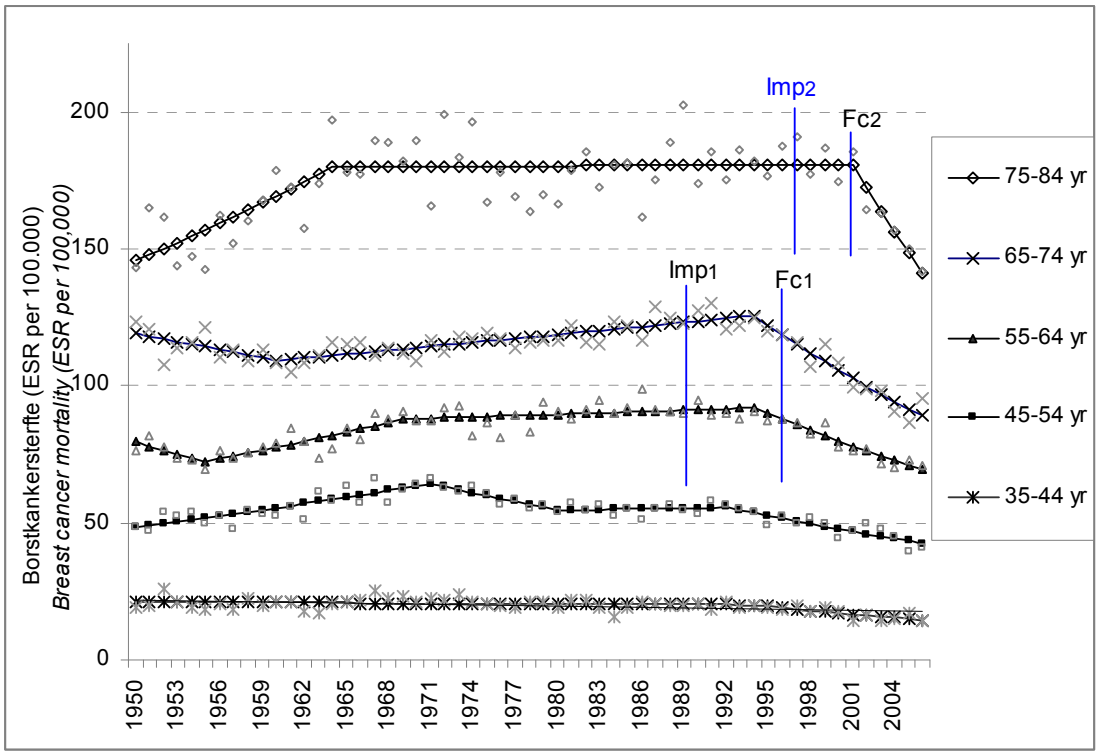


Figure 4.8 Age-adjusted (European standard population) breast cancer mortality rates per 100,000 women aged 35-84 in the Netherlands.
Coverage population 50-69 years: Start implementation in 1989 (Imp1); percentage of targeted women annually invited: 11% ('90), 26% ('91), 48% ('92), 69% ('93), 77% ('94), 88% ('95) to full capacity in '96 (Fc1).
Coverage population 70-74 years: Start implementation in 1997 (Imp2); percentage of targeted women annually invited: 26% ('98), 86% ('99), 91% ('00) to full capacity in '01 (Fc2). Grey dots: observed mortality rates.

4.4 Pilot study into the effects of the screening programme on breast cancer mortality using individual data

Introduction

Determining the effects of the breast cancer screening programme on breast cancer mortality is part of the continued evaluation of the programme. The main objective of this preventive measure is the reduction of breast cancer mortality among the female population. This anticipated effect is based on the positive results of foreign randomised trials, and pilot projects in the Netherlands. Implementation of a nation-wide screening programme commenced in the Netherlands in 1989. The evaluation of breast cancer mortality in the Netherlands is essential from a public health perspective, as well as the perspective of the individual female participants. If breast cancer mortality drops less than expected, the balance between positive and negative effects for the target group will need to be reviewed. The necessity of evaluating the effects is further emphasised by the discussion surrounding the benefits of mammography screening into breast cancer, that since 2000 has been repeatedly called into doubt by Scandinavian researchers.

Since 1997 there has been a decline in breast cancer mortality in the Netherlands, which has been shown to be not unrelated to the implementation of the breast cancer screening programme (Otto, 2003; Otten 2008). In 2008, this drop was equal to 26.3% among the 55-74 age group, compared to the year in which screening commenced. However, trend analyses at population (and sub-population) level are insufficient to determine the effects of the breast cancer screening programme on the related mortality rate. For this reason, a detailed analysis must be carried out into the relationship between screening history, treatment, mortality and cause of death at an individual level to enable an evaluation of the effects of the screening programme on breast cancer mortality. The case-control research approach is one method which is suitable for studying the effects of screening on breast cancer mortality during a screening programme that is already underway.

Required data

The starting point for a case-control study is a group of 'patients', in this case women with breast cancer who died as a result (cases), and a control group of women who have the same age (year of birth) as the corresponding case, who were breast cancer free before and invited for the relevant screening round, and who were alive on the date of death of the case

and free from breast cancer before diagnosis of the case. For each 'case', one or more control women are sought who 'match' in terms of certain features, e.g. age and the date of the first invitation. One condition is that the control women are still alive on the date of death of the case. Next, in each set of case-control women, the screening history of the cases (i.e., whether or not screening took place after the invitation) is compared to that of the controls.

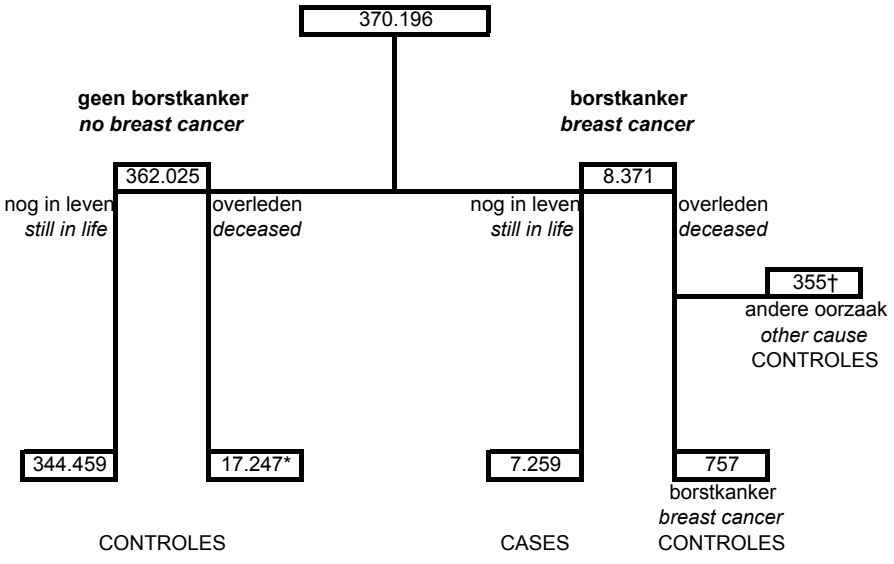
To carry out this case-control study, it is necessary to compare the individual screening data with the data from the regional cancer registers and, for those who died, with the causes of death register of Statistics Netherlands (CBS). The following data is collected from all women who were ever invited to take part in the breast cancer screening programme:

- Data from the municipal personal records database (GBA): date of birth, the number of the death certificate (or citizen service number, *burgerservicenummer*) of every woman aged 49 or over and, if deceased, also the relevant file number and date and place of death. This data is required for linkage with the causes of death register of CBS, if the death certificate number is not available.
- Screening data: data that indicates whether a woman who was ever invited ever took part in the screening programme in the relevant screening round.
- Breast cancer data: this data provides additional information on aspects such as the date of diagnosis, tumour stage and treatment of breast cancer among the women in question (also among women who never attended).
- Cause-of-death information on every deceased woman: the underlying cause of death and complications as registered at CBS.

Pilot

With the approval of the national Supervisory Board for Breast Cancer Screening programme Registers *(Commissie van Toezicht voor de Registraties Bevolkingsonderzoek Borstkanker,* October 2004) a pilot case-control study was initiated in collaboration with the screening region South-West (SBBZWN) and the Comprehensive Cancer Centre Rotterdam (IKR). The required data, in anonymised form, was sent to the CBS where it was combined with the cause-of-death register. The combined database, consisting of data on both deceased women and women who were at that time still alive, was then analysed by the CBS in accordance with privacy legislation. The research results generated by this database were released after having been tested by the CBS for confidentiality and the anonymity of individual elements.

Data eligible for inclusion in this pilot came from women who had received an official invitation to participate in the breast cancer screening programme up until the end of 2003, and who had made no objection to their data being exchanged. Women who died prior to the date of the initial screening invitation were also excluded, as were breast cancer patients whose date of diagnosis turned out to be prior to the date of the first invitation registered in the database of the SBBZWN. Figure 4.9 contains an overview of the number of women eligible for inclusion in the case-control study. These are all women who received their first invitation between 1990 and 2003.



* n=319 overleden vrouwen zijn geëxcludeerd; deze waren overleden a.g.v. borstkanker terwijl geen diagnose was geregistreerd bij het IKR / *n=319 excluded; deceased due to breast cancer, but not recorded in cancer registry.*

† inclusief n=2 waarvan doodsoorzaak onbekend / *2 women with unknown cause of death included.*

Figure 4.9
Flowchart of the number of records eligible for selection of cases and controls in the SBBZWN database (1990-2003)

Table 4.3 Distribution of the breast cancer among the cases by tumor stage and primary therapy

Opsporingsmethode *Method of detection*	Stadium *Stage*			Primaire behandeling *Primary therapy*					
				BSC BCS	Mast	Radio TH	Chemo Th	Horm Th	Overig/ onbekend *Other/ unknown*
		N	%	%	%	%	%	%	%
Screeningscarcinoom *Screen-detected*		226		45	47	0	4	1	3
	0	9	4	67	22	0	0	0	11
	I	68	30	66	34	0	0	0	0
	IIA	73	32	48	51	0	0	0	1
	IIB	46	20	24	72	0	4	0	0
	IIIA	5	2	20	80	0	0	0	0
	IIIB	4	2	0	75	0	0	25	0
	IV	13	6	8	0	0	46	15	31
	X	8	4	38	50	0	0	0	13
	missing	0	0						
Intervalkanker *Interval cancer*		261		27	51	0	14	5	3
	0	1	0	100	0	0	0	0	0
	I	27	10	52	48	0	0	0	0
	IIA	77	30	42	52	0	4	0	3
	IIB	77	30	14	78	0	6	1	0
	IIIA	16	6	25	75	0	0	0	0
	IIIB	15	6	33	27	7	33	0	0
	IV	39	15	5	8	0	49	26	13
	X	6	2	33	0	0	67	0	0
	missing	3	1	0	0	0	0	33	67
Nooit gescreend *Never screened*		268		18	35	0	22	16	8
	0	2	1	50	50	0	0	0	0
	I	26	10	50	38	0	4	8	0
	IIA	39	15	41	49	0	5	0	5
	IIB	55	21	24	67	0	4	4	2
	IIIA	15	6	0	87	0	7	0	7
	IIIB	42	16	10	33	0	45	10	2
	IV	79	29	0	0	1	38	42	19
	X	7	3	14	14	0	43	29	0
	missing	3	1	0	0	0	33	0	67

BSC: borstsparende chirurgie *BCS: breast conserving surgery*
Mast: mastectomie *mastectomy*
RadioTh: externe radiotherapie *external radiotherapy*
ChemoTh: chemotherapie *chemotherapy*
HormTh: hormonale therapie *hormonal therapy*

LETB/*NETB,* 2009

Of the 8,371 women who were at some point diagnosed with breast cancer (see figure 4.9), 1,112 had died, 757 as a result of breast cancer (the 'cases'). Of these 757 cases, 2 were excluded given the rather long interval (>4 years) between the date of the last invitation prior to the diagnosis, and the date of the diagnosis. Table 4.3 presents the tumour stages and initial therapy of the remaining 755 cases (women with breast cancer who died as a result). Of the women with a screen-detected carcinoma, 86% were discovered at stage II or lower. This figure is 70% for women with an interval carcinoma, whereas less than half of women who were never screened were diagnosed at these stages (47%). Fewer cancers are

Table 4.4 Characteristics of the cases (breast cancer deaths) and the controls

	Cases N=755	**Controls N=3.739**
Gemiddelde leeftijd bij / *Mean age at* (jaren */ years)*		
Eerste uitnodiging */ first invitation*	58,30 (49-75)	58,28 (49-75)
Uitnodiging vlak voor diagnose / *index invitation*	60,26 (49-75)	60,31 (49-75)
Diagnose / *diagnosis*	61,51 (49-79)	
Overlijden (cases)/einde observatieperiode (controles) *Death (cases) or end of observation (controls)*	64,44 (51-80)	67,17 (52-80)
Aantal uitnodigingen, N (%)* / *Number of invitations, N (%)**		
1	348 (46,1)	1.740 (46,5)
2	210 (27,8)	1.027 (27,5)
≥ 3	197 (26,1)	972 (26,0)

* aantal uitnodigingen binnen de observatieperiode / *number of invitations in the exposure period*

Table 4.5 Odds ratio, adjusted for age at index invitation, for the risk of breast cancer mortality

		Controles / *Controls*	
		Gescreened *Screened*	Niet gescreened *Not screened*
Cases	Gecreened *Screened*	1.878	476
	Niet gescreened *Not screened*	1.015	368
		2.893	844

odds ratio 0.44 (95% BI/CI 0.37 – 0.53)
gecorrigeerde/*adjusted* odds ratio 0.68 (95% CI 0.48 – 0.97)

discovered by screening at stage IV (6%) compared to women who were diagnosed in-between screening rounds (15%) or women with breast cancer who were never screened (29%). In all three groups, women with an advanced tumour were primarily treated with chemotherapy or hormonal therapy.

For each case, 5 suitable control women were selected from those available based on: vital status (i.e. still alive) on the date of death of the case, no breast cancer diagnosis prior to the case diagnosis, age at last invitation, year of birth, year of first invitation and the same number of invitations. The characteristics of the 755 and their matched controls are listed in table 4.4. This table shows that the cases and controls are quite comparable.

The preliminary analyses of this case-control study as presented in table 4.5 show that screening reduces the likelihood of death due to breast cancer by 56%. Once results are adjusted for the self-selection bias according to the method and data provided by Duffy et al., the reduction is limited to 32%. From this we can conclude that women's chances of dying of breast cancer were reduced by 32% from 1990-2003 in the SBBZWN region due to participation in screening. These results are consistent with the results from the randomised screening trials and the case-control studies from the pilot population studies.

Literature

Duffy SW, Cuzick J, Tabár L, Vitak B, Chen TH, Yen M, Smith RA. Correcting for non-compliance bias in case-control studies to evaluate cancer screening programmes. Appl. Statist 2002;51(Part 2):235-43.

Otten JD, Broeders MJ, Fracheboud J, Otto SJ, de Koning HJ, Verbeek AL. Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975-2006. Int J Cancer 2008;123(8):1929-34.

Otto SJ, Fracheboud J, Looman CWN, Broeders MJM, Boer R, Hendriks JHL, Verbeek ALM, de Koning HJ and the National Evaluation Team for Breast cancer screening. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003;361:1411-1417.

4.5 Preventing breast cancer mortality: which causes of death next?

Background

Screening allows breast cancer to be diagnosed at an early stage. In theory, early treatment and/or removal of the tumour mean that the mamma carcinoma cannot progress further in the body, preventing death due to the disease. Thanks to randomised and observational breast cancer screening studies, we know that periodic mammograms genuinely reduce the breast cancer mortality rate. The flip side of this success is that other life-threatening conditions are then given the chance to manifest themselves.

In this chapter we will provide a statistical picture of the shifts in the causes of death among the female Dutch population from 1989 until the end of 2007. After that, we devote some attention at individual patient level to the promptness of 'early' detection and the role played by tumour size and histological stage in the chances of survival of patients with a screen-detected carcinoma. Lastly we discuss the possible excess mortality among women who are diagnosed with breast cancer as a result of the screening programme.

Breast cancer mortality overtaken by lung-cancer mortality

The life expectancy for 50-year-old women was 32 years in 1989 (Statistics Netherlands, 2009). This life expectancy increased by two years in 2007, reaching 34 years. Among other reasons, this was due to the positive developments related to mortality due to acute myocardial infarction (table 4.6).

Although mortality remained almost unchanged in the 'all malignities' category, mortality due to breast cancer has decreased among the entire population, by as much as 20% over the past decade, and continues to drop (Netherlands Cancer Registry, 2009). Of all malignities, lung cancer forms an exception, moving in the opposite direction with a spectacular rise in mortality. In absolute terms, it is known that in 1950 only 167 women died of lung cancer. Gradually, this number has increased every year and is now at 3,500. Trend analyses have calculated that the mortality rate for lung cancer has now exceeded breast cancer mortality – see figure 4.10 (Verbeek en Otten, 2008).

Early detection of mamma carcinomas

At over 80%, participation in the screening programme is very high. In addition to high-level sensitivity of screening mammography, this means that many carcinomas are currently diagnosed at an early stage among women aged 50-74. Table 4.7, containing data material from the cancer register from the IKO-region, shows the tumour diameter of invasive cancers as determined by clinical pathological examination. Patients with a tumour diameter of less than 15 mm have an excellent prognosis, even if the histological malignancy grade is less promising (Tabár et al., 2000).

Alongside the tumour diameter and the status of the axillary lymph nodes, the histological malignity grade is important in determining the prognosis and the associated treatment plan. This is the reason why the Netherlands Cancer Registry began including the histological grade in its records. To determine the histological grade, the clinical pathologist measures the tubular formation, pleomorphism of the cell nucleus and the number of mitoses. Using the Elston & Ellis method, these factors determine the histological grade, categorised as grade 1 (favourable), grade 2 (moderate) or grade 3 (serious malignity) (Elston and Ellis, 1991).

Table 4.7 shows an overview of the tumour size and histological grade of the invasive breast cancers that were diagnosed among 2,365 patients in the IKO region aged 50-74 between 2002 and the end of 2006. The total number of registered patients is larger, yet

Table 4.6 Mortality in the Netherlands in $\frac{1989}{2007}$ per 100.000 women aged 50-74 year. Cell entries first specify mortality rates per 100,000 in 1989, and below in 2007

Leeftijd Age	Alle doodsoorzaken All causes of death	Alle maligniteiten All malign neoplasms	Borstkanker Breast cancer	Longkanker Lung cancer	Acute myocardinfarct Myocardial infarction	Diabetes Mellitus
50-54	344 299	191 181	65 47	24 50	20 11	9 4
55-59	536 438	287 264	82 61	37 69	48 15	17 7
60-64	816 676	394 391	99 73	54 109	87 25	34 12
65-69	1293 1011	525 504	115 84	57 116	172 56	68 22
70-74	2177 1662	704 692	136 99	50 167	355 93	98 52

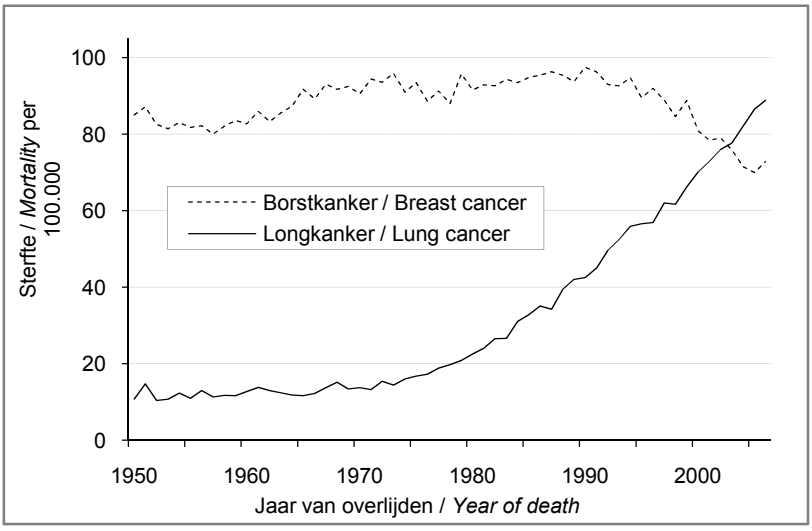


Figure 4.10
Age-standardised mortality rates for breast cancer and lung cancer among the age-group 50-74 year in the Netherlands

Table 4.7 Clinical pathological tumour size and histological grade in 2,365 patients aged 50-74 year with invasive breast cancer diagnosed in the IKO-region in 2002-2006.

Invasief carcinoom *Invasive carcinoma*			**Histologische graad** *Histological grade*							
PA-tumordoorsnede			**Graad / *Grade* 1**		**Graad / *Grade* 2**		**Graad / *Grade* 3**		**Totaal / *Total***	
<10 mm	19%	445	35%	154	45%	202	20%	89	100%	445
10-14 mm	23%	545	33%	182	44%	240	23%	123	100%	545
15-19 mm	22%	523	20%	105	48%	252	32%	166	100%	523
20-29 mm	22%	513	13%	65	43%	222	44%	226	100%	513
30+ mm	14%	339	10%	33	43%	144	48%	162	100%	339
Totaal / *Total*	100%	2.365	23%	539	45%	1.060	32%	766	100%	2.365

the histological grade was missing for 416 patients, and the tumour size for 208. Further division of the table according to screen-detected carcinoma, interval cancer or 'outside the screening programme' was not possible for the time being.
Forty-two per cent of the invasive carcinomas were diagnosed with the notably favourable tumour size of less than 15 mm in diameter (see the first two columns in table 4.7). Of the remaining 58% with larger invasive tumours (with a diameter of 15 mm or larger), two-thirds had a favourable histological grade of 1 or 2.

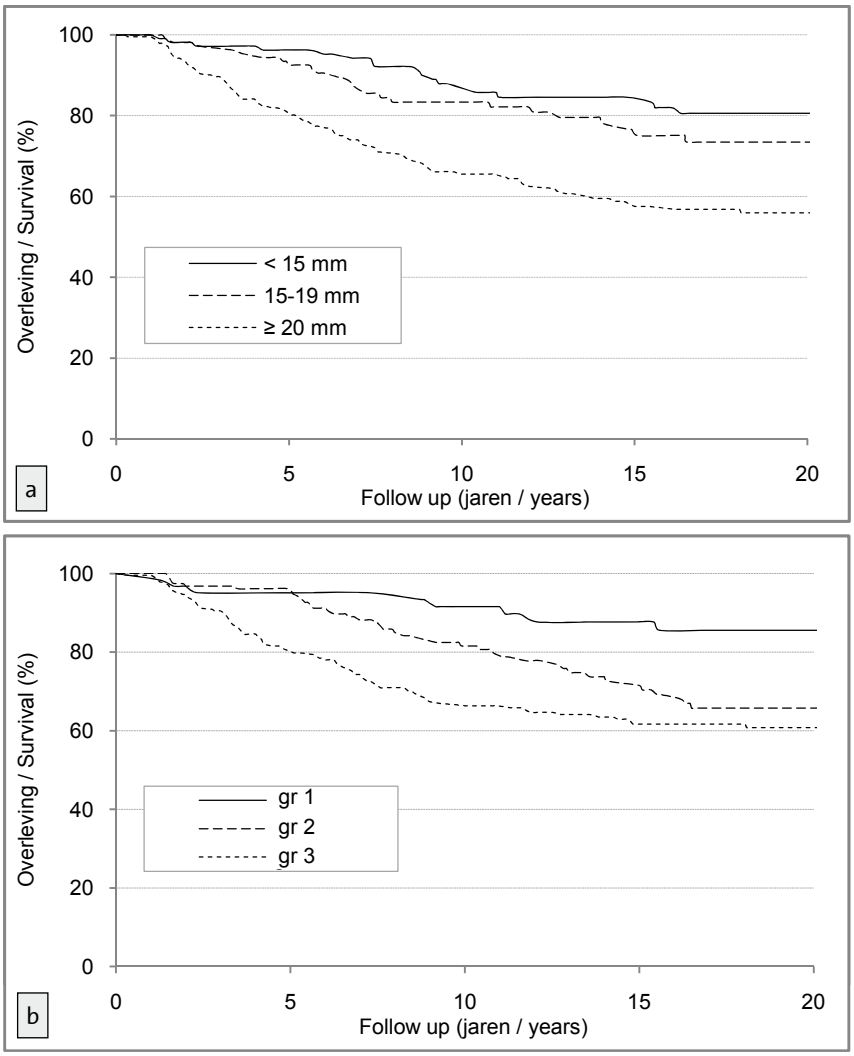
Prognostic features of mamma carcinomas detected early

The histological grade is now used worldwide when determining systemic adjuvant therapy. One difficulty in this respect is that determining the histological grade is subject to variation both within the same assessor and between assessors, which can probably be reduced by determining the mitotic activity index (MAI). Nijmegen pathologists Bult and Holland embarked on a prognostic study into the predictive capacity of the histological grade on chances of survival. In this way, a reproducibility study could also be carried out into the findings of Tabár et al. regarding a tumour diameter of less than 15 mm as a favourable factor for chances of survival, performed here within the setting of the so-called service screening on breast cancer.

Bult et al. examined 739 patients from Nijmegen who were successively diagnosed with a primary invasive mamma carcinoma (Bult et al., 2009). The median follow-up lasted for 12 years (range 0-28 years). In total 477 of the patients were not treated with adjuvant systemic therapy. This group was therefore involved in the study in order to estimate the 'pure' prognostic value of tumour size and histological grade. In figure 4.11, breast cancer specific survival curves have been generated according to the Kaplan & Meier method. The top panel shows the favourable chance of survival for patients with a tumour diameter of less than 15 mm. The lower panel gives the chances of survival according to histological grade.

Converting this result to the IKO figures for the entire patient population (see above) means 42% [with a diameter of less than 15 mm] + (58% [with a diameter of ≥ 15 mm] x 2/3 [with grade 1 or 2]) = 42% x 1 + (58% x 0.67) = 81% of the current breast cancer patients have an excellent prognosis *quoad vitam*.

Figure 4.11
Breast cancer specific survival for patients categorized to a: tumour size, and b: histological grade (gr)



Lastly, the Bult et al. study also showed that the histological grade measured according to the Elston & Ellis method (which is practised nationally and internationally) has the same prognostic value as the MAI index (not presented here).

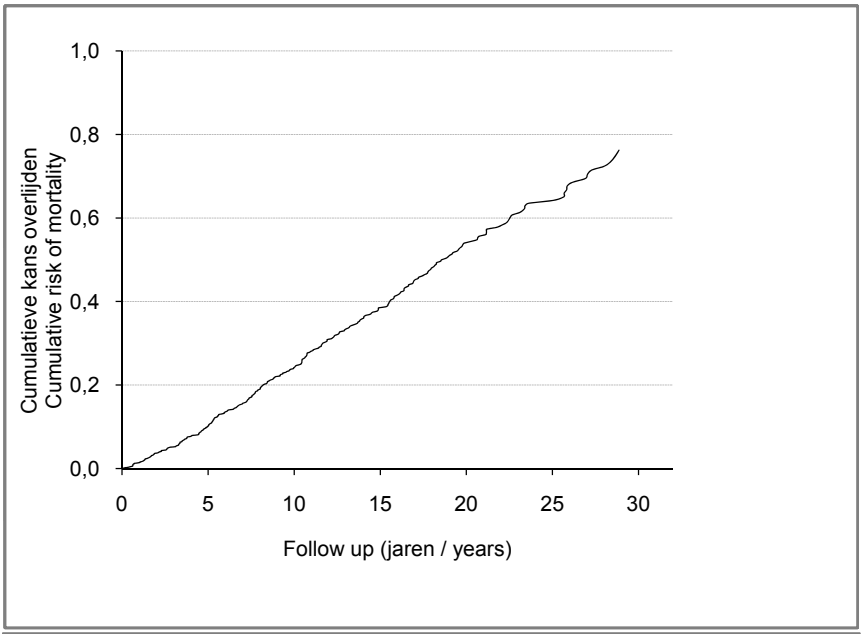
Shift in the causes of death

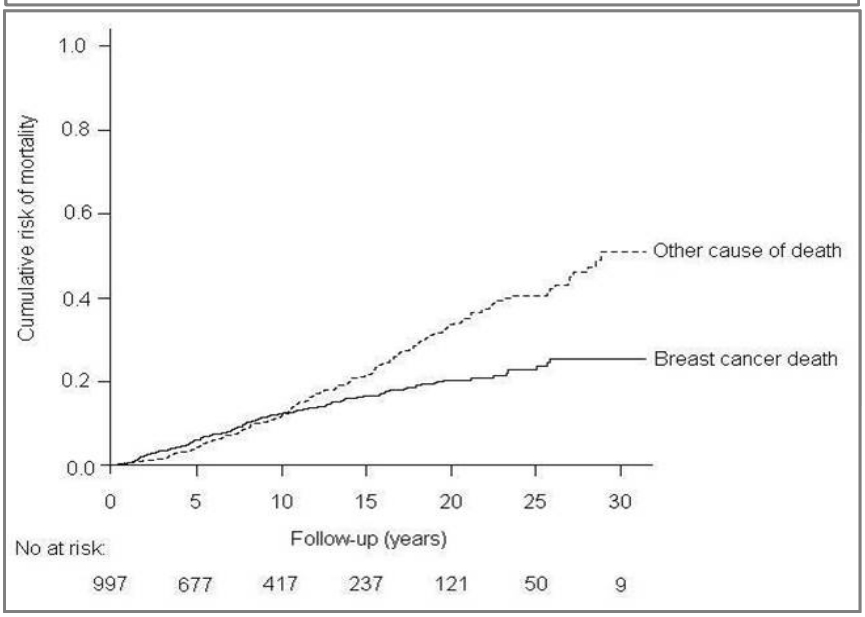
Nowadays, partly thanks to screening, mamma carcinoma that are discovered early have a favourable prognosis. This brings us to the third part of this section, i.e. the question of what breast cancer patients actually die of, and whether this pattern is the same as in the general population. Considerations here are the initial therapy, and etiological factors that are also risk factors for other diseases.

The favourable prognosis of breast cancer has led to views that treatment with 'radiation and systemic adjuvant chemotherapy, which are both expensive and toxic' is possibly too severe (Tabár and Dean, 2008). The radiation therapy used to treat breast cancer in the past could especially induce heart disease and lung cancer (Darby et al., 2005). Such causal links are suggested by randomised studies and have been shown by several observational follow-up investigations (Early Breast Cancer Trialists' Collaborative Group, 2000; Hooning et al., 2007).

The other consideration relates to the etiology of breast cancer. The appearance of breast cancer is explained by the interaction of a variety of risk factors, which involve the maturation of mammary gland tissue and endogenous oestrogen concentrations. The former concerns factors such as early menarche, number of children, and the mother's age when the first child was born. The second type of factor is linked to lifestyle, and is expressed in aspects such as inactivity, high calorie uptake, abdominal fat deposits and the presence of metabolic syndrome. It is precisely these risk factors that raise the question of whether breast cancer patients who survive the cancer are not also at risk of heart disease due to the same factors.

To find out more about this, a study was launched in 2008 with the data of all 997 Nijmegen breast cancer patients who were 50-74 years old when they were diagnosed with breast cancer through screening. The follow-up of this patient cohort was updated up until the end of 2006 regarding possible death, and if





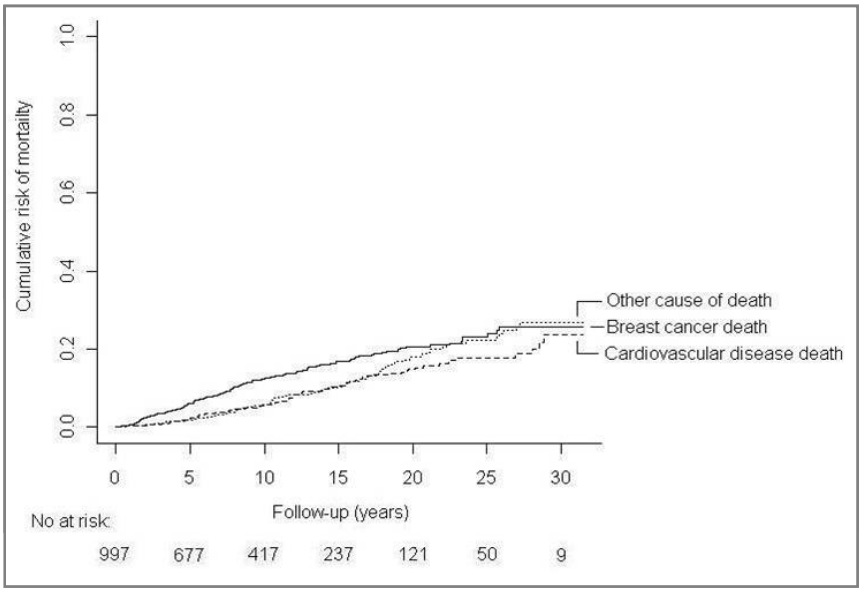


Figure 4.12
a: Cumulative risk of death;
b: risk of breast cancer death or death from other causes; and
c: risk of breast cancer death, death from cardiovascular disease or death from other causes, among 997 screen-detected patients from the Nijmegen screening programme

so, what the cause was. Keeping to the privacy legislation, the data was then analysed by Statistics Netherlands, the body that manages the cause-of-death register. Figure 4.12 shows the most salient initial results.

Panel A (figure 4.12) shows the duration of the (now lengthy) follow-up with a corresponding cumulative likelihood of mortality. From panel B can be deduced that, despite early detection by screening, there are still women who die of breast cancer. Ultimately the long-term likelihood of mortality must total 100%, as in panel C. Here, the likelihood of death due to breast cancer is higher than that due to cardiovascular disease.
The survival curves in figure 4.12 form the prelude to the analysis of possible excess mortality due to heart attack or lung cancer. To this end, the patients with breast cancer detected by screening were divided according to age within the calendar year of diagnosis, at which point the follow-up began, with the focus on deaths and their cause. The numbers of specific observed deaths were compared to the anticipated numbers of specific deaths based on the general age-specific death statistics from the same calendar years.
The observed number of deaths due to heart attack (n=35) divided by the anticipated number amounted to a statistically insignificant ratio of 0.88, leading to the conclusion that there is no excess mortality due to heart attack. For lung cancer, the ration of observed deaths (n=10) to anticipated deaths was equal to 2, again statistically insignificant. It is not known whether the breast cancer patients included a higher percentage of smokers than the control group, which in this case was the general population.

Concluding remarks

The Dutch population statistics from the past two decades show that mortality due to cancer has more or less remained the same, yet with the understanding that mortality due to breast cancer is decreasing and that of lung cancer is rising. Analyses using data from the Nijmegen breast cancer screening programme and from the cancer registry of the Comprehensive Cancer Centre East (which includes Nijmegen) support the previously demonstrated positive effects of screening. The register data also shows that nowadays, mamma carcinoma is often diagnosed at an early stage, measured according to tumour size and histological malignity grade. This results in a correspondingly favourable likelihood of surviving breast cancer. There does not seem to be any excess mortality due to cardiovascular disease.

Literature

Bult P, Manders P, Straatman HMPM, Tjan-Heijnen VCG, Beex LVAM, Hendriks JHCL †, Mravunac M, Leer JW, Verbeek ALM, Holland R. In primary breast cancer the mitotic activity yields similar prognostic information as the histological grade. A study with up to 28 years follow-up. Submitted.

Centraal Bureau voor de Statistiek: http://www.cbs.nl.

Darby SC, MCGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US-SEER cancer registries. Lancet Oncol 2005; 6: 557-565.

Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 2000; 355: 1757-70.

Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991; 19: 403-10.

Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 2007; 99: 365-75.

Nederlandse Kanker Registratie: http://www.ikcnet.nl.

Tabár L, Chen HH, Duffy SW, Yen MF, Chiang CF, Dean PB, et al. A novel method for prediction of long-term outcome of women with T1a, T1b, and 10-14 mm invasive breast cancers: a prospective study. Lancet 2000; 355: 429-33.

Tabár L, Dean PB. Thirty years of experience with mammography screening: a new approach to the diagnosis and treatment of breast cancer. Breast Cancer Research 2008; 10: 1-3.

Verbeek ALM, Otten JDM. Longkankersterfte gaat borstkankersterfte voorbij. Nu ook longkankerscreening? [Lung cancer overtakes breast cancer. Should lung-cancer screening be next?] Tijdschrift Kanker 2008; april: 5-9.

5

The effects of population-based breast cancer screening on the breast cancer incidence and mortality rates in the Netherlands

Validation and predictions using micro-simulation

The effects and costs of a population-based screening programme can be determined by comparing the life span of non-screened women to that of women who did receive screening. One way to do this is to use microsimulation. The MISCAN microsimulation model produces an accurate model of the incidence of breast cancer and screening results in the Netherlands. Previous models, however, did not incorporate the increase of the screening programme's upper age limit from 69 to 74 years. It was necessary to update the MISCAN breast cancer model with the increase of the upper age limit in order to continue to estimate the effects of the screening programme. This chapter presents the initial results of the new model. The model predictions are compared to the screening results as described in Chapters 2 and 3, and new predictions are presented with relation to breast cancer incidence and mortality rates for the coming decade.

MISCAN

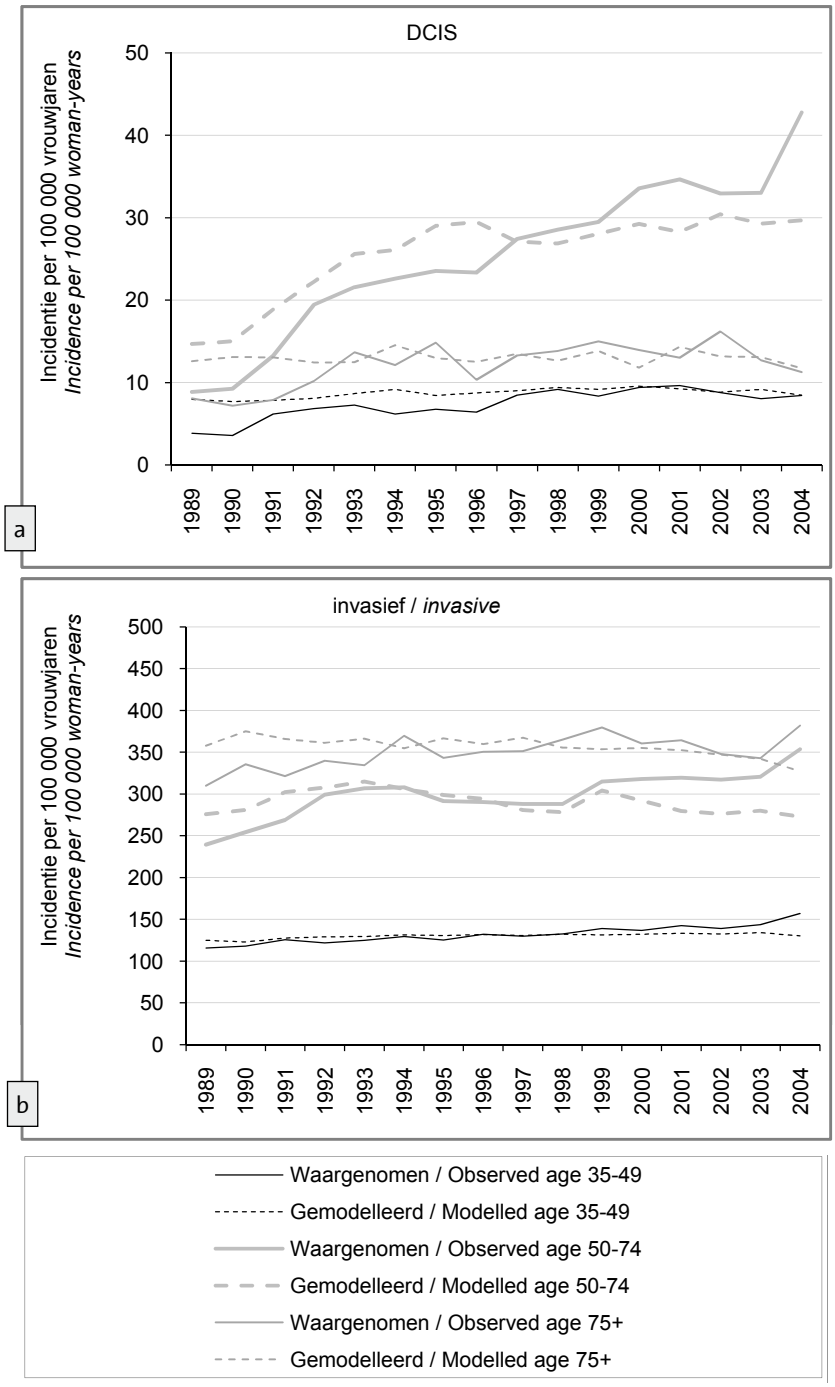
MISCAN was developed in the 1980s by the Public Health *(Maatschappelijke Gezondheidszorg)* department of the Erasmus MC in order to determine the impact of screening on breast cancer incidence and mortality (van Oortmarssen et al., 1990). After that time, the model underwent further developments for the evaluation of the Dutch breast cancer screening programme, as well as for other international screening programmes. The model is made up of two sections: one section that models the life span of women and the progression of breast cancer, and a section that simulates the screening programme. First of all, the 1989 female Dutch population is modelled, of which a certain number develop breast cancer. The natural course of breast cancer is modelled as a stepwise progression from pre-clinical screen-detectable T1A to pre-clinical T1B, T1C and T2+. T1A may or may not be preceded by screen-detectable pre-clinical DCIS. Cancers can become symptomatic and be diagnosed during any of these pre-clinical stages. Next, the screening programme is simulated. A certain percentage of the simulated population is screened and, depending on the characteristics of the screening programme, some women's tumours are diagnosed during the pre-clinical stage. The average duration of the tumour stages, the likelihood of transition between various pre-clinical stages, the sensitivity of screening, survival after diagnosis and increased survival rates following screen detection are then estimated using data from the Dutch screening programme and the Swedish breast cancer screening trials (Bjurstam et al., 2003; Nystrom et al., 2002; Tabar et al., 2000; de Koning et al., 1995). In the past, results from the Utrecht and Nijmegen population-based pilot screening programmes were also used.

The model described in this chapter was validated based on age and stage-specific incidence figures of breast cancers in the entire population that had been clinically diagnosed or detected by screening between 1989 and 2004. Age and stage-specific screen-detected and interval cancer figures from women screened between 1990 and 2004 were also used.

Breast cancer reduction in the entire population

Since 1989, the incidence of ductal carcinoma in situ (DCIS) and invasive breast cancer in women aged 35-49 has been rising (figure 5.1 a, b). Incidence of DCIS has also increased in women aged 75 and over, yet the incidence of invasive tumours has decreased since 1999. MISCAN somewhat overestimates the incidence of both DCIS and invasive cancer in both age groups until 1996; from 1999 onwards, the

Figure 5.1
Incidence of (a) DCIS and (b) invasive breast cancer between 1989 and 2004, in the age groups 35-49, 50-74 and 75 years and older, observed (solid lines) and modeled (dashed lines)



number of modelled invasive tumours is too small.
The rise in DCIS incidence among women aged 50-74 over the years is particularly striking. The incidence of invasive tumours has also increased, especially between 1990 and 1993, and between 1998 and 1999. This can be partially explained by the commencement of the screening programme in 1989/90, and its expansion in 1998. However, MISCAN has shown that the screening alone cannot explain the increased incidence. From 2000 on, the modelled incidence of DCIS and invasive cancer among women aged 50-74 was approximately 15% lower than the observed incidence. The modelled incidence remains low when the model assumes that the sensitivity of mammography increases significantly over time. We therefore assume that the rise in the incidence of breast cancer is also partially due to factors other than the screening programme, such as improved breast cancer diagnostics, a rise in opportunistic screening, greater attention to the possible symptoms of breast cancer, and/or a higher prevalence of breast-cancer risk factors over time. This could also explain the rising incidence in the age group not eligible for screening.
Despite the fact that the model overestimates the incidence of DCIS and invasive breast cancer until around 1996 and underestimates the incidence after 2000, MISCAN nevertheless gives a reasonable representation of the average incidence over the entire period from 1990-2004, therefore making it possible to use the model to estimate the risks and impact of the screening programme over this period.

Stage distribution of invasive breast cancer within the entire population

The stage-specific incidence of invasive tumours among women aged 35-49 was modelled successfully (figure 5.2 a, b, c, d).

Among women aged 50-74, the incidence of tumours with a diameter of 20 mm or smaller (T1a, T1b, T1c) increases with time up to 2004 (figure 5.2 a, b, c). In 2004, a drop is observed in T1a and T1b. MISCAN models the incidence of these tumours reasonably well. Among women aged 50-74, the incidence of T1c from 2000 onwards is underestimated by around 15%. The observed number of tumours larger than 20 mm (T2+) decreases from 1994 (figure 5.2 d). In MISCAN this drop is larger than observed, causing the predicted T2+ incidence from 2000 onwards to be lower than observed. Because the average incidence of T1c and T2+ among women aged 50-74 is modelled reasonably well between 1989 and 2004, the model can be used to estimate the effects of screening over this period.

Among women aged 75+, the incidence of all invasive tumours rises somewhat between 1989 and 2000 after which the incidence again seems to drop. Although MISCAN does not show the trends over time in the incidence of small invasive tumours, it does predict a drop in the incidence of T2+ from 1998 onwards. The average incidence of T1a, T1b and T2+ tumours is modelled correctly between 1989 and 2004. The model somewhat overestimates the incidence of T1c in this age group.

Stage-specific incidence of tumours within the entire population that were clinically diagnosed or detected by screening

The incidence of clinically diagnosed DCIS among women within the screening age group remains fairly constant (Figure 5.3a), whereas the incidence of clinically diagnosed invasive tumours decreases (figure 5.3b). The incidence of all tumours detected by screening increases. MISCAN provides a reasonably accurate simulation of the incidence of clinically diagnosed tumours and those detected by screening. Incidence according to tumour stage and the manner of detection was also well-modelled (not depicted).

Detection rates at initial and subsequent screening examinations

Breast cancer detection increases with time at both

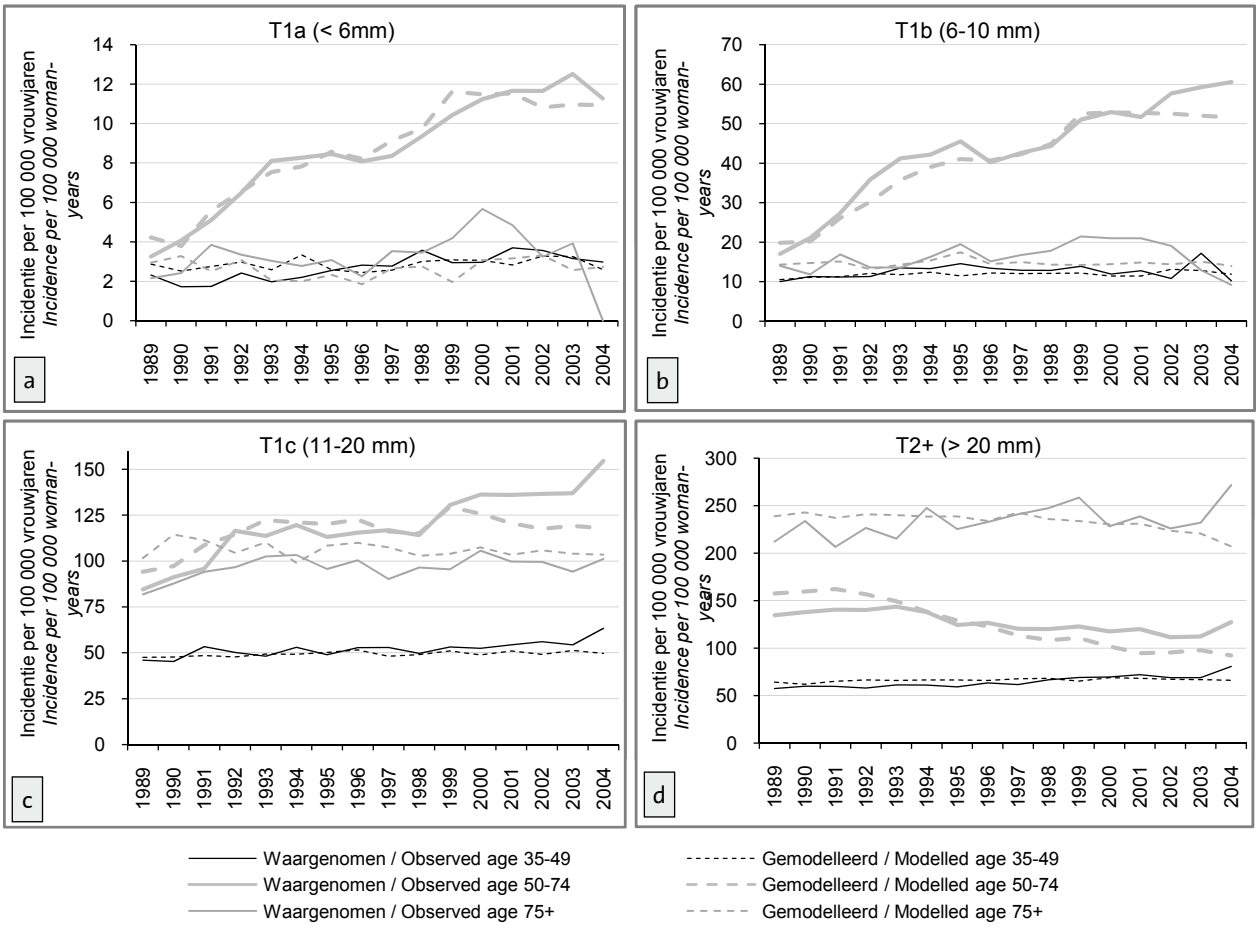


Figure 5.2 Stage-specific invasive breast cancer incidence between 1989 and 2004. (a) T1a, (b) T1b, (c) T1c, and (d) T2+, in the age groups 35-49, 50-74 and 75 years and older, observed (solid lines) and modeled (dashed lines)

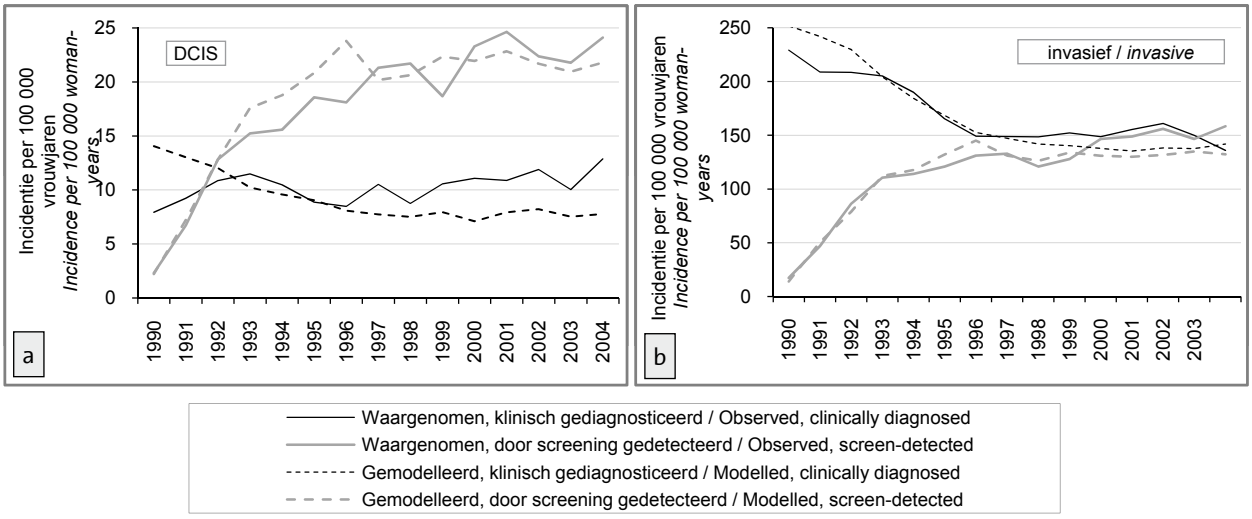


Figure 5.3 Incidence of clinically diagnosed (black lines) and screen-detected (grey lines) (a) DCIS and (b) invasive breast cancer between 1990 and 2004, in the age group 50-69, observed (solid lines) and modelled (dashed lines)

initial and subsequent screenings (figure 5.4 a, b). This can be partially related to improvements in referral policy, technical developments (e.g. digital mammography) and the expansion of the screening programme to include women aged 50-74. The rise can also be attributed to a non-screening-related increase in the incidence of breast cancer, also observable in women aged under 50 (see also figure 5.2).

The detection of DCIS and T2+ is modelled reasonably accurately. The observed detection of T1, on the other hand, is in initial screening rounds higher, and in subsequent rounds lower than predicted by the model. The difference between the observed and modelled detection figures can mostly be attributed to T1b and T1c tumours (not depicted). It is possible that the average duration of the pre-clinical stage or the sensitivity of mammography was not modelled optimally. The assumption that incidence will not increase.

Because the combined detection figures for initial and subsequent screenings are modelled accurately (not depicted), we do not expect the poor fit of T1 tumours to have any impact on the predicted mortality or overdiagnosis.

Interval cancers in the screened population

Simultaneously with the commencement of the breast cancer screening programme, interval cancers increase with time until 2000 (figure 5.5). The number of interval cancers modelled by MISCAN is a little too high. One possible explanation is that the model slightly overestimates the growth rate of preclinical tumours, or slightly underestimates the sensitivity of mammography. Another possibility is that

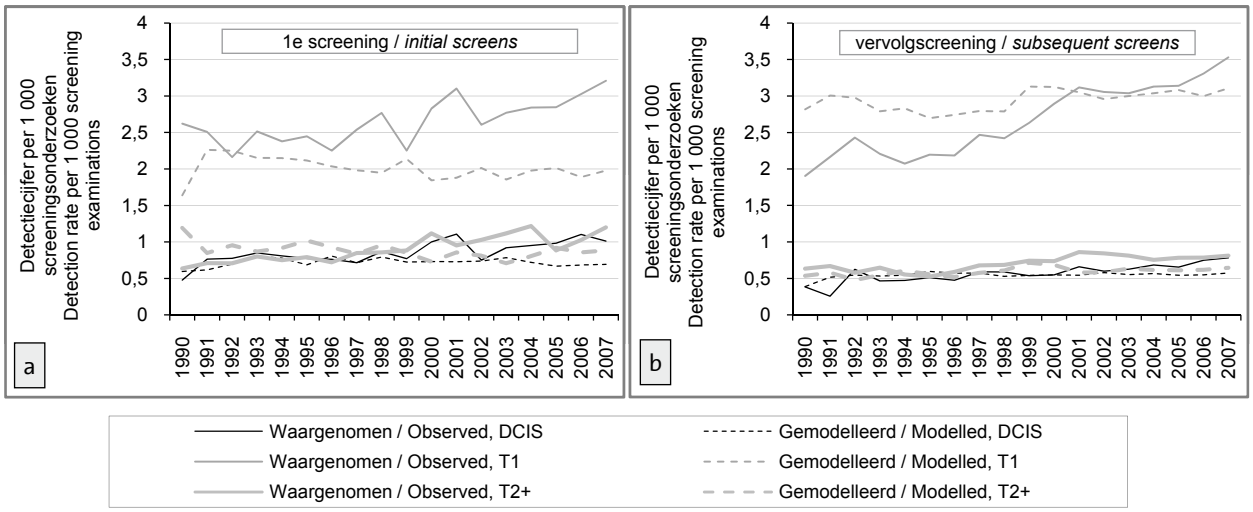


Figure 5.4 Stage-specific breast cancer detection rates among 49-74 years old women between 1990 and 2007. (a) First screening examinations and (b)subsequent screening examinations, with an interval <2.5 years from the previous screening examination. Observed (solid lines) and modelled (dashed lines)

interval cancers are not always registered as such. The registration of interval cancers is incomplete from 2000 onwards, meaning that the data must be interpreted with some caution.

Model parameters

Based on the incidence figures and screening results, we estimate that a pre-clinical screen-detectable DCIS has a 61% chance of developing into an invasive cancer in the absence of a screening programme, and a 2% chance of going into regression. The average duration of pre-clinical breast cancer at the age of 50 is estimated at 4.3 years (on average 2.1 years non-invasive, 2.2 years invasive). For women aged 75, these figures are 2.1 years for non-invasive and 3.9 years for invasive breast cancer. The sensitivity of mammography in 1990 is estimated at 80% for DCIS, 47% for T1a, 62% for T1b, 90% for T1c, and 95% for T2+.

Predicted breast cancer incidence within the entire population

Because MISCAN in general models the average stage and age-specific incidence of clinical and screen-detected breast cancer as well as the detection and interval cancer figures in the screening programme reasonably accurately, it is possible to estimate the effects of screening between 1990 and 2004. However, figure 5.1a showed that the modelled breast cancer incidence was lower than the observed incidence in 2000; the difference for women aged 50-74 was around 15%. Yet we do not expect the underestimated number of predicted breast cancers to have any impact on the estimated screening risks, such as overdiagnosis.

MISCAN has shown that the difference between the observed and the predicted incidence cannot be explained by the screening programme. Significantly raising the test sensitivity in MISCAN did not provide a better model fit. This means that an explanation for the difference must be sought elsewhere, for example, improved breast cancer diagnostics, increased breast cancer awareness, and/or a higher prevalence of breast cancer risk factors. The research by Louwman et al. has shown that, during the period prior to the introduction of the screening programme, the incidence among women in all age groups increased by around 1.5% per year (Louwman et al., 2008). If MISCAN assumes that the same trend continues between 1990 and 2005, the incidence in a situation with screening is correctly simulated (not shown).

If the rise in the number of breast cancers is indeed not attributable to screening, the simulated incidence in a situation without screening will be underestimated by the same amount as in a situation with screening. The estimated overdiagnosis (i.e., the number of extra breast cancers detected by screening in comparison to a situation without screening, minus the number of breast cancers prevented by screening later in life compared to a situation without screening) will therefore stay the same. It is for this reason that the long-term risks of screening can be estimated using the model as described in the sections above.

We assumed that the current screening programme will continue to operate unchanged: every two years, women aged 49-74 are invited for screening. We also assumed that the attendance rates and the sensitivity of mammography will remain the same as in 2004, the last year in which the model was validated. In practice, this last assumption is probably too pessimistic, because factors such as technological development (e.g. digital mammography) will cause mammogram sensitivity to increase. The con-

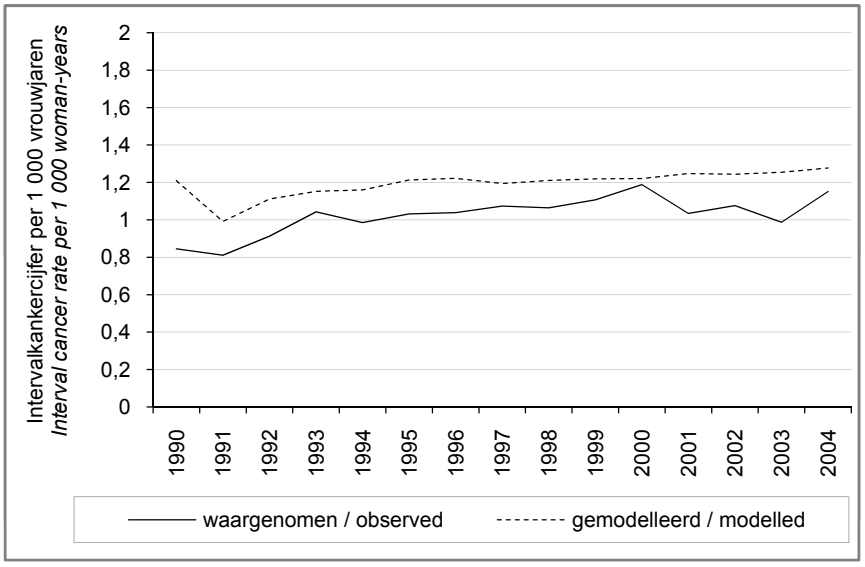


Figure 5.5
Interval cancers among women aged 49-74, 0-23 months after the previous screening examination, observed (solid lines) and modelled (dashed lines) per 1,000 women years, 1990-2004

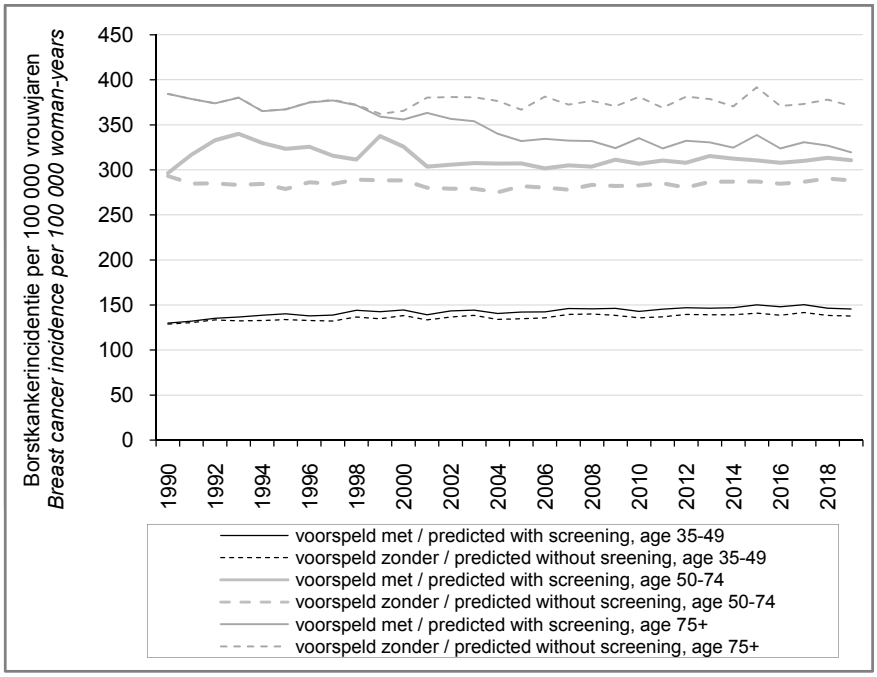


Figure 5.6
Predicted breast cancer incidence per 100,000 women years, for women aged 35-49, 50-74 and 75-100, in the presence (solid lines) and absence (dashed lines) of screening, 1990-2019

sequences of increased test sensitivity due to digital screening will be discussed in a subsequent section.

Figure 5.6 compares the modelled breast cancer incidence in a situation with screening to the expected incidence without screening. From the outset of the screening programme, breast cancer incidence among women aged 50-74 in a screening situation was higher than in a hypothetical situation without screening. From 2001 onwards, the difference between the situations with and without screening remained constant at around 10%. Among women aged 75 and over, breast cancer incidence decreases from 2000, to an incidence equal to that of women aged 50-74. In 2010, twenty years after the start of the screening, the drop in breast cancer incidence among women in this age group reaches its maximum, and is around 12.5% lower than the incidence in a situation without screening. Based on this data, we estimate that the risk of overdiagnosis in the Dutch population compared to the non-screened population is 2% - 5%. This calculation is based on a stable screening situation, in which the proportion of initial and subsequent screenings with a long interval remains constant. The Dutch screening programme has a steady state from 2002 onwards (see chapter 3).

Predicted breast cancer mortality within the entire population

In 2004, the reduction in breast cancer mortality among women aged 55-79 was 25.5% (figure 5.7). Based on the current screening results, we predict that the drop in mortality among women aged 55-79 will continue to decrease to 30.5% in 2019. After that, breast cancer mortality is not expected to drop much further. The predicted drop corresponds to previous model predictions and the results of the Swedish screening trials. Because the lower number of breast cancers from 2000 onwards cannot be traced back to screening, breast cancer mortality is underestimated somewhat in situations both with and without screening. For this reason, the relative reduction in mortality due to screening will not change. Because the model underestimates the incidence of breast cancer from 2000 onwards, MISCAN will also underestimate the absolute number of breast cancer deaths. However, breast cancer mortality seems to be estimated correctly in figure 5.7. We suspect that the reason why the current model still predicts breast cancer mortality correctly is that mortality also drops due to factors outside of the screening programme (e.g. improved treatment options, adjuvant therapy). Because this is not yet included in the current MISCAN model, mortality is probably overestimated, which most likely cancels out the underestimated incidence of breast cancer.

Digital mammography

In our predictions regarding breast cancer incidence and breast cancer mortality, we assumed that the characteristics of the current screening programme would not change over time. In practice, this will not be the case. Digital mammography was introduced in three screening regions in 2004, and it is expected that digital screening will be used nation-wide as of mid-2010. Chapter 3 described how the referral and detection rates are significantly higher for digital screening than for analogue screening. The results from the first three years of digital screening (2004-2006) showed that the rise in detection rates is primarily due to increased DCIS detection. Digital

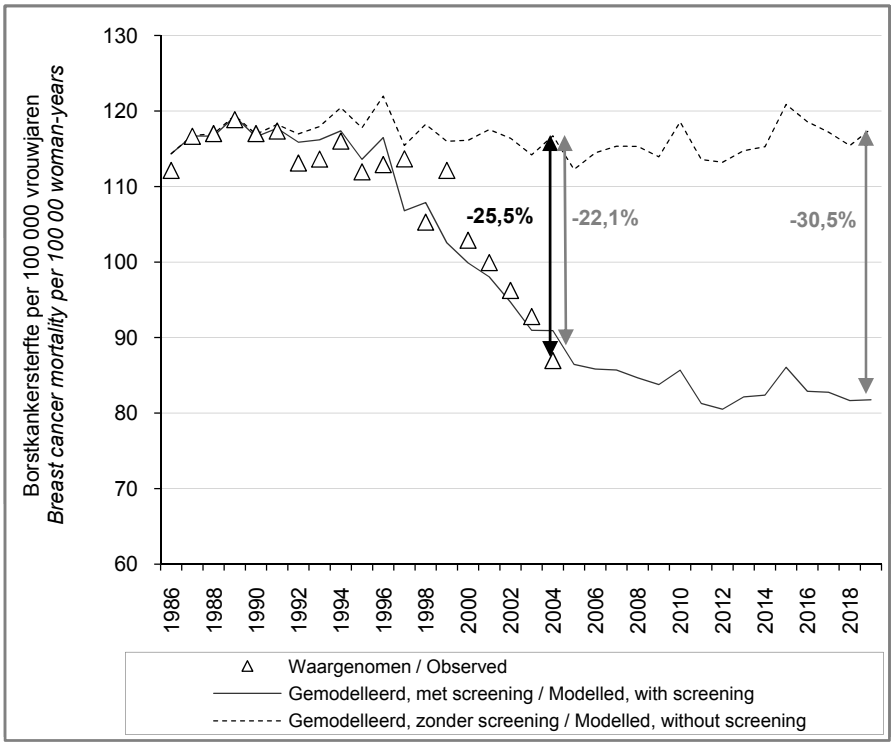


Figure 5.7
Breast cancer mortality per 100,000 women years in women aged 55-79, observed (triangles) and predicted in a situation with screening (solid lines) and without screening (dashed lines), 1986-2019

screening detects 82% more DCIS than analogue screening. If the detection of DCIS can prevent cancers from developing into an invasive stage, such an increase could prevent more breast cancer deaths in the future. On the other hand, increased detection of DCIS tumours that are growing either slowly or not at all could lead to an increase in the number of overdiagnosed tumours. Comparative studies between digital and analogue mammography provide no unequivocal answer to the question of whether the increase in DCIS relates primarily to slow-growing (grade 1) or fast-growing types (grade 3) (Pisano et al., 2005; Vigeland et al., 2008; Rosselli del Turco et al., 2007).

The effects of the introduction of digital screening on the population were determined using MISCAN. The increased detection of DCIS can be attributed to increased referral figures and the increased test sensitivity of a digital mammogram. The increased contrast possibilities especially allow the microcalcifications associated with DCIS and small invasive tumours to be detected more effectively. In MISCAN, this is modelled by increasing the sensitivity of mammography in the detection of DCIS. Based on the 2004-2006 detection rates, the sensitivity was raised from 80% (analogue screening) to 98%. Because between 2004 and 2006 the detection of invasive tumours through digital screening was not so very different from analogue screening, we assumed in the model that the sensitivity for the detection of invasive cancer would be no different from analogue mammograms. The most recent digital screening results (2007) indicate that the detection of invasive tumours smaller than 1 cm also increased compared to analogue screening. This will also cause the model predictions to be slightly under the mark. The consequences of increased detection of invasive tumours will be determined in more detail in the future.

In order to be able to compare the effects and risks of increased DCIS detection using digital screening to those using analogue screening, we assume in MISCAN that from 1990 onwards women aged 50-69 are screened once every two years (as is the case for analogue screening). From 1998 onwards, the screening programme was expanded to include women aged 70-75. Attendance figures for digital screening are no different to those for analogue screening. Using this model, we predicted that breast cancer mortality can be reduced by a further 1% - 2% using digital screening. The predicted decrease in breast cancer mortality among women aged 55-79 in 2019 is 30.5% for analogue screening and 30.8% for digital screening (table 5.1). Digital screening will cause the number of overdiagnosed tumours to increase by around 5%, to a maximum total of 5.1% of the total expected number of tumours diagnosed in the population in 2004 (for analogue screening, the maximum figure is 5.0%).

Literature

Bjurstam N, Bjorneld L, Warwick J, et al. The Gothenburg Breast Screening Trial. Cancer. May 15 2003;97(10):2387-2396.

de Koning HJ, Boer R, Warmerdam PG, Beemsterboer PM, van der Maas PJ. Quantitative interpretation of age-specific mortality reductions from the Swedish breast

cancer-screening trials. J Natl Cancer Inst. Aug 16 1995;87(16):1217-1223.

Louwman WJ, Voogd AC, van Dijck JA, Nieuwenhuijzen GAP, Ribot J, Pruijt JFM, et al. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: a long-term population-based study in southeastern Netherlands. Cancer Causes Control. Feb 2008;19(1):97-106.

Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet. Mar 16 2002;359(9310):909-919.

van Oortmarssen GJ, Habbema JD, van der Maas PJ, et al. A model for breast cancer screening. Cancer. Oct 1 1990;66(7):1601-1612.

Pisano ED, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med 2005;353(17):1773-83.

Rosselli del Turco MR, Mantellini P, Ciatto S, Bonardi R, Martinelli F, Lazzari B, et al. Full-field digital versus screen-film mammography: comparative accuracy in concurrent screening cohorts. AJR Am J Roentgenol 2007;189(4):860-6.

Tabar L, Vitak B, Chen HH, et al. The Swedish Two-County Trial twenty years later. Updated mortality results and new insights from long-term follow-up. Radiol Clin North Am. Jul 2000;38(4):625-651.

Vigeland E, Klaasen H, Klingen TA, Hofvind S, Skaane P. Full-field digital mammography compared to screen film mammography in the prevalent round of a population-based screening programme: the Vestfold County Study. Eur Radiol 2008;18(1):183-91.

Table 5.1 Breast cancer mortality and over-diagnosis at screen-film and digital mammography

Analoge mammografie/ *Screen-film mammography*	
Maximale voorspelde afname in borstkankersterfte bij 55-79 jarige vrouwen, ten opzichte van de voorspelde borstkankersterfte zonder screening in 2019 *Maximal predicted reduction in breast cancer mortality in women aged 55-79, relative to the predicted breast cancer mortality without screening, in 2019*	-30,5%
Maximale fractie overgediagnosticeerde tumoren van het totale verwachte aantal gediagnosticeerde tumoren in de populatie, 2004 *Maximal fraction of overdiagnosed breast cancers of the total expected number of diagnosed breast cancers in the population, 2004*	5,0%
Digitale mammografie/ *Digital mammography*	
Maximale voorspelde afname in borstkankersterfte bij 55-79 jarige vrouwen, ten opzichte van de voorspelde borstkankersterfte zonder screening in 2019 (+ extra voorkomen sterfgevallen (%) ten opzichte van analoge screening) *Maximal predicted reduction in breast cancer mortality in women aged 55-79, relative to the predicted breast cancer mortality without screening, in 2019 (+ extra prevented breast cancer deaths (%) compared to screen-film mammography)*	-30,8% (+1,0%)
Maximale fractie overgediagnosticeerde tumoren van het totale verwachte aantal gediagnosticeerde tumoren in de populatie, 2004 (+ extra overdiagnose (%) ten opzichte van analoge screening) *Maximal fraction of overdiagnosed breast cancers of the total expected number of diagnosed breast cancers in the population, 2004 (+ extra overdiagnosis (%) compared to screen-film mammography)*	5,1% (+2.7%)

6

Costs 2005-2007

6.1 National cost trends for the breast cancer screening programme

Since 2005, various substantive and organisational changes have been taking place that influence the screening programme in the mid-to-long term.

- A start has been made on preparing for and implementing the conversion of the screening programme to digital screening during the 2007-2011 period.
- The prevention budget in the Netherlands was transferred from being included in the Exceptional Medical Expenses Act (AWBZ) to the budget of the Ministry of Health, Welfare and Sport (VWS) The management, planning and monitoring of the screening programme was transferred in 2006 from the Health Care Insurance Board (CVZ) to the National Institute for Public Health and the Environment (RIVM)
- The decision was also made to streamline the organisation of regional management at the same time as the implementation of digitisation. The number of regions was reduced from nine to five, and they were combined with the regional organisation of the population-based screening programme for cervical cancer (table 6.3).

Changes to the costs of the screening programme between 2005 and 2007 are limited. In 2006, the

Table 6.1 Annual allocated and realised costs in euro (Health Care Insurance Board till 2006 and from 2006 RIVM) and volume of breast cancer screening in the Netherlands, 2000-2009

	2000	2001	2002	2003	2004	2005	2006[1]	2007	2008	2009
Kosten (x miljoen) *Costs (x million)*										
- Vooraf toegekend budget (in lopende prijzen) - *Allocated budgets (current prices)*[2]	36,0	36,4	40,3	42,0	43,2	43,7	45,5[1]	48,7[2]	50,4[2]	52,0[2]
- Achteraf gerealiseerd (in lopende prijzen) - *Realisation (current prices)*	35,6	37,2	40,4	42,3	44,4	45,5	45,6[1]	49,1[2]		
Aantal onderzoeken (x 1.000) *Number of screens (x 1,000)*										
- Vooraf toegekend budget - *Allocated budget*	802	819	835	854	863	872	893[1]	911[2]	929[2]	933[2]
- Achteraf gerealiseerd - *Realisation*	793	804	833	866	889	893	886[1]	912[2]		

[1] Vanaf 2006 wordt de planning en controle van CVZ overgenomen door het RIVM
From 2006 CVZ planning and control is taken over by RIVM

[2] Voorlopige cijfers / *preliminary figures*

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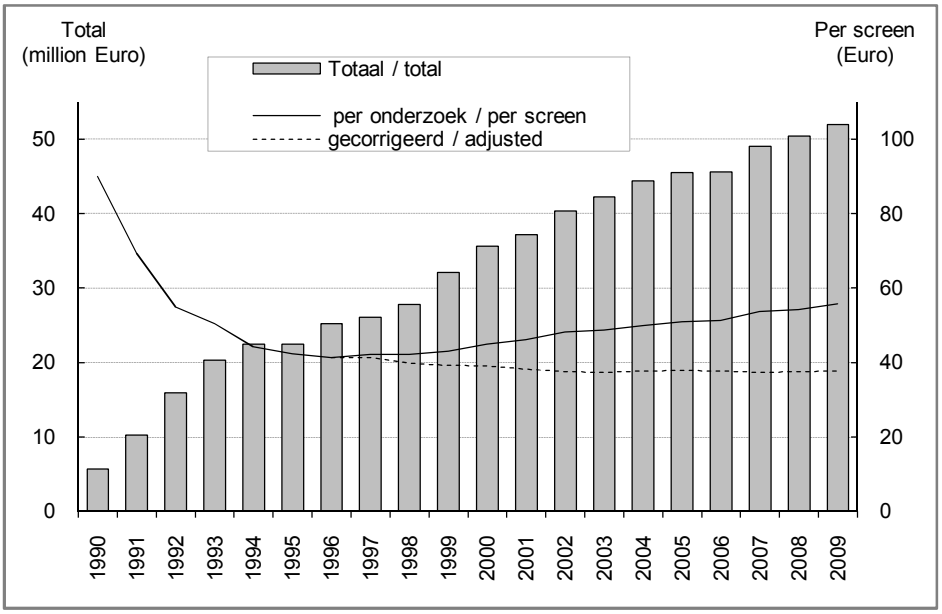

Figure 6.1
Annual total cost breast cancer screening programme and cost per screen examination (adjusted for inflation from 1997 on) (in euro)

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total costs of the national programme hardly rose at all (table 6.1, figure 6.1). It is true that the number of examinations performed decreased by 0.78%, and that the costs per examination increased by 0.88%. This increase per examination is covered mostly by higher national costs for the digitisation of the screening programme. In 2007, the total costs rose by 7.7%, due to a further 2.9% increase in the number of examinations performed. In addition to the continuing preparations for digitisation, the 2007 increase in costs can also be attributed to the further ageing of the population and an increase in attendance percentages from 81.1% in 2006 to 82.4% in 2007. The total costs for 2007 amount to €49.1 million, or €53.77 per examination performed.

The productivity of screening units between 2005 and 2007 is somewhat difficult to determine. In addition to the analogue units, three extra digital units were also operating during this period. However, they were experimental and not optimised for production. For this reason, the calculations for the average utilisation rate of each screening unit (per region) were not adjusted to include digital production, which may have caused the utilisation rate to be slightly overestimated in some regions. The average number of examinations for each screening unit showed a slight 2.2% increase, from 14,167 examinations in 2005 to 14,480 in 2007 (table 6.2).

If the costs per examination are adjusted to accommodate inflation, the (actual) costs up to the end of 2007 continue to drop slightly. If the trend is extrapolated to the expected costs from 2008 and 2009, the costs increase somewhat. (figure 6.1).

The national costs for quality assurance (NETCB), evaluation (NETB), project costs, digitisation, etc. rose in the 2005-2007 period from €3 million per year in 2005 to €4.6 million in 2007, amounting to 9% of the total costs for the national screening programme. In 2007, these costs totalled €5 per examination.

6.2 Regional cost distribution

The regional costs per examination in 2007 showed a limited 3% increase. Staff costs rose by the same amount as the nonstaff costs, i.e. 3%. In 2006 the regional costs per study dropped slightly (by 0.5%). This was the year in which the RIVM took over planning and monitoring from the Health Care Insurance Board (CVZ).
In addition to equipment, depreciation, maintenance, etc., the nonstaff costs also include the transfer to reserve of the screening organisations. In 2006, €0.08 per examination was transferred to the reserve. In 2007, this figure was €0.11. However, partly depending on the size of the reserves, this amount can differ considerably from region to region and year to year.
The number of examinations per screening unit increased in all regions during the 2005-2007 period (table 6.2). Whereas in 2005 the number of examinations was above 14,000 in four regions, this was the case for six regions in 2007.

Regional costs per examination remained within 5% of the national average in 2007. SVOB, SVOKON, BOB-West and SKsL were relatively more expensive from 2005-2007; SVOBMN, SK and IKA were relatively cheaper (table 6.2).

Table 6.2 Task and realisation of production and costs in euro per region, 2005, 20065 and 20075 (preliminary figures)[5]

Screeningsorganisatie *Screening organisation*	Aantal onderzoeken[4] *Number of screens[4]*						Screeningseenheden *Screening units*			Regionale kosten per onderzoek *Regional cost per screen*								
	Taakstelling per regio *Task set per region*			Realisatie per scr.eenheid *Realisation per scr.unit*			Aantal[4] *Number[4]*			Naar kostensoort *Functional costs*						Totaal per onderzoek *Total per screen*		
										Personele kosten *Costs personnel*			Materieel[1] *Material[1]*					
	2005	2006	2007	2005	2006	2007	2005	2006	2007	2005	2006	2007	2005	2006	2007	2005	2006	2007
SBBNN	126.000	127.000	131.500	14.207	14.141	14.307	9	9	9	28,84	28,74	29,86	19,11	19,02	18,53	47,95	47,76	48,39
SVOB	66.800	67.735	68.400	13.658	13.851	13.712	5	5	5	29,92	30,56	30,82	19,46	18,82	19,20	49,39	49,38	50,02
SVOKON	65.000	72.000	72.000	13.836	14.192	14.912	5	5	5	27,31	29,17	31,18	22,62	20,09	19,75	49,93	49,36	50,94
SVOBMN	70.000	72.000	74.000	14.586	14.516	15.039	5	5	5	26,83	29,81	29,30	19,65	16,09	17,28	46,48	45,90	46,58
SK IKA	139.000	143.500	145.000	14.116	13.634	14.240	10	10	10	27,44	28,58	28,89	17,62	16,29	19,66	45,06	44,87	48,55
BOBWest	94.000	94.000	94.000	13.506	13.416	13.640	7	7	7	28,34	30,33	32,98	19,98	18,20	16,91	48,32	48,53	49,89
SBBZWN	118.500	120.500	124.500	13.456	13.252	13.826	9	9	9	28,76	29,86	30.74	18,76	18,09	17,65	47,51	47,95	48,39
SBOBZ	138.000	141.000	145.000	15.736	15.637	16.273	9	9	9	28,10	30,44	31,80	19,01	15,86	16,01	47,11	46,30	47,81
SKsL	55.050	55.600	56.500	13.961	13.978	14.101	4	4	4	29,86	31,40	30,37	19,58	16,95	19,67	49,44	48,35	50,04
Totaal onderz) *Total (screens)*	872.350	893.335	910.900	892.528	866.224	912.254	63	63	63									
Benchmark/gemiddeld[2] *Benchmark/average[2]*	13.846	14.180	14.459	14.167	14.067	14.480												
Gemiddelde regionale kosten / onderzoek *Average regional cost / screen*										28,30	29,74	30,63	19,28	17,59	18,13	47,58	47,33	48,76
Totaal = regionaal + landelijk[3] *Total = regional + national[3]*																50,96	51,41	53,77

[1] Inclusief kapitaallasten en reserves / *capital costs and reserves included*

[2] Per analoge screeningseenheid / *per analog screening unit*

[3] Inclusief vervroegde afschrijving / *accelerated capital costs included*

[4] Registratie CVZ/RIVM / *Registration CVZ /RIVM*

[5] Vanaf 2006 wordt de planning en control van CVZ overgenomen door RIVM / *Started in 2006 CVZ planning and control is taken over by RIVM*

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Table 6.3 Reorganisation breast cancer screening regions 2007-2011

Versterking Infrastructuur KankerScreening
Reinforcement infrastructure cancer screening

Landsdeel *County*	**Organisatie** *Organisation*	**Formele naam na fusie** *Official name*	**Activiteiten *** *Activities **
Landsdeel noord	BBNN	stichting bevolkingsonderzoek noord	BOB
	St. Prev. GHZ Groningen		BMHK
	St. Prev. GHZ Friesland		BMHK
	SBB Noord Drenthe		BMHK
	BCNN		BMHK
Landsdeel midden-west	Preventicon	stichting bevolkingsonderzoek midden-west	BOB/BMHK
	St. BMHK NH/Flevoland		BMHK
	SKA/IKA		BOB
Landsdeel zuid-west	BOBwest	stichting bevolkingsonderzoek zuid-west	BOB
	BBBW		BMHK
	SBZWN		BOB/BMHK
Landsdeel zuid	SKSL	stichting bevolkingsonderzoek zuid	BOB/BMHK
	SBB Noordbrabant/Noordlimburg		BMHK
	BOBzuid		BOB
Landsdeel oost	Svokon	stichting bevolkingsonderzoek oost	BOB
	St. Bev.Oz. BMHK Stedendriehoek		BMHK
	SVOB		BOB
	SBBTwente		BMHK
	SBO		BMHK

* BOB: Bevolkingsonderzoek naar Borstkanker / breast cancer screening
* *BMHK: Bevolkingsonderzoek naar Baarmoederhalskanker / cervical cancer screening*

6.3 Anticipated additional costs and savings of digital screening and reorganisation

The actual digitisation of the screening programme at regional level will take place between 2007 and the end of 2011. The regional organisation will be reduced from nine regions to five, and expanded to include all cancer screening activities. Table 6.3 shows the changes.

The changes above have had a large influence on the activities and associated costs of the coming years, in which conversion is to take place. This influence was only partially noticeable in 2007. There are currently only figures available for the budgeted additional costs and yields for 2007-2011. Except for the additional costs for storage, management and distribution of the digital mammograms (IMS), these projections only include the national component. Table 6.4 provides an overview.

The most significant part of the digitisation process will occur between 2008 and 2010; the crux of the reorganisation process will occur slightly later, in 2010 and 2011. The non-recurring costs for the combined conversion total approximately €1.54 million per year (€7.72 million across 2007-2011). Approximately 9% of these costs go towards training personnel, and another average of 9% is required for the conversion of existing analogue mammograms to digital format. An average 15% production loss during this period has also been taken into account. The disinvestment of not-yet fully amortised accommodation, inventory and equipment totals approximately 14%. The temporary additional IMS costs (Information Management System, including the storage and distribution of digital mammograms) account for an average of 7% of the total non-recurring costs. The organisational costs (which include not only the reorganisation but also the activities related to the conversion to digital format) form the largest part at 46%. Unforeseen expenses have also been included here.

The recurring additional costs (€8.5 million per year) and savings (€5.2 million) will reach their full scope in 2011. Forty-five per cent of the additional costs are for more expensive equipment, and 55% is related to IMS. On the other hand, savings will be realised through no longer having to develop, use or store analogue mammograms, and through a reduction in the number of central assessment units (74%). There are also additional savings due to the reorganisation of the regions (26%). The total savings will amount to €5.2 million per year at the end of the period (in 2011).

Table 6.4 Calculated differential costs and savings for digitalisation and reorganisation breast cancer screening programme 2007-2011

	2007	2008	2009	2010	2011	2007 - 2011
Eenmalige kosten / *Non-recurring costs*						
Exploitatie / *Operating costs*						
- opleiding / *training*	35.300	488.886	175.620	23.771	0	723.577
- omzetting analoge foto's *conversion*	0	87.696	270.690	308.767	45.926	713.079
- organisatie / *management*	224.432	1.100.218	1.142.629	844.117	260.585	3.571.981
- productieverlies *production losses*	0	269.186	675.574	202.123	0	1.146.883
Infrastructuur / *Infrastructure*						
- desinvesteringen *desinvestments*	55.051	257.378	597.923	75.938	76.957	1.063.247
- IMS / *IMS**	0	100.000	400.000	0	0	500.000
Totaal / *Total*	314.783	2.303.364	3.262.436	1.454.716	383.468	7.718.767
Structurele kosten / *Structural costs*						
- materieel / *material*	12.500	366.393	2.071.317	3.453.887	3.657.298	9.561.395
- IMS / *IMS**	0	1.438.953	3.742.908	4.644.977	4.457.887	14.284.725
Totaal / *Total*	12.500	1.805.346	5.814.225	8.098.864	8.115.185	23.846.120
Totale Kosten / *Total costs*	*327.283*	*4.108.710*	*9.076.661*	*9.553.580*	*8.498.653*	*31.564.887*
Structurele opbrengsten / *Structural benefits*						
- productie / *production*	0	385.079	2.064.779	3.505.679	3.838.982	9.794.519
- reorganisatie / *reorganisation*	0	0	157.263	805.850	1.381.952	2.345.067
Totaal / *Total*	0	385.079	2.222.042	4.311.529	5.220.934	12.139.586
Structurele kosten -/- structurele opbrengsten *Structural costs -/- structural benefits*						
	-12.500	-1.420.267	-3.592.183	-3.787.335	*-2.894.251*	*-11.706.534*
Structurele kosten -/- structurele opbrengsten (excl IMS) *Structural benefits -/- structural costs (IMS excluded)*						
	-12.500	*18.686*	*150.725*	*857.642*	*1.563.636*	*2.578.191*

* IMS: Management Information System (distribution and storage digital mammograms) LETB/*NETB,* 2009
(opslag en distributie digitale mammogrammen / *distribution and storage digital mammograms)*

Reconciling the recurring costs with the recurring proceeds results in a loss of €2.9 million per year, necessitating a fundamental increase in the annual costs of the screening programme (5%). This does not include the recurring additional costs of the national component (excluding IMS). Table 6.4 shows that the additional costs are more than fully accounted for by the recurring costs of the storage and management of the digital mammograms. The recurring additional equipment costs are more than compensated for by the savings related to analogue photo technology. The savings due to the reorganisation are on top of these. Leaving IMS out of the equation would even create a profit of €1.6 million per year. In other words, 35% of the recurring additional IMS costs are paid for by production and reorganisation.

6.4 Conclusions

The total costs amounted to €49.1 million in 2007, or €53.77 per examination. The cost and productivity trends of the national breast cancer screening programme from 2005 to 2007 present a stable picture. The rise in the total costs of the national screening programme is caused by the preparations for digitisation, the reorganisation of the regions and an increase in the number of examinations as a result of increased participation.

At regional level, the productivity of screening units has further increased and is approaching 14,500 examinations per analogue screening unit. It should be noted here that digital screening has already

taken place on a small scale during this period, for which no adjustment has been made. The regional costs per examinations remained fairly stable in this period, and no differences between the regions diverge more than 5% from the average.

The current screening programme seems to have entered a stable period financially in 2005-2007, which is necessary in order to enter a period involving major medical and organisational changes. The move away from the Exceptional Medical Expenses Act (AWBZ) seems to have had little financial influence.

The period from 2008 to 2011 will involve major changes to the screening programme. The estimates for this period have revealed anticipated temporary additional costs (non-recurring investments) of €7.7 million. There will also be recurring additional costs of €2.8 million per year, representing a fixed 5% increase in the annual costs of the screening programme. This percentage is limited by the fact that nearly two-thirds of the recurring additional costs of producing, storing and processing digital mammographies is paid for by savings in the production, assessment centres and storage of analogue mammograms, and the reorganisation of the regions. It is important to keep in mind that these positive figures are prognoses. It will be exciting to see how these plans will turn out in the years to come, and the extent to which the implementation can be realised within the established schedule. Annual monitoring will be essential.

7

Discussion

7.1 Criteria for screening

In 1968, Wilson and Jungner were among the first to attempt to create order from the sea of possibilities and obscurities in early detection by creating a list of ten principles that are important to the screening process. Although in their foreword they emphasise that they are 'merely principles', the 10 principles now seem to have grown to the status of dogmas. Various commissions have extended the list of principles over the years, yet it is actually possible to distil the criteria for early detection in the 21st century down to three clear principles:

- There must be at least the expectation of considerable potential positive health outcomes, in terms of increased life expectancy, improved cognitive, motor and/or socio-emotional development, and/or significantly increased treatment and/or other options. These effects must be set out unequivocally, in a randomised study if possible.
- Secondly, any side effects must be limited in nature. The incidence of early diagnosis, overdiagnosis and other side effects must be estimated and expressed in terms of additional quality-of-life-adjusted life-years. The anticipated ratio of positive health outcomes to side effects must be made clear at group level and be explained in a manner understandable to potential participants.
- There must be a reasonable cost-effectiveness ratio (this creates opportunities for programmes that can be expected to produce greater effect for the same investment) and steps must be taken to ensure that implementation will not have widespread unintended consequences, such as unacceptable pressure on the healthcare system. Lastly, developments in other fields that could have a possible influence on early detection should not substantially alter the balance of the benefits and harms of screening.

7.2 Does breast cancer screening fulfil the criteria?

Breast cancer is the most common form of cancer among women in the Netherlands, causing over 3000 fatalities per year. Women who die of breast cancer first undergo an average of 2-3 years of palliative care. An effective screening programme can therefore represent significant positive health outcomes. Randomised studies clearly showed that mortality due to breast cancer ultimately dropped by 25% among women aged 50 or higher (in the trials usually 50-69 or 50-74) who were invited to receive mammography (US Preventive Task Force, 2009). Case-control studies showed that this represented approximately a 35% better chance of survival among women who had allowed themselves to be screened (Vaino and Bianchini, 2002). On average, women who do not die of breast cancer gain an extra 15 years of life. The number of treatments that preserve the breast is also relatively higher due to breast cancer being discovered at an earlier stage. The first criterion was therefore satisfied when the Dutch screening programme on breast cancer was implemented.

However, screening at population level also carries disadvantages for a large group of people. There are false positive results, i.e. people are referred on because of an abnormal screening result, but turn out not to have the disease. Diagnoses can be made sooner, which may seem positive, however the relevant patients also become aware sooner that they have the disease, and remain aware for a longer

period. This may also mean that they suffer side effects from treatment for longer. Some women with a carcinoma detected by screening do not benefit at all from an earlier diagnosis, and there will even be people who would otherwise never have been diagnosed, because they would have died beforehand from a different disease. Such people then even receive too much treatment. Lastly, it can give false peace of mind, which means that people with a clear screen result will delay a visit to the doctor if they have symptoms because they believe that they can derive assurance from the screening results. A recently published study showed that there are no indications hereof in the Dutch breast-cancer screening programme (de Gelder et al., 2008).
All of these facets were quantified prior to the start of the Dutch screening programme (de Haes et al., 1991). The conclusion read that correction for such negative effects on the women's quality of life reduced the positive health outcomes by an estimated 8%, and was therefore low enough that breast cancer screening could be offered nonetheless. In this way, the balance between the scope and type of positive and negative effects had been made clear. The information provided to potential participants was subsequently modified at several points in time, and reviewed in 2008 based on a study among a number of experts in the field of cancer screening and 200 women from the Leiden area (van Agt et al., 2009).
Thirdly, breast cancer screening proved to be cost-effective, an estimated three times more effective than the existing cervical cancer screening programme. No significant developments presented themselves upon implementation that would bring these considerations into question.

7.3 Does the Dutch programme still fulfil these criteria?

Over 14 million invitations for a screening mammography have now been sent out in the Netherlands. The trials themselves are over, as are any emerging discussions about them. Over three million Dutch women have made the decision of whether or not to take part in the national screening programme. Over 90% of them have had their breasts screened at least once. Now, however, it is important to maintain a critical view on whether the anticipated positive health outcomes, the scope of the negative effects and the costs made are all in proportion to one another. In this 12th extensive evaluation report, we review this topic.
In 2003, we were the first country to demonstrate the effectiveness of a breast-cancer screening programme at national level (Otto et al., 2003). Because a continuous programme effectively makes randomisation impossible, we opted for a different approach. We knew the exact starting month and year for the screening programme for each municipality. With this knowledge, we were able to set out and analyse the likelihood of breast cancer mortality prior to and after the screening in the (then) 650 municipalities. It turned out that the persistent increase of 0.3 cases of breast cancer per 100,000 women years had been converted to an annual decline of 1.7 cases per 100,000 women years, and that the turning point coincided with the start of screening in the municipalities (Otto et al., 2003).

In Chapter 4, we now demonstrate the positive health outcomes of the Dutch screening programme in three different ways. First and foremost, breast cancer mortality has decreased by 24% in the target age group (55-74) from 1986 up until the last complete year (2008). In the previous publication by Otto et al., we showed that the turning points occurred independently of the changes in therapy. Another study (of which Chapter 4 includes a summary) shows the same pattern in an update according to age class: around five years after the gradual introduction of the screening programme in the Netherlands (not regarded here at the level of individual municipalities), breast cancer mortality decreased significantly in the 55-64 and 65-74 age groups, and after extending the study up to age 75, also in the 75-84 age group (Otten et al., 2008). Yet another approach, i.e. that of a case-control study, revealed that screened women in the south-west Netherlands region have at least a 32% smaller chance of dying from breast cancer than non-screened women (after correcting for self-selection bias). Although it is important to conduct case-control analyses like these for all regions simultaneously, this is new proof that in practice, the Dutch breast-cancer screening programme has led to major positive health outcomes outside of a trial context. Other regional comparisons abroad show comparable results (Schopper and de Wolf, 2009). In Chapter 4 we also demonstrate that the likelihood of having to undergo a breast amputation is reduced by at least 15%, thereby disproving previous claims that a screening programme would lead to an increase, at least in the Netherlands (Olsen and Gøtzsche, 2001).
The first criterion (demonstrable positive health outcomes) was therefore met at the time when implementation of the breast-cancer screening programme commenced, and is still met today now that we find ourselves in a stable position within this high-quality programme. These outcomes were achieved through a large-scale stage shift, followed by effective treatment of the cancers that have since been detected in 56,250 women by the screening programme.

Chapters 3 and 5 devote much attention to the negative effects of breast cancer screening. The estimates regarding negative effects in the Netherlands were produced by combining screening trial data from abroad with specific data from the Utrecht and Nijmegen trial population studies conducted in the 1970s and 1980s. It is a fact that the number of referrals and the rate of breast cancer detection have undergone considerable changes over the last 10 years. Referral figures have doubled since 1996, however it should be noted here that this figure is (still) among the lowest in the world (Yankaskas, J Med Screen 2004). In 2007, almost 2 in 100 women screened were referred for further testing, at least 60% of which turned out to be false positives. In Chapter 3, we now estimate that women who commence participation in the screening programme at age 50 and take part in all 13 rounds of screening have a 9% chance of being given a false positive result (Chapter 3). It is important to realise that in some countries, this percentage is reached in every round of screening. Unfortunately, due to nationwide changes to the cancer registers, we do not have any complete information on interval cancers. However based on the available information, the sensitivity of the examination seems quite high (i.e. 84%) despite the high referral threshold. In regions with slightly higher initial detection figures, fewer interval cancers are discovered in the two years that follow, reaching higher sensitivity as a result. However, we have not enough information to demonstrate the exact cause of higher breast cancer detection in some regions.

The increasing examination numbers with a false positive result mean that more women are experiencing the negative effects of the screening programme in the Netherlands. On the other hand, breast cancer detection (and therefore the chances of survival) have increased for another portion of women who have taken part in the programme. Earlier we showed that a higher referral rate improves breast cancer detection, and that the ratio of positive and negative effects to a referral rate of 2% is probably still very favourable (Otten et al., 2005; Groenewoud et al., 2007).
Chapter 5 of this report also contains a new calculation for the rate of overdiagnosis, the new aspect being that we have included the actual incidence of breast cancer between 1989 and 2004 in the calculations. Effective screening leads to earlier diagnosis. A significant proportion of these earlier diagnoses would otherwise be clinically diagnosed later in life. For this reason, incidence in women aged 50-69 (or 50-74) has increased by around 10% since the introduction of the screening programme. At the same time we also show that, in the stable position we are now in, the actual incidence has dropped by 12% among women aged 75-79. In Chapter 5, we calculate that the increase in incidence in the screened group is compensated to a large extent by the drop in the next age group above, so that only 2-5% of all cases are overdiagnosed. This contrasts sharply with the recently quoted overdiagnosis percentages of 30-50%, which we believe originate from an incorrect interpretation of the incidence pattern influenced by screening (Jørgensen and Gøtzsche, 2009).

A completely separate aspect of the evaluation of the screening programme are the actual costs. Both the government as provider of the screening programme and citizens who are either directly or indirectly involved as taxpayers have an interest in annual monitoring and thorough accounting of the expenses incurred by the programme. In 2007 the costs amounted to €53.77 per examination, which is in line with the forecasts. The capacity of the screening units has increased more and more since the start of the programme, and the 70-75 age group was integrated into the programme almost effortlessly. Despite considerably lower initial attendance among the older women, the costs per examination have remained almost unchanged in 10 years. This is clearly an indication of the high level of efficiency of the Dutch screening programme. Although significantly higher costs can be expected in the years to come arising from the digitisation of the programme, the new technology may enable an even greater stage-shift, as shown in Chapter 3.

Lastly, two more developments are worthy of mention. The first of these is the introduction of the sentinel lymph node biopsy. Over the last few years, this has made the drop in the number of advanced tumours no longer usable as an outcome measure, given that the majority of negative lymph node stages are based on this technique. Until 1997, the decrease in breast cancer mortality kept pace with the decline in advanced stages of breast cancer. Because the sentinel node procedure has led to an increase in the number of lymph-node-positive breast cancers, the current advanced stages of the illness can no longer be compared to those of the 1990s.
Secondly, this report contains clear indications for the first time that the incidence of breast cancer (regardless of screening) seems to be increasing in the Netherlands. Between 1999 and 2004, approximately 10% more breast cancers were found than anticipated. This can only be partly attributed to increased detection, e.g. due to more referrals or the digitisation of screening mammography. The consequences of increased underlying incidence in the population will be further examined during the year to come, in particular the breast cancer mortality rate to be expected if there had been no screening.

7.4 Screening of the 70-75 age group

For the first time, this report presents detailed information on the performance and decline in mortality rates for the older age group. The 79% participation rate in 2007 was exceptionally high, and the screening performance measures up to that among women aged 50-69. Within 6 years after implementation of the extension of the study, breast cancer mortality rates had dropped by 27% in the 70-75 age group. However, these positive results do not necessarily mean that the upper age limit can be 'done away with' (van Bekkum, 2008).

One of the most important reasons to also choose an upper age limit when offering early detection relates to the balance between positive and negative effects. It is for this reason that a 76-year age limit has been set for breast cancer. Two years ago, the national government was summoned to interlocutory proceedings for the abolition of this age limit. The judge formulated as follows:

> 'By setting the breast-cancer screening programme age limit at 76 years, the government is making a distinction according to age. The crux of these proceedings can be summarised by the question of whether the risk-to-benefit ratio for the 76+ age group is different than for the 50-76 age group (the current target group for the screening programme). This ratio applies at *collective* level, as population-based programmes by their very nature concern categories of people.
> The reasons why the government applies this upper age limit cannot be seen as unjustified.
> As the age of those involved increases, serious consideration must be taken of the fact that early detection and ensuing treatment (which always involves disadvantages) will improve longevity and quality of life less and less.
> The distinction made is not discriminatory and is therefore not unlawful.'

Overdiagnosis and overtreatment are specific serious disadvantages of early detection. For example, even simply the diagnosis of prostate or other cancer can cause a significant temporary decrease in self-reported quality of life (Korfage et al., 2006).

7.5 Concluding remarks

We can safely conclude that the Dutch breast-cancer screening programme has passed the test of criticism, and more importantly the test for the introduction and continuation of screening, with flying colours. This does not excuse us from our obligation to remain constantly critical, in order to create the best possible programme that hundreds of people will be working on every day. Thanks to the continual evaluation of the Dutch screening programme, now summarised in a 12th report, it is possible to refute any blunt criticism. This is also a very important responsibility towards asymptomatic women, who need to be able to make a choice about whether or not to participate in the screening programme.

Literature

Van Agt HME, Fracheboud J, Rebolj M, Korfage IJ, de Koning HJ. Volledige, evenwichtige en eerlijke voorlichting over nut en risico's van bevolkingsonderzoek naar kanker. [Complete, balanced and fair information on the benefits and risks of cancer population studies] Eindrapport (November 2008). Rotterdam: Afd. Maatschappelijke Gezondheidszorg, Erasmus MC, 2008.

van Bekkum DW. Bevolkingsonderzoek op borstkanker ook zinvol bij 75-plussers. Laat los die grens. [The benefits of breast-cancer population research to those aged over 75: Away with the age limit] Med Contact 2008;63:764-8.

de Gelder R de, van As E, Tilanus-Linthorst MM, Bartels CCM, Boer R, Draisma G et al. Breast cancer screening: evidence for false reassurance? Int J Cancer 2008;123:680-6.

Groenewoud JH, Otten JDM, Fracheboud J, Draisma G, van Ineveld BM, Holland R, Verbeek ALM, de Koning HJ (NETB). Cost-effectiveness of different reading and referral strategies in mammography screening in the Netherlands. Breast Cancer Res Treat 2007;102:211-8.

de Haes JC, de Koning HJ, van Oortmarssen GJ, van Agt HM, de Bruyn AE, van der Maas PJ. The impact of a breast cancer screening programme on quality-adjusted life-years. Int J Cancer 1991;49(4):538-44.

Jørgensen KJ and Gøtzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. BMJ 2009;339:b2587

Korfage IJ, de Koning HJ, Roobol M, Schröder FH, Essink-Bot ML. Prostate cancer diagnosis: the impact on patients' mental health. Eur J Cancer. 2006 Jan;42(2):165-70.

Olsen O and Gøtzsche PC. Screening for breast cancer with mammography. Cochrane Database Syst Rev 2001;(4):CD001877

Otten JDM, Karssemeijer N, Hendriks JHCL, Groenewoud JH, Fracheboud J, Verbeek ALM, de Koning HJ, Holland R. Effect of recall rate on earlier screen detection of breast cancers based on the Dutch performance indicators. J Natl Cancer Inst 2005; 97:748-54.

Otten JD, Broeders MJ, Fracheboud J, Otto SJ, de Koning HJ, Verbeek AL. Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975-2006. Int J Cancer 2008 Oct 15;123(8):1929-34.

Otto SJ, J Fracheboud, CWN Looman, MJM Broeders, R Boer, JHL Hendriks, ALM Verbeek, HJ de Koning and the National Evaluation Team for Breast cancer screening. Initiation of population-based mammography screening

in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003;361:1411-1417.

Schopper D, de Wolf C. How effective are breast cancer screening programmes by mammography? Review of the current evidence. Eur J Cancer. 2009;45(11):1916-23.

U.S. Preventive Services Task Force Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2009;151:716-726.

Vainio H and Bianchini F: *Breast Cancer Screening - IARC handbooks of cancer prevention* volume 7. Lyon: IARC press. 2002.

Yankaskas BC, Klabunde CN, Ancelle-Park R, Rennert G, Wang H, Fracheboud J, Pou G and Bulliard JL, for the International Breast Cancer Screening Network. International comparison of performance measures for screening mammography: can it be done? J Med Screen 2004;11:187-193.

8

Summary, conclusions and recommendations

National results 1990-2007

This evaluation report presents the complete figures from the 1990-2007 period, with the exception of the data on interval cancers, which is still delayed.

Invitation and participation

From 1990-2007, over 14 million invitations for screening examinations were sent to around 3 million women. In addition to a one-off increase of the target population in 1998 by 25.6%, the annual target population grew by 16% from 1.02 to 1.18 million in 2007. Based on the age pyramid, we can conclude that the target population will continue to grow over the next ten years.

Over 1.1 million women were invited in 2007, which was coupled with a total attendance rate of 82.4% and a significant increase in participation among women aged 70-74. Attendance was 79.0% at initial screening examinations (11.2%), and 82.8% at subsequent examinations (88.8%). Of the women who were already participating, 93.8% took part once again in 2007. The proportion of definitive non-participants has remained at 4-4.5% since 2004.

Screening examinations

The number of screening examinations carried out exceeded 900,000 for the first time in 2007. The proportion of digital screening examinations increased from 1.1% in 2004 to 7.4% in 2007.

The average individual invitation and screening intervals were around 24-24.5 months. Outliers in the (sometimes unavoidable) annual variations in intervals can affect the detection rates.

Referrals, detection rates and the predictive value of referrals

The previous rise in referral rates continued on into 2007, and is currently 18 per 1000 women. This is more than twice the rate in 1996. Initial screening examinations showed triple the amount, reaching 34.4 referrals per 1000 women.

Between 1990 and 2007, nearly 145,000 women (1.27%) were referred for additional diagnostic assessment in hospital due to a suspected abnormality in their mammogram. The results of the further diagnosis are known for 98.1% of these referrals.

The detection rates increased, and reached 5.5 per 1000 women in 2007, with a consistently higher detection rate for all age groups in subsequent screenings. Initial screenings detected cancer in 5.9 per 1000 women; regular subsequent screenings within 2.5 years detected 5.2 per 1000 (9.4 per 1000 in subsequent screenings with an interval greater than or equal to 2.5 years). An inevitable effect of a significantly increased referral rate is a decline in the predictive value, which dropped from 43% for initial screening examinations in 1990 to 17% in 2007, and from 56% in 1992 to 34% in 2007 for subsequent screenings.

Screen-detected carcinomas, tumour size and lymph node status

Since 1990, the screening programme has diagnosed 56,254 women with breast cancer (screen-detected carcinomas).

Of the 4,999 breast cancers detected by screening in 2007, 15.1% were ductal carcinomas in situ (DCIS), and 65.8% invasive carcinomas with a diameter of 2 cm or less.

In 2007, 72.8% of the screen-detected carcinomas showed no metastases in the lymph nodes. Across

the entire period from 1990 until the end of 2007, this figure was 69.2%. The proportion of lymph negative tumours was lower for initial screenings (65.9%) than for subsequent screenings (70.6%).

Screening performance

Screening performance is determined by factors such as age, the type of technology (analogue or digital), the type of screening examination (initial or subsequent), the length of the screening interval, the technical quality and the expertise and experience of the screening radiologists and radiographers. The Dutch breast cancer screening programme can be divided into four stages, in which the above-mentioned factors influence screening performance at varying levels: the implementation stage for women aged 50-69 (1990-1997), extension of the age limit to 75 (1998-2001), the steady-state stage following extension (2002-2004) and the commencement of digitisation (2005-2007).

Screening programme for women aged 70-75

During the first ten years of the 70+ screenings, around 1.6 million invitations were sent to women aged 70-75. Attendance increased from 63% in 1998 to 79% in 2007. The referral rates, biopsies, detection rates and positive predictive values of both referrals and biopsies were significantly higher compared to those of the younger women. The proportion of ductal carcinomas in situ was significantly lower (11.4% vs. 15.2%) and the proportion of invasive tumours 6-10 mm in size (T1b) significantly higher (21.9% vs. 18.1%) than in the younger group. The proportion of lymph node-negative tumours was clearly higher in women aged 70-75, evidence which argues that the tumours are in fact less aggressive in this group (length time bias).

Digital screening

An initial evaluation of the three digital screening pilots (Utrecht, Heerenveen, Dordrecht) revealed that production decreased by 30% and that the referral rate rose by a factor of 2-3, which led to a non-significant increase in breast cancer detection, especially of carcinomas in situ. These initial results were the reason why a training programme was set up by the National Expert and Training Centre for Breast cancer screening (NETCB) and a short-cycle monitoring system was defined by the National Institute for Public Health and the Environment (RIVM), in order to optimise and safeguard the conversion to a digital screening system. Between 2004 and 2007, five screening units carried out a total of 155,548 digital screening examinations. There was a temporary strong 50% increase in the referral rates, and a 22% increase in the detection rates. Of all detected breast cancers, 45% were carcinomas in situ or invasive carcinomas not larger than 10 mm, compared to 37% from analogue examinations. Referral rates decreased after some time, partly due to the screening radiologists gaining more experience with digital screening. Conversely, both the detection rates of invasive carcinomas and carcinomas in situ were significantly higher (16% and 64% respectively) than for analogue examinations.

Screening performance in each stage of the screening programme

It was already known that there were relatively large differences in screening performance between the regions. In order to interpret this correctly, reliable data regarding interval cancers is required. Unfortunately, data of this type is not available nationally subsequent to 1994 (8 of the 9 regions), and only from some regions between 2002 and 2004. The programme sensitivity and specificity can therefore not be reliably determined for the more recent years until the cancer register is nationally linked to the screening information database (iBOB).

In 1996, referral rates had reached a low, so that the screening radiologists were encouraged to refer more women. After 1996, the referral rate rose continuously until it had tripled for initial screenings and almost doubled for subsequent screenings ten years later, with increased breast cancer detection as a result. During the period from 2005-2007, the detection rate from initial analogue screening examinations was 24% higher, and from regular subsequent screenings 31% higher than the average during the implementation stage from 1990-1997. The rise in the detection rate can be primarily attributed to increased detection of invasive tumours 11-20 mm in size (T1c). In recent years there has also been a perceptible increase in DCIS and the smallest invasive tumours (T1a and T1b), possibly partly due to the growing number of digital screening examinations. All regions have shown a clear increase in the 2005-2007 detection rates corrected for age differences relative to 1990-1997, although there were also major differences between regions, partly also influenced by digital screening.

False positive results

The lower predictive values raise the likelihood of a false positive result for participants in all 13 screening rounds to 9.1%. Seen in an international context, this is still quite low.

Interval cancers

Data is available for 77.7% of the 8.7 million screening examinations conducted up to 2004 on whether breast cancer was discovered outside of the study

within the first two to three years following screening. A total of 16,866 interval cancers were reported, 13,654 of which were found within 24 months of screening (over 80%), amounting to 2.0 interval cancers per 1000 screened women.
The average programme sensitivity up until 2004 was 71.0%, meaning that over two-thirds of all (latent) present breast cancers were detected by screening. The sensitivity of initial screening examinations among women aged 49-54 was 74.5%, and 67.7% for regular subsequent screenings among women aged 50-69. The specificity (i.e. the percentage of women whose mammogram was correctly identified as being non-suspicious) amounted to 99.0% and 99.5%, respectively.
The site visits by the NETCB revealed that over half of the interval cancers were not visible on previous screening mammograms. Leaving aside these interval cancers places the sensitivity of mammography at around 84%.
The frequency of interval cancer clearly declines with age. At 80.1%, programme sensitivity among women aged 70+ was significantly higher than in the 50-69 age group, and the specificity slightly lower (99,17% versus 99,25%). Despite the rise in breast cancer detection since 1990, the frequency of interval cancers is not declining for the time being.

The regional evaluation shows that screening regions with higher detection figures generally have a lower interval cancer frequency. However, it is not the case that a higher referral rate automatically leads to a higher detection rate, a fact supported by international comparisons. The relationship between the various indicators can only be analysed definitively if the full figures for interval cancer frequency are made available from years following 2000.

Breast cancer incidence and mortality

Chapter 4 describes several aspects of the trends in breast cancer incidence and therapy, based on the data from the Dutch Cancer Registry. However, this data is outdated due to the connection problems associated with the conversion from a regional to a national cancer registration database.

In 1989, we see an almost linear rise in *age-specific breast cancer incidence* up to the age of 84 years. In 1997 it has significantly and considerably risen, in women as young as 35. An exception is the 70-74 age group, in which the incidence dropped to below the level in 1989. A similar phenomenon then shifts to the 2006 incidence among women aged 75-79, only here it is more pronounced. These declines are the result of the screening that eliminated the tumours in previous years that would normally be diagnosed among women in this age group. It is also striking that the increase in incidence has also affected all age groups outside the target group for the screening programme. In addition to the increased risk factors such as exposure to oestrogen, this may also have to do with greater awareness and possibly also opportunistic screening.
Following a previously demonstrated decrease in the frequency of *advanced stages of illness* until 1997, it started rising again in 1998. More detailed analyses indicate that this is probably related to the introduction of the sentinel node procedure from the second half of the 1990s, which caused more diagnoses of lymph node-positive breast cancers.

Seven regional cancer registers provided data concerning the *primary treatment of breast cancer* between 1990 and 1999, which shows a clear rise in the number of breast conserving surgery. The slight rise in the number of mastectomies comes entirely from the under-50 age group.

Breast cancer mortality shows a fluctuating trend. For example, mortality in 2007 had decreased by 28.7% in 2007, but by 'only' 24.5% in 2008. Mortality among women aged 75-79 in 2002 in particular was considerably lower than predicted based on the microsimulation. This is a consequence of extending the screening programme up to age 75. A sharp decline in breast cancer mortality among women in both age groups (50-69 and 70-75) commenced in the first year of the screening programme, and within only a few years had reached a significantly lower level than in the 20 years beforehand.

Long-term trends of breast cancer incidence and mortality
An earlier study examined long-term trends of breast cancer incidence from 1975-2003 and breast cancer mortality from 1950-2006 (Otten et al., 2009). Using join-point analyses, breaks in trends were identified for various age categories. Clear changes in trends were found for the age categories that are eligible for screening and that are related to the (full-scale) implementation/extension of the nation-wide screening programme. Immediately following the start of the screening programme, there is a perceptible rise in incidence which plateaus following full-scale implementation. The commencement of screening led to an impressive drop in breast cancer mortality in the relevant age groups within several years.

Effect estimates: Case-control study
In collaboration with the South-West screening

region (SBBZWN), over the last few years the NETB has been working on setting up a case-control study in order to determine the effects of the screening programme on breast cancer mortality in greater detail. In this type of study, women who die of breast cancer (the 'cases') are compared to women who are similar in a number of respects (such as age, place of residence, whether or not invited for screening) but who did not die of breast cancer. For this reason, studies of this type require information about individual people from the screening organisation, the regional cancer register and the cause-of-death registry of Statistics Netherlands. This necessitated a protocol with solid guarantees to protect the privacy of the people included in the study, which required a lot of time before the (anonymised) data could start to be analysed.

Initial analyses showed that women who had taken part in the screening programme were more than 50% less likely to die of breast cancer. Introducing a correction factor to exclude the possibility that the women who took part were mostly those who were less likely to die of breast cancer anyway *(selection bias),* decreases the likelihood by a smaller amount. Based on a certain correction method according to Duffy et al., the likelihood of not dying of breast cancer through participation in the screening programme should decrease by 32%.

Other causes of death

The continuing decline in breast cancer mortality will lead to a shift in the cause of death among women. A recent Nijmegen histo-pathological study on breast cancers diagnosed between 2002 and 2006 showed that 42% of invasive tumours had a diameter of less than 15 mm when they were diagnosed, and 58% had a histological malignancy grade of 1 or 2. Both the small tumour diameter and the low histological malignancy grade have had a positive effect on the survival of the patients in question. Estimates show that 81% have an excellent chance of survival, which is also an indication of the beneficial effect of breast cancer screening.

However, this means that women will be more likely to die of a different cause. For example, the lung cancer mortality rate among women has been higher than that of breast cancer in recent years. Factors that come into play during the treatment of breast cancer can also increase the risk of other conditions, and especially increase excess mortality from cardiovascular diseases. Yet initial results from a Nijmegen study have shown no excess mortality due to cardiovascular diseases.

The effects of population-based breast cancer screening on breast cancer incidence and mortality rates in the Netherlands:

Validation and predictions using microsimulation

In order to estimate the long-term effects of the screening programme, it was necessary to update the MISCAN model. For validation, data was used on breast cancer incidence, the stage distribution of invasive tumours, stage-specific incidence of clinically diagnosed and screen-detected tumours, detection rates per tumour stage and screening round, and interval cancers. After adjustment, ductal carcinomas in situ (DCIS) and invasive tumours proved to be easily modellable; from 2000 onwards the simulation was less accurate.

The average duration of pre-clinical breast cancer at the age of 50 is 4.3 years (on average 2.1 years non-invasive, 2.2 years invasive). For women aged 75, these figures are 2.1 years for non-invasive and 3.9 years for invasive tumours.

MISCAN predicts that in 2010, 20 years after the start of screening, the decrease in breast cancer incidence among women aged over 75 will be at its greatest, and will be 12.5% lower than the incidence without screening. Of all tumours diagnosed annually, 2% - 5% will be overdiagnosed. Based on the current screening results, MISCAN predicts that in 2019, the decline in mortality will continue to grow to 30.5% among women aged 55-79. After that, the anticipated breast cancer mortality rate will not decrease much further.

Based on the digital pilot results, we estimate the influence of digital screening on the predicted decrease in breast cancer mortality among women aged 55-79 at 30.8%. Digital screening will cause the number of overdiagnosed tumours to increase by an average of 5%, to a maximum of 5.1% of all diagnosed tumours.

Costs

Changes to the costs of the screening programme between 2005 and 2007 are limited. The transfer of financing from the Exceptional Medical Expenses Act (ABWZ) to the Ministry of Health, Welfare and Sport (VWS) has had no noticeable negative effects. In 2007, the total costs amounted to €49.1 million (provisional figure), and the costs per examination including the national overheads at €53.77. The small 0.88% rise in the cost per examination is mostly due to the national costs for digitisation, the ageing population and an increase in participation.

The national costs constitute 9% of the total costs of the national screening programme, and amounted to €5 per examination in 2007.
The non-recurring costs for the combined conversion to digital screening and to 5 regions come to an average of €1.54 million per year (€7.72 million from 2007-2011). Of this amount, an average of 9% is for staff training and another 9% for the conversion of existing analogue mammograms into digital form. Fifteen percent production losses have also been taken into account.
The recurring additional costs (€8.5 million per year) and savings (€5.2 million per year) related to the digitisation of screening will reach their maximum in 2011. It is expected that 35% of the recurring additional costs for IMS will be paid for by production and the reorganisation.

Conclusions

The results over a period of 18 years presented in this report reveal that the Dutch breast-cancer screening programme has shown a continuously high level of quality. There is a constant decline in breast cancer mortality, now approximately 25% lower among women eligible to take part in the screening programme than in the years before national screening commenced. Various methods of analysis have demonstrated that this decline is largely related to the implementation and subsequent extension of breast cancer screening.
Over the last few years there has been a further increase in attendance among women who have received invitations, in productivity and in screening performance, while costs have essentially remained stable. The efforts of the Dutch National Expert and Training Centre for Breast Cancer Screening (NETCB) combined with the results from the optimisation study carried out in the late 1990s and the reviewed cost effectiveness calculations have led to a 25-30% increase in breast cancer detection within 10 years. The initial digital screening examinations which started in 2004 indicate a further (future) increase in breast cancer detection, which may, however, cause a possibly fixed increase in the number of referrals.
Ten years after extending the upper age limit of the study to 75, we can conclude that this increase was justified. Breast cancer mortality has decreased significantly among women aged 70-79, partly due to screening examinations for women aged 70 and over. Attendance among this group is hardly lower than that of women aged 50-69, and the screening parameters are even slightly more beneficial. The expansion of the study has not led to increased costs per examination.

Recommendations

The Dutch breast-cancer screening programme is currently undergoing two major changes, namely: the reduction of the number of screening regions and their reorganisation into general cancer screening centres, and the rapid roll-out of digital mammography. This demands careful monitoring that must be consistent with the evaluation of the previous analogue period.
For example, the relationship between the screening examinations conducted in the past and the region that originally conducted them must remain traceable for the time being, so that interval cancers (and thereby also regional screening performance) starting from the 2000 reporting year can also be properly recorded. The linkage to the national and other cancer registers should now be given priority, in order to enable analysis of programme sensitivity and specificity at regional and other levels, in relation to the transition from analogue to digital mammography. The experience gained through establishing the linkage at a national level is also important for the future evaluation of other cancer screening programmes.

The increasing referral rate also remains a point of concern, especially considering the rapid growth in the number of digital screening mammograms. All evidence indicates that analogue screening has become increasingly more effective over the years, but relatively little is currently known about digital mammography in this respect. At over 70%, the programme sensitivity of the Dutch screening programme is so high that we should not automatically expect a further increase due to digital screening. Firstly, it remains to be seen whether digital screening will be able to confirm at national level the performance in recent years and the trends shown by the pilots. It is no longer exclusively a matter of trying to detect more breast cancers *(maximising),* but also of trying to reduce the number of unnecessary referrals *(minimising)*.
Digitisation also provides a number of opportunities. For example, new aspects to be studied such as breast-tissue density measurements may provide a better understanding of dense and other breast patterns and the risk of developing breast cancer and regional and sub-regional distributions thereof, and therefore also in the screening performance at regional and sub-regional level.

The coming period will also require a critical examination of the age limits that currently apply to the screening programme. A decision will need to be made relatively soon about whether digital screening will enable the lower age limit to be dropped further, and whether extending the programme to

include younger age groups will be cost-effective. We recommend that age-specific overdiagnosis be calculated and factors examined that may be of influence here, especially also for the age groups surrounding the upper age limit of the programme.

Literature

van Agt HME, Fracheboud F, Rebolj M, Korfage IJ, de Koning HJ. Volledige, evenwichtige en eerlijke voorlichting over nut en risico's van bevolkingsonderzoek naar kanker. [Complete, balanced and fair information on the benefits and risks of cancer screening] Eindrapport (November 2008). Rotterdam: Afd. Maatschappelijke Gezondheidszorg, Erasmus MC, 2008.

Bleiker EM, Hendriks JH, Otten JD, Verbeek AL, van der Ploeg HM. Personality factors and breast cancer risk: a 13-year follow-up. J Natl Cancer Inst 2008;100:213-8.

Broeders MJM, Scharpantgen A, Ascunce N, Gairard B, Olsen AH, Mantellini P, et al. Comparison of early performance indicators for screening projects within the European Breast Cancer Network: 1989-2000. Eur J Cancer Prevention 2005;14:107-116.

Bulliard JL, Sasieni P, Klabunde CN, de Landtsheer JP, Yankaskas BC, Fracheboud J. Methodological issues in international comparison of interval breast cancers. Int J Cancer 2006;119:1158-63.

Bult P, Manders P, Straatman HM, Tjan-Heijnen VC, Beex LV, Hendriks J, Leer JW, Verbeek AL, Holland R. In primary breast cancer the mitotic activity yields similar prognostic information as the histological grade: a study with long-term follow-up. Breast Cancer Res Treat. 2009 Sep 17. [Epub ahead of print].

Clarke LD, Plevritis SK, Boer R, Cronin KA, Feuer EJ. A comparative review of CISNET breast models used to analyze U.S. breast cancer incidence and mortality trends. JNCI Monographs: Oxford University Press; 2006. p. 96-105.

Duijm LEM, Groenewoud JH, Roumen RMH, de Koning HJ, Plaisier ML, Fracheboud J. A decade of breast cancer screening in The Netherlands: trends in the preoperative diagnosis of breast cancer. Breast Cancer Res Treat 2007;106:113-9.

Duijm LE, Groenewoud JH, Fracheboud J, Plaisier ML, Roumen RM, Ineveld BM van, et al. Utilization and cost of diagnostic imaging and biopsies following positive screening mammography in the southern breast cancer screening region of the Netherlands, 2000-2005. Eur Radiol 2008 May 20;18(11):2390-7.

Duijm LE, Groenewoud JH, Koning HJ, Coebergh JW, Beek MV, Hooijen MJ et al. Delayed diagnosis of breast cancer in women recalled for suspicious screening mammography. Eur J Cancer 2008 Nov 29;45(5):774-81.

Fracheboud J, Groenewoud JH, Boer R, Draisma G, de Bruijn AE, Verbeek ALM et al. Seventy-five years is an appropriate upper age limit for population-based mammography screening. Int J Cancer 2006;118:2020-5.

Fracheboud J, de Koning HJ. Screening for breast cancer. In: Wildschut HIJ, Weiner CP, Peters TJ, editors. When to screen in Obstetrics and Gynecology 2nd edition. Philadelphia: Saunders/Elsevier; 2006. p. 591-602.

Fracheboud J, Koning HJ de. Preventie van borstkanker. [Prevention of breast cancer] Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Website: www.nationaalkompas.nl. Bilthoven: RIVM; 2006. p. website.

Fracheboud J, JH Groenewoud en HJ de Koning. Bevolkingsonderzoek naar borstkanker. [Breast cancer screening] In: Wobbes T, Koning CCE, Nortier JWR (red.). Handboek Mammacarcinoom. Utrecht: de Tijdstroom, 2007.

Fracheboud J, Groenewoud JH, de Koning HJ. Fifteen years of population-based breast cancer screening in the Netherlands. Semin Breast Dis 2007;10:72-82.

Fracheboud J en de Koning HJ. Digitale pilots: vergelijking analoge en digitale screeningsperformance van drie digitale pilots in het Nederlandse bevolkingsonderzoek naar borstkanker. [Digital mammography screening pilots: comparison of analogue and digital screening performance in the Dutch breast cancer screening programme] Eindverslag voor RIVM. Rotterdam: Afd. MGZ; Oktober 2007.

Fracheboud J en de Koning HJ. Population-based breast cancer screening: from predictions to outcomes. In: Klijn JGM, editor. Daniel den Hoed Cancer News - Breast Cancer. Rotterdam: Erasmus MC; 2008. p. 7-9.

Fracheboud J, de Koning HJ, de Broeder JM. Borstkankerpreventie. Doel en organisatie. [Prevention of breast cancer. Objective and organisation] Volksgezondheid Toekomst Verkenning Nationaal Kompas Volksgezondheid (www.nationaalkompas.nl) 2008. [Available from: http://www.rivm.nl/vtv/object_document/o2510n19966.html].

de Gelder R, van As E, Tilanus-Linthorst MM, Bartels CCM, Boer R, Draisma G et al. Breast cancer screening: evidence for false reassurance? Int J Cancer 2008;123:680-6.

de Gelder R, Bulliard JL, de Wolf C, Fracheboud J, Draisma G, Schopper D et al. Cost-effectiveness of mammography screening in Switzerland: a microsimulation analysis. Rotterdam: Dept. of Public Health, Erasmus MC; October 2007.

de Gelder R, Draisma G, Fracheboud J, de Koning HJ. Cost-effectiveness of opportunistic versus organized mammography screening in Switzerland. Eur J Cancer 2009;45:127-38.

Groenewoud JH, Otten JDM, Fracheboud J, Draisma G, van Ineveld BM, Holland R, Verbeek ALM, de Koning HJ (NETB). Cost-effectiveness of different reading and referral strategies in mammography screening in the Netherlands. Breast Cancer Res Treat 2007;102:211-8.

Habbema JDF, Tan SYGL, Cronin KA. Impact of mammography on U.S. breast cancer mortality, 1975-2000: are intermediate outcome measures informative? JNCI Monographs: Oxford University Press; 2006. p. 105-11.

HKZ Centraal College van Deskundigen voor de Zorgsector. Bevolkingsonderzoek naar borstkanker. [Breast cancer screening] Utrecht: Stichting HKZ; 2006.

den Heeten GJ en Broeders MJM. Het bevolkingsonderzoek op borstkanker in Nederland 2008. [The Dutch breast cancer screening programme in 2008] MemoRad 2008;13(4):6-8.

Hofvind S, Yankaskas B, Bulliard JL, Klabunde CN, Fracheboud J. Comparing interval breast cancer rates in Norway and North Carolina: results and challenges. J Med Screen 2009;16:131-39.

Karssemeijer N, Otten JD, Rijken H, Holland R. Computer aided detection of masses in mammograms as decision support. Br J Radiol. 2006;79 Spec No 2:S123-6.

Karssemeijer N, Bluekens AM, Beijerinck D, Deurenberg JJ, Beekman M, Visser R, van Engen R, Bartels-Kortland A, Broeders MJ. Breast cancer screening results 5 years after introduction of digital mammography in a population-based screening program. Radiology 2009; 253(2):353-8.

Koning HJ de, Draisma G, Fracheboud J, de Bruijn AE. Overdiagnosis and overtreatment of breast cancer: Microsimulation modelling estimates based on observed screen and clinical data. Breast Cancer Res 2006;8:202-6.

Koning HJ de. LETB Tussenrapportage 2006. Belangrijkste resultaten bevolkingsonderzoek borstkanker. [NETB interim report 2006. Main results breast cancer screening programme] In: Pijnappel R, editor. EduRad - Syllabus Mammadiagnostiek en Interventie nr 58. 's Hertogenbosch: NVVR; 2007. p. 37.

Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker (LETB). [National evaluation of breast cance screening in the Netherlands. Eleventh evaluation report] Fracheboud J, Otto SJ, Draisma G, Groenewoud JH, Ineveld BM van, Broeders MJM, et al. Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland LETB(XI); 2005. Rotterdam: afd. MGZ, Erasmus MC en UMC St Radboud Nijmegen; 2005.

Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker (LETB). Tussenrapportage 2006. Belangrijkste resultaten bevolkingsonderzoek borstkanker. [Interim report 2006. Main results breast cancer screening programme in the Netherlands] Rotterdam: afd. MGZ, Erasmus MC en UMC St Radboud Nijmegen; 2007.

Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker (LETB). Tussenrapportage 2007. Belangrijkste resultaten bevolkingsonderzoek borstkanker. [Interim report 2007. Main results breast cancer screening programme in the Netherlands] Rotterdam: afd. MGZ, Erasmus MC en UMC St Radboud Nijmegen; 2008.

Lemmers O, Broeders M, Verbeek A, Heeten G, Holland R, Borm GF. League tables of breast cancer screening units: worst-case and best-case scenario ratings helped in exposing real differences between performance ratings. J Med Screen 2009;16(2):67-72.

Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann Oncol. 2008;19(4):614-22.

Mandelblatt JS, Cronin KA, Bailey S, Berry DA, de Koning HJ, Draisma G et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. Ann Int Med 2009;151:738-47.

Okonkwo LQ, Draisma G, der Kinderen A, Brown M, de Koning HJ. Breast cancer screening policies in developing countries: a cost-effectiveness analysis for India. J Natl Cancer Inst 2008;100(18):1290-300.

Otten JDM, N Karssemeijer, JHCL Hendriks, JH Groenewoud, J Fracheboud, ALM Verbeek, HJ de Koning, R Holland. Effect of recall rate on earlier screen detection of breast cancers based on the Dutch performance indicators. J Natl Cancer Inst 2005; 97:748-54.

Otten JD, Broeders MJ, Fracheboud J, Otto SJ, de Koning HJ, Verbeek AL. Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975-2006. Int J Cancer 2008 Oct 15;123(8):1929-34.

Paap E, Broeders MJ, van Schoor G, Otten JD, Verbeek AL. Large increase in a Dutch women's lifetime risk of developing breast cancer. Eur J Cancer 2008;44(11):1485-7.

Perry N, Broeders M, Wolf C de, Törnberg S, Holland R, von Karsa L, eds. European guidelines for quality assurance in breast screening and diagnosis. 4th Ed. Luxembourg: European Commission. Europe Against Cancer programme, 2006.

Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann Oncol. 2008;19(4):614-22.

RIVM Centrum voor Bevolkingsonderzoek. Guijt PC, Reij R, van der Veen N, editors. Fracheboud J et al. Beleidskader bevolkingsonderzoek naar kanker. [Framework population-based screening on cancer] Bilthoven: RIVM; 2009.

Rijnsburger AJ, Essink-Bot ML, van As E, Cockburn J, de Koning HJ. Measuring psychological consequences of screening: adaptation of the Psychological Consequences Questionnaire into Dutch. Qual Life Res 2006;15:933-40.

Segnan N, Ohuchi N, Scharpantgen A, Ballard-Barbash R, Fracheboud J et al. (on behalf of the International Cancer Screening Network). Designing print materials: a communication guide for breast cancer screening. Bethesda: NIH/NCI; 2007. p. 1-120.

Schoor G van, Broeders MJ, Paap E, Otten JD, den Heeten GJ, Verbeek AL. A rationale for starting breast cancer screening under age 50. Ann Oncol 2008;19(6):1208-9.

Vereniging van Integrale Kankercentra VKC, Kwaliteitsinstituut CBO, Nationaal Borstkanker Overleg Nederland (NABON). Richtlijn mammacarcinoom 2008. [Practice guideline breast cancer 2008] Amsterdam: Nationaal Borstkanker Overleg Nederland (NABON); 2008.

Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Vlastos G, Bernard-Marty C et al. Management of breast cancer in the elderly: Recommendations of the International Society of Geriatric Oncology (SIOG). Lancet Oncology 2007;8:1101-15.

Zoetelief J, Veldkamp WJ, Thijssen MA, Jansen JT. Glandularity and mean glandular dose determined for individual women at four regional breast cancer screening units in the Netherlands. Phys Med Biol. 2006;51(7):1807-17.

Zonderland HM, Tuut MK, den Heeten GJ, Asperen CJ, de Bock GH, Rutqers EJ, Westenend PJ, Smit GM, Benraadt J. Richtlijn 'screening en diagnostiek van het mammacarcinoom' (herziening). [Revised practice guideline 'Screening and diagnosis of breast cancer'] Ned Tijdschr Geneeskd. 2008;152(43):2336-9.

Appendices

Screening regions and Comprehensive Cancer Centres (regional cancer registry) in 2007

A Stichting Kankerpreventie en –screening Limburg (SKsL)
Integraal Kankercentrum Limburg (IKL)

B Stichting Preventicon voor de Vroege Opsporing van Borstkanker in Midden-Nederland
Integraal Kankercentrum Midden-Nederland (IKMN)

C Bevolkingsonderzoek Borstkanker Noord-Holland en Flevoland, Stichting Kankerpreventie IKA (SKP IKA)
Integraal Kankercentrum Amsterdam (IKA)

D Stichting Bevolkingsonderzoek Borstkanker Noord-Nederland (BBNN)
Integraal Kankercentrum Noord-Nederland (IKN)

E Stichting Vroege Opsporing Kanker Oost-Nederland (SVOKON)
Integraal Kankercentrum Oost (IKO)

F Stichting Vroege Opsporing Borstkanker (SVOB)
Integraal Kankercentrum Stedendriehoek Twente (IKST)

G Stichting Bevolkingsonderzoek Borstkanker West-Nederland (BoB West)
Integraal Kankercentrum West (IKW)

H Stichting Bevolkingsonderzoek Borstkanker Zuidwest Nederland (SBBZWN)
Integraal Kankercentrum Rotterdam (IKR)

I Stichting Bevolkingsonderzoek Borstkanker Zuid-Nederland (BoBZ)
Integraal Kankercentrum Zuid (IKZ)

Tables

2.1 Kengetallen bevolkingsonderzoek naar borstkanker 1990-2007 ([ ] gegevens niet of niet volledig beschikbaar)

2.1 Main results breast cancer screening programme in the Netherlands 1990-2007 *([ ] data incomplete or not yet available)*

	1990-1997[1]	1998-2002	2003	2004	2005	2006	2007	1990-2007
Vrouwelijke populatie[2] (mln.) *Female population[2] (million)*	7,32-7,87	7,91-8,13	8.177	8.212	8.240	8.257	8.269	–
Doelgroep per jaar (x 1000) *Targeted per year (x 1000)*	733 - 813	1.021-1.090	1.109	1.126	1.145	1.164	1.183	–
Uitnodigingen *Invitations*	4.071.120	4.878.221	1.070.692	1.088.827	1.089.810	1.083.050	1.108.163	14.389.883
Screeningsonderzoeken *Screen examinations*	3.128.241	3.838.601	865.689	888.830	892.299	886.025	911.547	11.411.232
- eerste / *initial* (%)	47,3%	15,8%	12,9%	12,9%	12,5%	12,6%	12,0%	23,2%
- vervolg / *subsequent* < 2,5 jaar (%)	51,1%	76,9%	82,5%	82,5%	83,5%	83,3%	84,0%	72,3%
- vervolg / *subsequent* >= 2,5 jaar (%)	1,6%	7,3%	4,6%	4,5%	4,1%	4,0%	4,0%	4,6%
- digitaal / *digital* (% van totaal / *of total*)	–	–	–	1,1%	4,0%	4,8%	7,4%	–
Screeningseenheden *Screening units*	5 -> 47	47 -> 62	62	62	63	65	65	5 -> 65
Gemidd. uitnodigingsinterval (maanden) *Mean individual invitation interval (months)*	–	–	24,05	24,05	24,14	24,37	24,69	–
Gemidd. screeningsinterval (maanden) *Mean individual screen interval (months)*	21,8-25,1	24,8-25,2	24,17	23,96	23,92	24,18	24,56	–
Follow-up verwijsadviezen (%) *Follow-up of screen-positives (%)*	97,7%	98,1%	98,1%	98,6%	98,0%	99,0%	97,8%	98,1%
Onderzoeken per screeningseenheid *Screens per screening unit*		13.705	14.195	14.336	14.163	13.631	14.024	–
Verwijsadviezen *Referral recommendations*	30.901	45.962	11.326	12.523	12.910	14.289	16.414	144.325
(Naald-)Biopsieën t.g.v. screening *(Needle)Biopsies due to screening*	21.313	26.647	6.347	6.199	5.906	6.439	7.497	80.348
Screeningscarcinomen *Screen-detected cancers*	14.966	18.723	4.232	4.399	4.353	4.582	4.999	56.254
Volledigheid tumorkenmerken (%) *Completeness tumour characteristics (%)*	97,9%	98,9%	96,4%	98,1%	98,7%	98,5%	98,3%	98,3%
- in-situ carcinoom (DCIS) (%) *ductal carcinoma in situ (%)*	14,3%	13,9%	13,7%	15,0%	14,5%	15,8%	15,1%	14,4%
- T1N- (<=20 mm, lymfkliernegatief) (%) *T1N- (<=20 mm, lymph node negative) (%)*	47,2%	47,7%	48,2%	48,5%	50,8%	50,8%	51,7%	48,5%
- T2+N+ (>20 mm, lymfklierpositief) (%) *T2+N+ (>20 mm, lymph node positive) (%)*	8,9%	9,4%	9,1%	9,8%	8,3%	7,4%	8,0%	8,9%
Bereik doelgroep (%) *Coverage target population (%)*	11 -> 97%	82->100%	100%	100%	100%	100%	100%	–
Totale opkomst (%) *Overall attendance (%)*	78,2%	78,8%	80,8%	80,8%	81,7%	81,8%	82,4%	79,7%
Verwijscijfer per 1000 *Referral rate per 1000*	9,9	12,0	13,1	14,1	14,5	16,1	18,0	12,7
(Naald-)Biopsieën per 1000 *(Needle) Biopsies per 1000*	6,8	6,9	7,3	7,0	6,6	7,3	8,2	7,0
Borstkankerdetectie per 1000 *Breast cancer detection per 1000*	4,8	4,9	4,9	4,9	4,9	5,2	5,5	4,9
PVW~ verwijsadvies (%) *PPV[3] referral recommendation (%)*	48%	41%	37%	35%	34%	32%	30%	39%
PVW~ (naald-)biopsie (%) *PPV[3] (needle) biopsy (%)*	70%	70%	67%	71%	74%	71%	67%	70%
(Gemiddelde) Totale kosten per jaar ~ (mln euro) *(Average) Annual total cost[4] (million euros)*	18,5	34,6	42,3	44,4	45,5	45,5[5]	48,7[5]	30,4
Kosten per onderzoek (euro) *Cost per screen examination (euros)*	47,43	45,11	48,80	49,91	50,96	51,37[5]	53,36[5]	47,85

	2002	2003	2004	2005	2006	2007	
Verandering borstkankersterfte t.o.v. 1986-1988 (%) *Change in breast cancer mortality since 1986-1988 (%)*	-18,5	-22,0	-25,5	-25,8	-23,5	-28,7	

LETB/*NETB,* 2008

[1] Leeftijd 49-68 jaar; vanaf 1998 49-75 jaar
[2] Bron: CBS
[3] PVW: positief voorspellende waarde
[4] Achteraf gerealiseerd (in lopende prijzen)
[5] Voorlopige cijfers

[1] *Ages 49-68 years; as of 1998 49-75 years*
[2] *Source: Statistics Netherlands*
[3] *PPV: positive predictive value*
[4] *Realised (current prices)*
[5] *Preliminary figures*

2.2 Signaalwaarden
2.2 Default values ("signal values")

		"Signal value" **National film-screen**
Opkomst (%) *Attendance rate (%)*	Alle uitnodigingen *All invitations*	**> 80%**
Gemiddeld uitnodigingsinterval *Mean invitation interval*	% binnen 22,0-25,9 maanden % within 22.0-25.9 months	**> 80%**
Verwijscijfer (per 1000) *Referrals (per 1000)*	• eerste screeningsonderzoeken *initial screen examinations* • vervolgscreeningen (< 2,5 jaar) *subsequent screens (< 2.5 years)*	**25-35** **13-20**
Volledigheid follow-up verwijsadviezen *Completeness follow-up screen-positives*	Einduitslag bekend binnen 3 maanden *Final result known within 3 months*	**> 95%**
Screeningscarcinomen (per 1000) *Screen-detected breast cancers (per 1000)*	• eerste screeningsonderzoeken *initial screen examinations* • vervolgscreeningen (< 2,5 jaar) *subsequent screens (< 2.5 years)*	**> 5,5** **> 4,5**
Volledigheid TNM-classificatie screeningscarcinomen *Completeness TNM-classification screen-detected BC*	Binnen 3 maanden na screening *Within 3 months after screening*	**> 95%**
Bepaalde tumorgroottes *Specific tumour sizes*	• eerste screeningsonderzoeken *initial screen examinations* DCIS T2 • vervolgscreeningen (< 2,5 jaar) *subsequent screens (< 2.5 years)* DCIS T2	 **15-20%** **< 20%** **10-15%** **< 17,5%**

2.3 Jaarlijkse regionale indicatoren in vergelijking met landelijk gemiddelde in de periode 2003-2007
2.3 Annual regional outcome parameters compared to the national mean in the period 2003-2007

Indicator / ***Outcome parameter***	**NL**	**Regio's / *Regions*** A					B					C					D					E					F					G					H					I				
	2003-2007	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007
Opkomst totaal *Total attendance*	81,5%	+	‡	+	‡	+	-	-	-	-	-	=	=	=	-	-	‡	‡	‡	‡	#	-	+	+	+	+	+	+	‡	+	‡	=	=	-	=	0	=	≡	=	≡	-	+	+	‡	‡	‡
Gemiddeld individueel uitnodigingsinterval *Mean individual invitation interval*	77,1%	-	=	0	‡	‡	=	=	≡	0	+	0	-	0	≡	≡	‡	‡	‡	‡	‡	‡	‡	‡	‡	‡	‡	0	‡	‡	#	≡	=	0	‡	‡	≡	≡	≡	≡	=	+	‡	‡	‡	+
Verwijscijfer 1e screening (per 1000) *Referral rate initial screens (per 1000)*	27,7	=	-	0	+	+	=	0	0	-	0	≡	=	-	0	‡	-	=	≡	≡	=	≡	=	=	‡	#	≡	≡	≡	=	0	≡	≡	≡	≡	0	0	‡	#	#	#	‡	#	#	#	#
1000) *Referral rate regular subsequent screens (per*	12,9	=	=	0	0	0	=	-	-	-	=	-	0	0	‡	#	0	=	=	=	-	=	=	=	0	#	=	=	=	=	‡	≡	=	-	‡	#	0	‡	‡	#	#	-	-	0	+	0
Detectiecijfer 1e screening (per 1000) *Detection rate initial screens (per 1000)*	5,5	0	0	+	0	=	#	‡	0	+	#	=	+	0	0	-	-	0	-	0	0	=	=	0	0	#	‡	‡	=	#	‡	0	0	-	=	-	0	+	=	0	+	-	=	-	-	+
1000) *Detection rate regular subsequent screens (per*	4,8	=	=	0	0	-	+	0	0	0	0	-	0	-	+	+	0	0	0	0	‡	0	=	=	0	#	-	-	0	+	‡	-	=	+	‡	‡	-	+	0	0	‡	0	0	-	-	-
Screeningscarcinomen / *detected breast cancers*																																														
DCIS eerste screeningen (%) *DCIS initial screens (%)*	18,1%	0	=	=	-	≡	‡	#	≡	#	+	≡	=	≡	‡	‡	≡	≡	=	0	-	≡	=	=	‡	0	=	‡	0	‡	=	+	+	#	#	≡	0	+	#	‡	-	#	‡	‡	≡	+
invasief >= T2 eerste screening (%) *invasive >= T2 inital screens (%)*	21,6%	0	‡	=	-	0	‡	≡	-	≡	‡	#	+	≡	=	-	=	#	0	‡	-	‡	‡	=	-	=	0	#	0	-	#	-	‡	0	≡	≡	0	‡	+	0	0	‡	≡	=	-	#
Tx / niet geclassified eerste screening (%) *Tx / not-classified inital screens (%)*	3,2%	≡	≡	#	≡	≡	#	#	≡	#	#	≡	#	#	≡	#	#	+	=	≡	≡	0	#	≡	≡	#	#	‡	#	#	≡	≡	#	#	#	≡	=	≡	≡	≡	≡	≡	≡	≡	≡	≡
DCIS reguliere vervolgscreeningen (%) *DCIS regular subsequent screens (%)*	14,4%	≡	-	=	≡	0	=	#	‡	#	0	0	-	=	+	‡	-	0	-	0	=	=	0	≡	=	0	=	0	0	0	=	‡	‡	‡	‡	‡	0	+	‡	‡	#	=	=	0	+	0
invasief >= T2 eerste screening (%) *invasive >= T2 inital screens (%)*	16,3%	=	0	0	‡	=	=	=	#	=	=	-	=	+	=	=	‡	‡	0	-	‡	#	0	+	=	=	#	‡	#	‡	0	=	≡	+	0	=	‡	‡	=	=	=	+	0	0	‡	‡
Tx / niet geclassified eerste screening (%) *Tx / not-classified inital screens (%)*	2,6%	≡	≡	≡	≡	≡	#	#	≡	‡	#	0	≡	#	=	≡	#	‡	≡	=	≡	≡	≡	≡	0	0	#	0	≡	≡	-	#	-	#	#	#	≡	≡	≡	≡	≡	0	≡	≡	≡	≡

vergeleken met landelijk gemiddelde 2003-2007:

	opkomst / *attendance*
≡	>=5% lager / *>=5% lager*
=	2,5-5% lager / *2.5-5% lower*
-	1-2,5% lager / *1-2.5% lower*
0	gemiddelde ± 1% / *mean ± 1%*
+	1-2,5% hoger / *1-2.5% higher*
‡	2,5-5% hoger / *2.5-5% higher*
#	>=5% hoger / *>=5% hoger*

compared to national mean 2003-2007:

	overige indicatoren / *other parameters*
≡	>=25% lager / *>=25% lager*
=	10-25% lager / *10-25% lower*
-	5-10% lager / *5-10% lower*
0	gemiddelde ± 5% / *mean ± 5%*
+	5-10% hoger / *5-10% higher*
‡	10-25% hoger / *10-25% higher*
#	>=25% hoger / *>=25% hoger*

Tables

3.1 Uitnodigingen en opkomst 1990-2007
3.1 *Invitations and attendance 1990-2007*

		Uitnodigingen *Invitations*			Herinneringen *Reminders*				Totaal *Total*	
Jaar *Year*	Leeftijd *Age*	Uitgenodigd *Invited*	Onderzocht *Screened*	Opkomst *Attendance*	Uitgenodigd *Invited*	Onderzocht *Screened*	van alle uitnod. *of all invitations*	herinneringen *of reminders*	Onderzocht *Screened*	Opkomst *Attendance*
		N	N	%	N	N	%	%	N	t
1990-1997	49-70	4.071.120	3.096.230	76,1%	565.113	88.462	2,2%	15,7%	3.184.692	78,2%
1998	49-75	832.470	650.644	78,2%	98.003	15.873	1,9%	16,2%	666.517	80,1%
1999	49-75	961.460	730.487	76,0%	117.234	16.266	1,7%	13,9%	746.753	77,7%
2000	49-75	1.005.029	774.192	77,0%	118.714	14.763	1,5%	12,4%	788.955	78,5%
2001	49-75	1.020.741	789.643	77,4%	112.900	13.677	1,3%	12,1%	803.320	78,7%
2002	49-75	1.058.521	824.074	77,9%	117.712	13.607	1,3%	11,6%	837.681	79,1%
2003	49-75	1.070.692	849.459	79,3%	124.668	15.800	1,5%	12,7%	865.259	80,8%
2004	49-75	1.088.827	861.734	79,1%	135.514	18.269	1,7%	13,5%	880.003	80,8%
2005	49-75	1.089.810	874.019	80,2%	119.008	16.166	1,5%	13,6%	890.185	81,7%
2006	49-75	1.083.050	868.137	80,2%	120.268	17.653	1,6%	14,7%	885.790	81,8%
2007	49-75	1.108.163	896.026	80,9%	111.298	16.653	1,5%	15,0%	912.679	82,4%
2007	49	60.307	46.640	77,3%	8.343	1.534	2,5%	18,4%	48.174	79,9%
2007	50-54	266.238	212.517	79,8%	31.348	4.780	1,8%	15,2%	217.297	81,6%
2007	55-59	257.277	210.683	81,9%	23.639	3.850	1,5%	16,3%	214.533	83,4%
2007	60-64	212.899	176.349	82,8%	18.323	2.900	1,4%	15,8%	179.249	84,2%
2007	65-69	166.206	136.626	82,2%	14.351	2.056	1,2%	14,3%	138.682	83,4%
2007	70-74	143.946	112.356	78,1%	15.083	1.513	1,1%	10,0%	113.869	79,1%
2007	> 74	1.290	855	66,3%	211	20	1,6%	9,5%	875	67,8%
1990-2007	49	838.309	639.235	76,3%	112.706	22.768	2,7%	20,2%	662.003	79,0%
1990-2007	50-54	3.772.654	2.954.104	78,3%	455.671	73.817	2,0%	16,2%	3.027.921	80,3%
1990-2007	55-59	3.260.006	2.605.350	79,9%	362.708	55.118	1,7%	15,2%	2.660.468	81,6%
1990-2007	60-64	2.752.941	2.190.802	79,6%	314.930	43.650	1,6%	13,9%	2.234.452	81,2%
1990-2007	65-69	2.297.262	1.775.778	77,3%	287.925	33.878	1,5%	11,8%	1.809.656	78,8%
1990-2007	70-74	1.354.171	968.247	71,5%	195.643	16.722	1,2%	8,5%	984.969	72,7%
1990-2007	> 74	16.233	9.236	56,9%	3.306	224	1,4%	6,8%	9.460	58,3%
1990-2007	49-75	14.291.576	11.142.752	78,0%	1.732.889	246.177	1,7%	14,2%	11.388.929	79,7%
Extra uitnodigingen (niet uitgesplitst naar leeftijd/screeningsronde) *Additional invitations (not subdivided by age/screening round)*										
1990-1996	49-70	98.307	71.893	73,1%	7.543	1.012	1,0%	13,4%	72.905	74,2%
1990-2007	49-75	14.389.883	11.214.645	77,9%	1.740.432	247.189	1,7%	14,2%	11.461.834	79,7%

3.2 Screeningsonderzoeken 1990-2007, alle leeftijden

3.2 Screen examinations 1990-2007, all ages

Jaar *Year*	1e onderzoeken *Initial screens*		Vervolgonderzoeken *Subsequent screens*						Alle onderzoeken *All screens*	Groei *Change*
			< 2,5 jaar/*years*		≥ 2,5 jaar/*years*		Totaal / *total*			
	N	%	N	%	N	%	N	%	N	%
1990-1997	1.478.573	47,3%	1.598.075	51,1%	51.593	1,6%	1.649.668	52,7%	3.128.241	
1998	125.881	19,0%	503.079	75,9%	33.865	5,1%	536.944	81,0%	662.825	
1999	130.495	17,5%	540.600	72,7%	72.808	9,8%	613.408	82,5%	743.903	+12,2%
2000	125.432	15,8%	588.392	74,2%	79.346	10,0%	667.738	84,2%	793.170	+6,6%
2001	109.693	13,6%	647.030	80,5%	47.002	5,8%	694.032	86,4%	803.725	+1,3%
2002	113.749	13,6%	674.538	80,8%	46.691	5,6%	721.229	86,4%	834.978	+3,9%
2003	111.912	12,9%	713.984	82,5%	39.793	4,6%	753.777	87,1%	865.689	+3,7%
2004	115.101	12,9%	733.396	82,5%	40.333	4,5%	773.729	87,1%	888.830	+2,7%
2005	111.187	12,5%	744.855	83,5%	36.257	4,1%	781.112	87,5%	892.299	+0,4%
2006	112.079	12,6%	738.464	83,3%	35.482	4,0%	773.946	87,4%	886.025	-0,7%
2007	109.486	12,0%	765.455	84,0%	36.606	4,0%	802.061	88,0%	911.547	+2,9%
1990-2007	2.643.588	23,2%	8.247.868	72,3%	519.776	4,6%	8.767.644	76,8%	11.411.232	

3.3 A Resultaten eerste screeningsonderzoeken 1990-2007

3.3 A Results of inital screen examinations 1990-2007

Jaar *Year*	Leeftijd *Age*	Screenings-onderzoeken *Screen examinations*	Verwijsadviezen *Referrals*		Aanvullende diagnostiek *Further diagnostics*					Borstkankers *Breast cancers*		PVW *PPV*	
					Geen follow-up of onbekend *No follow-up or unknown*	Beeldvormend onderzoek *Additional imaging*	Cytologie *Cytology*	Histologie *Histology*	Biopsie-cijfer *Biopsy rate*	Detectiecijfer *Detection rate*		Verwijzing *Referral*	(Naald-) Biopsie *(Needle) Biopsy*
		N	N	/1000	%	%	%	%	/1000	N	/1000	%	%
1990-1997	49-75	1.478.573	19.360	13,1	2,3	22,8	4,3%	70,9%	9,3	9.030	6,1	46,6%	65,3%
1998	49-75	125.881	1.961	15,6	1,9	33,7	5,3%	59,3%	9,2	663	5,3	33,8%	57,0%
1999	49-75	130.495	2.237	17,1	2,5	35,9	5,0%	57,0%	9,8	775	5,9	34,6%	60,4%
2000	49-75	125.432	2.324	18,5	2,5	31,8	5,1%	59,7%	11,1	740	5,9	31,8%	51,8%
2001	49-75	109.693	2.607	23,8	2,1	42,8	9,1%	46,0%	10,9	665	6,1	25,5%	52,7%
2002	49-75	113.749	2.479	21,8	2,0	42,5	7,9%	47,6%	10,4	624	5,5	25,2%	49,3%
2003	49-75	111.912	2.537	22,7	2,4	39,6	6,7%	51,3%	11,6	600	5,4	23,6%	44,9%
2004	49-75	115.101	2.961	25,7	1,4	32,6	6,7%	44,7%	11,5	642	5,6	21,7%	44,4%
2005	49-75	111.187	2.933	26,4	1,9	37,3	8,1%	37,6%	9,9	579	5,2	19,7%	48,3%
2006	49-75	112.079	3.318	29,6	1,1	41,0	6,3%	38,6%	11,4	620	5,5	18,7%	45,5%
2007	49-75	109.486	3.766	34,4	2,4	51,7	6,7%	39,1%	13,5	641	5,9	17,0%	40,1%
2007	49	47.423	1.571	33,1	1,9	52,1	6,6%	39,1%	13,0	249	5,3	15,8%	37,1%
2007	50-54	53.574	1.906	35,6	2,2	53,0	6,9%	37,9%	13,5	316	5,9	16,6%	40,6%
2007	55-59	3.978	129	32,4	10,1	38,0	5,4%	46,5%	15,1	27	6,8	20,9%	38,3%
2007	60-64	2.332	78	33,4	3,8	50,0	5,1%	41,0%	13,7	23	9,9	29,5%	65,6%
2007	65-69	1.319	50	37,9	6,0	40,0	2,0%	52,0%	19,7	18	13,6	36,0%	65,4%
2007	70-74	849	32	37,7	3,1	31,3	12,5%	56,3%	21,2	8	9,4	25,0%	44,4%
2007	> 74	11	0	0,0	0,0	0,0	0,0%	0,0%	0,0	0	0,0	0,0%	0,0%
1990-2007	49	643.441	12.296	19,1	1,8	39,3	6,7%	47,8%	9,1	2.888	4,5	23,5%	47,4%
1990-2007	50-54	1.040.034	18.805	18,1	2,1	36,9	6,5%	51,2%	9,3	4.990	4,8	26,5%	50,1%
1990-2007	55-59	353.395	4.920	13,9	2,7	25,2	4,7%	66,3%	9,2	2.141	6,1	43,5%	64,8%
1990-2007	60-64	316.612	4.787	15,1	2,3	20,8	3,8%	72,6%	11,0	2.423	7,7	50,6%	68,8%
1990-2007	65-69	240.207	4.334	18,0	2,2	19,0	3,1%	75,3%	13,6	2.446	10,2	56,4%	74,2%
1990-2007	70-74	48.261	1.301	27,0	2,4	25,0	4,3%	67,6%	18,2	669	13,9	51,4%	73,5%
1990-2007	> 74	1.638	40	24,4	0,0	20,0	10,0%	72,5%	17,7	22	13,4	55,0%	72,4%
1990-2007	49-75	2.643.588	46.483	17,6	2,1	32,6	5,7%	56,8%	10,0	15.579	5,9	33,5%	57,6%

PVW: positief voorspellende waarde

PPV: positive predictive value

3.3 B Resultaten vervolgscreeningen binnen 2,5 jaar na vorig onderzoek 1990-2007

3.3 B Results of subsequent screen examinations < 2.5 years since previous screen 1990-2007

					Aanvullende diagnostiek *Further diagnostics*					Borstkankers *Breast cancers*		PVW *PPV*	
Jaar *Year*	Leeftijd *Age*	Screenings-onderzoeken *Screen examinations*	Verwijsadviezen *Referrals*		Geen follow-up of onbekend *No follow-up or unknown*	Beeldvormend onderzoek *Additional imaging*	Cytologie *Cytology*	Histologie *Histology*	Biopsie-cijfer *Biopsy rate*	Detectiecijfer *Detection rate*		Verwijzing *Referral*	(Naald-) Biopsie *(Needle) Biopsy*
		N	N	/1000	%	%	%	%	/1000	N	/1000	%	%
1990-1997	49-75	1.593.817	10.993	6,9	2,4	27,8	4,4%	65,6%	4,5	5.642	3,5	51,3%	77,5%
1998	49-75	503.079	4.046	8,0	1,8	32,3	4,7%	61,4%	4,9	1.918	3,8	47,4%	76,9%
1999	49-75	540.600	4.690	8,7	2,6	31,2	5,2%	61,3%	5,3	2.166	4,0	46,2%	74,2%
2000	49-75	588.392	5.550	9,4	1,7	29,1	4,1%	64,1%	6,0	2.478	4,2	44,6%	67,8%
2001	49-75	647.030	7.475	11,6	1,7	37,1	6,9%	54,3%	6,3	3.066	4,7	41,0%	72,4%
2002	49-75	674.538	7.556	11,2	1,5	36,0	7,0%	55,5%	6,2	3.123	4,6	41,3%	70,9%
2003	49-75	713.984	8.091	11,3	1,8	35,4	5,9%	57,0%	6,5	3.352	4,7	41,4%	70,8%
2004	49-75	733.396	8.736	11,9	1,4	30,9	6,7%	50,8%	6,0	3.429	4,7	39,3%	70,9%
2005	49-75	744.855	9.177	12,3	2,0	31,9	6,8%	48,1%	5,9	3.469	4,7	37,8%	74,2%
2006	49-75	738.464	10.093	13,7	0,9	34,3	6,5%	47,2%	6,5	3.657	5,0	36,2%	72,6%
2007	49-75	765.455	11.646	15,2	2,1	43,0	7,5%	47,6%	7,2	4.013	5,2	34,5%	68,6%
2007	49	5	1	200,0	-	-	-	-	-	-	-	-	-
2007	50-54	158.879	2.343	14,7	1,7	53,0	8,0%	37,5%	5,5	525	3,3	22,4%	56,4%
2007	55-59	199.450	2.637	13,2	2,7	43,7	7,9%	45,9%	6,1	841	4,2	31,9%	65,2%
2007	60-64	167.938	2.444	14,6	1,9	39,4	7,7%	51,1%	7,4	940	5,6	38,5%	71,3%
2007	65-69	130.732	2.166	16,6	2,1	39,5	6,7%	52,1%	8,6	876	6,7	40,4%	73,9%
2007	70-74	107.568	2.039	19,0	2,0	38,6	7,1%	52,4%	9,9	826	7,7	40,5%	73,8%
2007	> 74	883	16	18,1	0,0	43,8	18,8%	37,5%	6,8	5	5,7	31,3%	83,3%
1990-2007	49	9.446	55	5,8	1,8	29,1	10,9%	60,0%	3,5	21	2,2	38,2%	63,6%
1990-2007	50-54	1.935.546	19.054	9,8	1,8	40,0	7,1%	47,3%	4,7	5.943	3,1	31,2%	63,5%
1990-2007	55-59	2.185.712	20.738	9,5	1,8	34,1	6,1%	54,3%	5,2	8.375	3,8	40,4%	71,6%
1990-2007	60-64	1.826.317	18.892	10,3	1,8	31,7	5,5%	58,2%	6,0	8.606	4,7	45,6%	75,4%
1990-2007	65-69	1.497.240	17.725	11,8	1,8	31,2	5,5%	58,5%	6,9	8.202	5,5	46,3%	76,1%
1990-2007	70-74	781.535	11.479	14,7	1,8	31,7	6,5%	55,7%	8,2	5.113	6,5	44,5%	75,9%
1990-2007	> 74	7.814	110	14,1	1,8	26,4	6,4%	58,2%	8,2	53	6,8	48,2%	78,1%
1990-2007	49-75	8.243.610	88.053	10,7	1,8	33,9	6,1%	54,7%	5,8	36.313	4,4	41,2%	72,5%

PVW: positief voorspellende waarde

PPV: positive predictive value

3.4 A Tumorgrootteverdeling en lymfklierstatus screeningscarcinomen, 1e screeningsonderzoeken 1990-2007

3.4 A Percent distribution of tumour size and lymph nodes screen-detected carcinomas, initial screens 1990-2007

Jaar *Year*	Leeftijd *Age*	Borstkankers *Breast cancers*	Tumorklasse/tumorgrootte in mm *Tumour class/tumour size in mm*									Invasieve carcinomen *Invasive cancers*				
			Tis (DCIS)	T1a 1-5	T1b 6-10	T1c 11-20	T2 21-50	T3	T4	Tx	n-c	N0	N1	Ns	Nx	M1
		N	%	%	%	%	%	%	%	%	%	%	%	%	%	%
1990-1997	49-75	9.030	14,2%	4,3%	18,7%	38,3%	17,7%	1,1%	0,9%	3,1%	1,7%	67,8%	27,5%	-	4,2%	0,4%
1998	49-75	663	17,9%	5,4%	17,8%	37,0%	17,6%	1,2%	0,5%	2,6%	0,0%	68,4%	27,0%	0,0%	4,4%	0,2%
1999	49-75	775	15,0%	4,8%	20,1%	34,5%	20,5%	0,8%	0,8%	1,9%	1,7%	61,0%	29,4%	0,0%	9,6%	0,0%
2000	49-75	740	17,4%	3,9%	16,1%	40,4%	20,3%	0,9%	0,5%	0,8%	-0,4%	59,0%	33,9%	0,0%	6,5%	0,7%
2001	49-75	665	18,3%	5,0%	14,7%	39,4%	18,2%	0,6%	0,3%	1,1%	2,4%	55,0%	36,6%	3,6%	4,0%	0,8%
2002	49-75	624	14,3%	4,5%	10,9%	42,6%	21,5%	1,3%	0,2%	0,2%	4,6%	42,1%	36,4%	19,6%	1,8%	0,2%
2003	49-75	600	17,0%	3,8%	14,7%	37,2%	22,0%	1,5%	0,3%	0,8%	2,7%	36,3%	30,9%	30,9%	1,7%	0,2%
2004	49-75	642	17,9%	4,2%	12,9%	37,2%	22,3%	0,8%	0,2%	1,6%	3,0%	29,9%	39,2%	27,8%	2,4%	0,8%
2005	49-75	579	18,3%	5,0%	14,0%	40,2%	18,5%	0,9%	0,0%	0,3%	2,8%	26,7%	31,7%	38,1%	3,1%	0,4%
2006	49-75	620	20,0%	4,2%	13,9%	40,5%	17,4%	1,5%	0,3%	0,2%	2,1%	19,3%	28,8%	49,9%	0,8%	1,2%
2007	49-75	641	17,3%	3,0%	16,4%	38,1%	20,9%	1,2%	0,3%	0,3%	2,5%	19,8%	33,3%	45,5%	1,2%	0,2%
2007	49	249	18,1%	2,0%	17,3%	40,6%	17,7%	0,8%	0,8%	0,0%	2,8%	17,8%	34,5%	46,7%	1,0%	0,0%
2007	50-54	316	18,0%	3,2%	17,1%	35,1%	21,8%	1,3%	0,0%	0,6%	2,8%	20,0%	32,8%	45,2%	1,6%	0,4%
2007	55-59	27	18,5%	7,4%	3,7%	37,0%	33,3%	0,0%	0,0%	0,0%	0,0%	18,2%	36,4%	45,5%	0,0%	0,0%
2007	60-64	23	13,0%	4,3%	8,7%	39,1%	34,8%	0,0%	0,0%	0,0%	0,0%	45,0%	20,0%	35,0%	0,0%	0,0%
2007	65-69	18	5,6%	0,0%	11,1%	55,6%	16,7%	11,1%	0,0%	0,0%	0,0%	17,6%	41,2%	41,2%	0,0%	0,0%
2007	70-74	8	0,0%	12,5%	37,5%	37,5%	12,5%	0,0%	0,0%	0,0%	0,0%	12,5%	25,0%	62,5%	0,0%	0,0%
2007	> 74	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1990-2007	49	2.888	19,5%	4,2%	15,1%	37,0%	18,2%	0,8%	0,4%	1,4%	3,4%	45,6%	31,9%	18,0%	4,0%	0,4%
1990-2007	50-54	4.990	18,3%	4,2%	16,1%	36,7%	18,4%	1,1%	0,4%	2,3%	2,4%	50,6%	33,0%	12,7%	3,2%	0,5%
1990-2007	55-59	2.141	14,9%	5,5%	17,5%	37,8%	19,4%	1,0%	1,0%	2,8%	0,1%	62,1%	30,5%	2,9%	3,9%	0,5%
1990-2007	60-64	2.423	13,2%	3,8%	18,3%	39,7%	18,9%	1,1%	0,9%	2,1%	1,9%	66,4%	26,6%	2,0%	4,6%	0,4%
1990-2007	65-69	2.446	9,9%	4,0%	19,7%	41,8%	18,2%	1,3%	1,1%	3,0%	1,0%	68,4%	25,0%	1,6%	4,6%	0,4%
1990-2007	70-74	669	9,0%	4,3%	21,5%	42,0%	21,2%	1,0%	0,4%	1,5%	-1,0%	65,7%	23,5%	4,2%	6,3%	0,2%
1990-2007	> 74	22	4,5%	0,0%	22,7%	45,5%	13,6%	4,5%	0,0%	0,0%	9,1%	52,6%	31,6%	5,3%	10,5%	0,0%
1990-2007	49-75	15.579	15,5%	4,3%	17,3%	38,4%	18,7%	1,1%	0,7%	2,2%	1,8%	57,7%	29,6%	8,2%	4,1%	0,5%

nc: niet geclassificeerd / *nc: not classified*

Ns: negatieve sentinel node / *Ns: negative sentinel node*

3.4 B Tumorgrootteverdeling en lymfklierstatus screeningscarcinomen, vervolgscreeningen < 2,5 jaar 1990-2007

3.4 B Percent distribution of tumour size and lymph nodes of screen-detected carcinomas, subsequent screens <2,5 years 1990-2007

Jaar *Year*	Leeftijd *Age*	Borstkankers *Breast cancers*	Tumorklasse/tumorgrootte in mm *Tumour class/tumour size in mm*									Invasieve carcinomen *Invasive cancers*				
			Tis (DCIS)	T1a 1-5	T1b 6-10	T1c 11-20	T2 21-50	T3	T4	Tx	n-c	N0	N1	Ns	Nx	M1
		N	%	%	%	%	%	%	%	%	%	%	%	%	%	%
1990-1997	49-75	5.642	14,4%	4,1%	22,7%	36,8%	15,7%	0,9%	0,4%	2,3%	2,7%	71,8%	22,7%	0,0%	5,0%	0,5%
1998	49-75	1.918	15,4%	4,2%	20,5%	38,8%	16,9%	0,9%	0,2%	1,9%	1,3%	69,0%	24,5%	0,0%	6,1%	0,4%
1999	49-75	2.166	13,4%	4,7%	20,5%	40,5%	17,5%	0,7%	0,4%	1,0%	1,4%	67,4%	24,7%	0,0%	7,6%	0,3%
2000	49-75	2.478	13,0%	4,4%	21,9%	42,4%	16,1%	1,0%	0,4%	1,0%	-0,2%	65,4%	27,2%	0,0%	6,9%	0,5%
2001	49-75	3.066	13,9%	5,0%	20,4%	40,4%	16,8%	0,8%	0,7%	1,0%	1,1%	65,9%	27,8%	2,4%	3,6%	0,3%
2002	49-75	3.123	12,9%	4,5%	19,6%	42,0%	16,8%	1,0%	0,4%	1,2%	1,6%	44,7%	26,9%	25,4%	2,5%	0,5%
2003	49-75	3.352	13,3%	3,7%	18,3%	42,8%	16,3%	0,8%	0,2%	1,0%	3,6%	38,4%	26,9%	32,4%	1,7%	0,6%
2004	49-75	3.429	14,6%	4,6%	19,1%	43,2%	14,9%	0,9%	0,3%	0,9%	1,5%	35,1%	27,6%	34,4%	2,2%	0,7%
2005	49-75	3.469	14,1%	4,1%	19,3%	44,0%	16,0%	0,7%	0,1%	0,7%	1,0%	28,4%	25,3%	44,2%	1,6%	0,5%
2006	49-75	3.657	15,1%	4,5%	19,0%	43,3%	15,1%	0,7%	0,1%	1,0%	1,3%	20,8%	24,7%	51,7%	2,0%	0,9%
2007	49-75	4.013	14,9%	4,2%	18,8%	44,3%	14,6%	0,8%	0,1%	0,8%	1,5%	20,1%	23,9%	54,1%	1,4%	0,5%
2007	49	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2007	50-54	525	22,9%	3,8%	15,0%	40,6%	13,5%	1,1%	0,0%	1,3%	1,7%	17,9%	31,6%	48,2%	2,0%	0,3%
2007	55-59	841	15,6%	4,2%	17,8%	44,8%	15,3%	1,0%	0,1%	0,4%	0,8%	19,5%	26,5%	52,6%	1,0%	0,4%
2007	60-64	940	14,9%	4,4%	16,4%	46,2%	14,9%	0,7%	0,0%	0,9%	1,7%	19,5%	25,6%	52,2%	1,7%	1,0%
2007	65-69	876	13,0%	4,1%	20,7%	45,5%	13,7%	0,2%	0,2%	0,8%	1,7%	21,0%	20,6%	56,5%	1,6%	0,3%
2007	70-74	826	11,1%	4,6%	23,1%	42,4%	15,3%	1,0%	0,0%	0,8%	1,7%	21,4%	18,5%	58,8%	1,1%	0,3%
2007	> 74	5	0,0%	0,0%	0,0%	80,0%	20,0%	0,0%	0,0%	0,0%	0,0%	40,0%	40,0%	20,0%	0,0%	0,0%
1990-2007	49	21	14,3%	0,0%	9,5%	38,1%	33,3%	0,0%	0,0%	4,8%	0,0%	61,1%	33,3%	0,0%	5,6%	0,0%
1990-2007	50-54	5.943	17,5%	4,6%	17,4%	38,8%	17,3%	0,8%	0,3%	1,4%	1,8%	46,5%	30,2%	19,4%	3,5%	0,4%
1990-2007	55-59	8.375	14,9%	4,8%	18,7%	41,9%	15,8%	1,0%	0,3%	1,2%	1,4%	45,8%	27,9%	22,3%	3,4%	0,5%
1990-2007	60-64	8.606	14,1%	4,1%	20,1%	42,0%	16,2%	0,8%	0,3%	1,1%	1,5%	48,4%	25,7%	22,0%	3,4%	0,5%
1990-2007	65-69	8.202	12,5%	4,0%	22,0%	42,0%	15,5%	0,8%	0,3%	1,3%	1,6%	49,8%	22,3%	23,7%	3,7%	0,6%
1990-2007	70-74	5.113	11,7%	4,2%	22,3%	43,0%	14,7%	0,6%	0,3%	1,0%	2,2%	39,9%	21,3%	35,5%	2,8%	0,5%
1990-2007	> 74	53	13,2%	3,8%	17,0%	43,4%	17,0%	1,9%	0,0%	0,0%	3,8%	47,7%	22,7%	20,5%	9,1%	0,0%
1990-2007	49-75	36.313	14,1%	4,3%	20,0%	41,6%	15,9%	0,8%	0,3%	1,2%	1,7%	46,6%	25,5%	24,0%	3,4%	0,5%

nc: niet geclassificeerd / *nc: not classified*

Ns: negatieve sentinel node / *Ns: negative sentinel node*

3.5 A Screeningscarcinomen en intervalkankers, eerste screeningen 1990-2004, 49-54 jaar

3.5 A Screen-detected breast cancers and interval cancers, inital screens 1990-2004, 49-54 years

Jaar en leeftijd *Year and age*		Bij screening *At screening* Jaar-verslagen *Annual reports*	 Na koppeling *After linkage*	Interval *Interval* Totaal *Total*	 <12	 <24	Verwijscijfer (Ref), sensitiviteit en specificiteit *Referral rate (Ref), sensitivity and specificity*	
1990-1997	Borstkankers/ *breast cancers*	2.678	2.629	1.601	496	1.329	ref/1000	11,4
49-54	Vrouw(jaren)/ *women (woman-years)*	638.249	628.753		623.432	1.207.220	sens	66,4%
	Per 1000	4,2	4,2		0,8	1,1	spec	99,3%
1998	Borstkankers/ *breast cancers*	444	446	278	87	227	ref/1000	15,1
49-54	Vrouw(jaren)/ *women (woman-years)*	96.580	93.630		92.819	179.216	sens	66,3%
	Per 1000	4,6	4,8		0,9	1,3	spec	99,0%
1999	Borstkankers/ *breast cancers*	380	380	253	83	209	ref/1000	15,5
49-54	Vrouw(jaren)/ *women (woman-years)*	91.463	87.758		87.042	168.523	sens	64,5%
	Per 1000	4,2	4,3		1,0	1,2	spec	98,9%
2000	Borstkankers/ *breast cancers*	425	418	259	70	219	ref/1000	18,2
49-54	Vrouw(jaren)/ *women (woman-years)*	87.637	85.937		84.935	163.373	sens	65,6%
	Per 1000	4,8	4,9		0,8	1,3	spec	98,7%
2001	Borstkankers/ *breast cancers*	433	407	187	52	164	ref/1000	24,2
49-54	Vrouw(jaren)/ *women (woman-years)*	81.498	78.941		77.740	149.521	sens	71,3%
	Per 1000	5,3	5,2		0,7	1,1	spec	98,1%
2002	Borstkankers/ *breast cancers*	376	389	194	66	171	ref/1000	23,9
49-54	Vrouw(jaren)/ *women (woman-years)*	74.497	73.826		72.689	139.861	sens	69,5%
	Per 1000	5,0	5,3		0,9	1,2	spec	98,1%
2003	Borstkankers/ *breast cancers*	278	289	127	53	117	ref/1000	22,9
49-54	Vrouw(jaren)/ *women (woman-years)*	57.429	57.426		56.334	108.502	sens	71,2%
	Per 1000	4,8	5,0		0,9	1,1	spec	98,2%
2004	Borstkankers/ *breast cancers*	175	175	99	30	81	ref/1000	23,2
49-54	Vrouw(jaren)/ *women (woman-years)*	32.617	32.464		31.752	62.000	sens	68,4%
	Per 1000	5,4	5,4		0,9	1,3	spec	98,2%
1990-2004	Borstkankers/ *breast cancers*	5.189	5.133	2.998	937	2.517	ref/1000	15,1
49-54	Vrouw(jaren)/ *women (woman-years)*	1.159.970	1.138.735		1.126.744	2.178.217	sens	67,1%
	Per 1000	4,5	4,5		0,8	1,2	spec	98,9%
1990-2004	Borstkankers/ *breast cancers*	12.405	12.154	5.351	1.486	4.170	ref/1000	15,3
49-75	Vrouw(jaren)/ *women (woman-years)*	2.066.357	2.019.588		1.998.544	3.868.144	sens	74,5%
	Per 1000	6,0	6,0		0,7	1,1	spec	99,1%
1990-2004	Borstkankers/ *breast cancers*	1.726	1.740	1.076	320	903	ref/1000	15,7
49	Vrouw(jaren)/ *women (woman-years)*	397.764	394.429		389.407	753.744	sens	65,8%
	Per 1000	4,3	4,4		0,8	1,2	spec	98,9%
1990-2004	Borstkankers/ *breast cancers*	3.463	3.393	1.922	617	1.614	ref/1000	14,8
50-54	Vrouw(jaren)/ *women (woman-years)*	762.206	744.306		737.337	1.424.472	sens	67,8%
	Per 1000	4,5	4,6		0,8	1,1	spec	99,0%
1990-2004	Borstkankers/ *breast cancers*	1.954	1.930	730	190	588	ref/1000	13,1
55-59	Vrouw(jaren)/ *women (woman-years)*	329.205	320.841		318.172	614.406	sens	76,6%
	Per 1000	5,9	6,0		0,6	1,0	spec	99,3%
1990-2004	Borstkankers/ *breast cancers*	2.309	2.238	689	184	561	ref/1000	14,7
60-64	Vrouw(jaren)/ *women (woman-years)*	302.209	294.915		292.083	564.054	sens	80,0%
	Per 1000	7,6	7,6		0,6	1,0	spec	99,3%
1990-2004	Borstkankers/ *breast cancers*	2.325	2.237	748	141	417	ref/1000	17,6
65-69	Vrouw(jaren)/ *women (woman-years)*	230.818	223.552		220.919	431.595	sens	84,3%
	Per 1000	10,1	10,0		0,6	1,0	spec	99,2%
1990-2004	Borstkankers/ *breast cancers*	610	584	168	30	80	ref/1000	27,0
70-74	Vrouw(jaren)/ *women (woman-years)*	42.643	38.962		38.090	74.826	sens	88,0%
	Per 1000	14,3	15,0		0,8	1,1	spec	98,8%
1990-2004	Borstkankers/ *breast cancers*	18	32	18	4	7	ref/1000	22,5
> 75	Vrouw(jaren)/ *women (woman-years)*	1.512	2.583		2.537	5.047	sens	82,1%
	Per 1000	11,9	12,4		1,6	1,4	spec	99,0%

3.5 B Screeningscarcinomen en intervalkankers, vervolgscreeningen < 2,5 jaar 1990-2004, 50-69 jaar

3.5 B Screen-detected cancers and interval cancers, subsequent screens < 2.5 year 1990-2004, 50-69 years

Jaar en leeftijd *Year and age*		Bij screening *At screening*		Interval *Interval*			Verwijscijfer (Ref), sensitiviteit en specificiteit *Referral rate (Ref), sensitivity and specificity*	
		Jaarverslagen *Annual reports*	Na koppeling *After linkage*	Totaal *Total*	<12	<24		
1990-1997	Borstkankers/ *breast cancers*	16.796	16.645	9.875	2.939	8.305	ref/1000	9,1
50-69	Vrouw(jaren)/ *women (woman-years)*	4.247.477	4.141.607		4.105.105	7.952.917	sens	66,7%
	Per 1000	4,0	4,0		0,7	1,0	spec	99,5%
1998	Borstkankers/ *breast cancers*	1.733	1.691	1.041	309	871	ref/1000	8,1
50-69	Vrouw(jaren)/ *women (woman-years)*	457.815	443.865		441.023	852.306	sens	66,0%
	Per 1000	3,8	3,8		0,7	1,0	spec	99,6%
1999	Borstkankers/ *breast cancers*	1.864	1.885	1.193	330	984	ref/1000	8,7
50-69	Vrouw(jaren)/ *women (woman-years)*	475.488	462.902		459.725	891.016	sens	65,7%
	Per 1000	3,9	4,1		0,7	1,1	spec	99,5%
2000	Borstkankers/ *breast cancers*	1.878	1.888	1.154	331	1.010	ref/1000	9,5
50-69	Vrouw(jaren)/ *women (woman-years)*	461.076	454.786		450.959	869.255	sens	65,1%
	Per 1000	4,1	4,2		0,7	1,2	spec	99,5%
2001	Borstkankers/ *breast cancers*	2.098	2.055	1.018	344	908	ref/1000	11,6
50-69	Vrouw(jaren)/ *women (woman-years)*	471.124	458.385		453.723	873.801	sens	69,4%
	Per 1000	4,5	4,5		0,8	1,0	spec	99,3%
2002	Borstkankers/ *breast cancers*	1.871	1.917	968	310	856	ref/1000	11,3
50-69	Vrouw(jaren)/ *women (woman-years)*	427.735	426.985		422.761	815.792	sens	69,1%
	Per 1000	4,4	4,5		0,7	1,0	spec	99,3%
2003	Borstkankers/ *breast cancers*	1.514	1.570	705	262	646	ref/1000	11,5
50-69	Vrouw(jaren)/ *women (woman-years)*	350.684	350.712		346.669	670.039	sens	70,8%
	Per 1000	4,3	4,5		0,8	1,0	spec	99,3%
2004	Borstkankers/ *breast cancers*	854	866	469	131	405	ref/1000	11,5
50-69	Vrouw(jaren)/ *women (woman-years)*	185.722	184.051		178.784	350.436	sens	68,1%
	Per 1000	4,6	4,7		0,7	1,2	spec	99,3%
1990-2004	Borstkankers/ *breast cancers*	16.796	16.645	9.875	2.939	8.305	ref/1000	9,1
50-69	Vrouw(jaren)/ *women (woman-years)*	4.247.477	4.141.607		4.105.105	7.952.917	sens	66,7%
	Per 1000	4,0	4,0		0,7	1,0	spec	99,5%
1990-2004	Borstkankers/ *breast cancers*	18.719	18.574	10.632	3.121	8.866	ref/1000	9,4
49-75	Vrouw(jaren)/ *women (woman-years)*	4.554.732	4.443.347		4.401.913	8.530.648	sens	67,7%
	Per 1000	4,1	4,2		0,7	1,0	spec	99,5%
1990-2004	Borstkankers/ *breast cancers*	17	8	7	1	6	ref/1000	5,5
49	Vrouw(jaren)/ *women (woman-years)*	6.707	3.195		3.173	5.609	sens	57,1%
	Per 1000	2,5	2,5		0,3	1,1	spec	99,7%
1990-2004	Borstkankers/ *breast cancers*	3.257	3.215	2.686	869	2.343	ref/1000	8,6
50-54	Vrouw(jaren)/ *women (woman-years)*	1.124.134	1.090.727		1.082.321	2.096.041	sens	57,8%
	Per 1000	2,9	2,9		0,8	1,1	spec	99,4%
1990-2004	Borstkankers/ *breast cancers*	4.414	4.376	2.758	841	2.369	ref/1000	8,4
55-59	Vrouw(jaren)/ *women (woman-years)*	1.202.692	1.172.877		1.162.544	2.250.903	sens	64,9%
	Per 1000	3,7	3,7		0,7	1,1	spec	99,5%
1990-2004	Borstkankers/ *breast cancers*	4.669	4.630	2.353	679	1.986	ref/1000	9,2
60-64	Vrouw(jaren)/ *women (woman-years)*	1.057.166	1.032.039		1.023.145	1.981.251	sens	70,0%
	Per 1000	4,4	4,5		0,7	1,0	spec	99,5%
1990-2004	Borstkankers/ *breast cancers*	4.456	4.424	2.078	550	1.607	ref/1000	10,5
65-69	Vrouw(jaren)/ *women (woman-years)*	863.485	845.964		837.095	1.624.722	sens	73,4%
	Per 1000	5,2	5,2		0,7	1,0	spec	99,5%
1990-2004	Borstkankers/ *breast cancers*	1.893	1.896	750	175	542	ref/1000	13,8
70-74	Vrouw(jaren)/ *women (woman-years)*	298.593	294.332		289.461	563.792	sens	77,8%
	Per 1000	6,3	6,4		0,6	1,0	spec	99,3%
1990-2004	Borstkankers/ *breast cancers*	13	25	34	6	13	ref/1000	11,3
> 75	Vrouw(jaren)/ *women (woman-years)*	1.955	4.213		4.174	8.330	sens	65,8%
	Per 1000	6,6	5,9		1,4	1,6	spec	99,5%

Appendix 4

Tables

4.1 Borstkankerincidentie/ *Breast cancer incidence 1989-2004*

Jaar *Year*	Regio's *Regions*	Leeftijd *Age*	Mid-year population	Invasief *Invasive*		In situ *In situ*		Totaal *Total*		LCIS	TNM-verdeling (%)/ *TNM distribution (%)*											
											Tis	T1a	T1b	T1c	T2	T3	T4	Tx+nc	N- + Nsn	N+	Nx	M1
			N	N	/1000	N	/1000	N	/1000	N	%	%	%	%	%	%	%	%	%	%	%	%
1990-1997	9	< 50	42.021.983	19.975	0,5	1.198	0,0	21.173	0,5	170	5,7%	1,7%	9,0%	35,7%	33,5%	5,2%	4,6%	4,7%	51,2%	41,9%	2,7%	4,2%
1998	9	< 50	5.256.477	2.779	0,5	214	0,0	2.993	0,6	24	7,2%	2,4%	8,6%	33,8%	36,8%	4,5%	4,2%	2,6%	47,2%	43,1%	4,4%	5,3%
1999	9	< 50	5.253.710	2.885	0,5	209	0,0	3.094	0,6	37	6,8%	1,8%	8,9%	34,3%	36,7%	5,1%	4,5%	2,1%	47,1%	46,0%	2,5%	4,3%
2000	*7*	*< 50*	*4.442.349*	*2.282*	*0,5*	*171*	*0,0*	*2.453*	*0,6*	*20*	*7,0%*	*2,0%*	*7,9%*	*34,0%*	*36,1%*	*5,7%*	*5,2%*	*2,2%*	*44,9%*	*48,4%*	*1,9%*	*4,8%*
2001	*7*	*< 50*	*4.468.025*	*2.457*	*0,5*	*183*	*0,0*	*2.640*	*0,6*	*16*	*6,9%*	*2,3%*	*7,9%*	*34,6%*	*37,1%*	*5,2%*	*4,0%*	*2,0%*	*44,0%*	*48,7%*	*3,1%*	*4,2%*
2002	*4*	*< 50*	*2.321.398*	*1.376*	*0,6*	*91*	*0,0*	*1.467*	*0,6*	*4*	*6,2%*	*2,2%*	*6,8%*	*36,2%*	*37,9%*	*5,0%*	*2,8%*	*2,9%*	*43,1%*	*51,9%*	*1,7%*	*3,3%*
2003	*3*	*< 50*	*1.555.508*	*936*	*0,6*	*57*	*0,0*	*993*	*0,6*	*3*	*5,7%*	*1,9%*	*10,6%*	*33,3%*	*38,1%*	*5,3%*	*2,7%*	*2,3%*	*48,0%*	*48,0%*	*1,1%*	*2,9%*
2004	*1*	*< 50*	*691.360*	*409*	*0,6*	*27*	*0,0*	*436*	*0,6*	*4*	*6,2%*	*1,6%*	*5,7%*	*36,9%*	*40,8%*	*5,5%*	*1,6%*	*1,6%*	*45,0%*	*50,1%*	*1,2%*	*3,7%*
1990-1997	9	50-69	11.718.975	33.960	2,9	2.802	0,2	36.762	3,1	181	7,6%	2,4%	12,5%	34,8%	29,1%	3,2%	5,8%	4,5%	57,3%	34,3%	3,6%	4,8%
1998	9	50-69	1.598.738	4.388	2,8	497	0,3	4.885	3,1	28	10,2%	3,1%	14,4%	35,4%	26,8%	3,0%	4,6%	2,6%	56,7%	32,8%	6,3%	4,2%
1999	9	50-69	1.616.866	4.570	2,8	481	0,3	5.051	3,1	34	9,5%	3,0%	14,3%	36,7%	27,0%	2,7%	4,6%	2,2%	58,4%	34,4%	3,0%	4,2%
2000	*7*	*50-69*	*1.407.890*	*4.213*	*3,0*	*490*	*0,3*	*4.703*	*3,3*	*31*	*10,4%*	*3,1%*	*14,1%*	*37,7%*	*27,1%*	*2,4%*	*3,7%*	*1,5%*	*57,0%*	*36,4%*	*2,9%*	*3,7%*
2001	*7*	*50-69*	*1.441.030*	*4.463*	*3,1*	*522*	*0,4*	*4.985*	*3,5*	*36*	*10,5%*	*3,2%*	*13,9%*	*37,6%*	*27,0%*	*2,2%*	*3,9%*	*1,7%*	*54,6%*	*36,7%*	*4,5%*	*4,2%*
2002	*4*	*50-69*	*773.347*	*2.464*	*3,2*	*268*	*0,3*	*2.732*	*3,5*	*11*	*9,8%*	*3,2%*	*15,6%*	*37,8%*	*25,6%*	*2,5%*	*2,7%*	*2,9%*	*57,1%*	*37,3%*	*2,4%*	*3,2%*
2003	*3*	*50-69*	*527.943*	*1.564*	*3,0*	*168*	*0,3*	*1.732*	*3,3*	*4*	*9,7%*	*3,4%*	*14,9%*	*38,2%*	*26,8%*	*2,1%*	*2,9%*	*1,9%*	*61,0%*	*34,2%*	*1,9%*	*2,9%*
2004	*1*	*50-69*	*240.653*	*708*	*2,9*	*89*	*0,4*	*797*	*3,3*	*2*	*11,2%*	*2,3%*	*14,3%*	*38,0%*	*25,2%*	*4,4%*	*2,4%*	*2,3%*	*56,8%*	*37,1%*	*1,1%*	*4,9%*
1990-1997	9	> 69	6.807.937	21.844	3,2	773	0,1	22.617	3,3	37	3,4%	0,9%	4,7%	26,6%	40,5%	4,4%	13,5%	6,1%	50,1%	31,1%	11,3%	7,6%
1998	9	> 69	903.074	3.058	3,4	149	0,2	3.207	3,6	2	4,6%	1,2%	6,4%	27,2%	40,3%	3,8%	12,6%	4,0%	48,6%	31,0%	12,9%	7,5%
1999	9	> 69	907.487	3.560	3,9	206	0,2	3.766	4,1	5	5,5%	1,7%	9,2%	28,8%	36,1%	3,5%	11,6%	3,6%	54,5%	30,7%	8,1%	6,6%
2000	*7*	*> 69*	784.221	*2.920*	*3,7*	*182*	*0,2*	*3.102*	*4,0*	*7*	*5,9%*	*2,1%*	*10,2%*	*31,7%*	*33,5%*	*3,0%*	*11,0%*	*2,7%*	*56,3%*	*30,6%*	*6,5%*	6,5%
2001	*7*	*> 69*	794.366	*2.957*	*3,7*	*183*	*0,2*	*3.140*	*4,0*	*2*	*5,8%*	*1,9%*	*9,2%*	*29,6%*	*36,0%*	*3,2%*	*10,7%*	*3,6%*	*55,5%*	*30,3%*	*7,8%*	6,4%
2002	*4*	*> 69*	414.716	*1.457*	*3,5*	*97*	*0,2*	*1.554*	*3,7*	*1*	*6,2%*	*1,7%*	*9,3%*	*29,2%*	*36,0%*	*3,2%*	*7,9%*	*6,5%*	*54,3%*	*30,8%*	*8,1%*	6,8%
2003	*3*	*> 69*	293.422	*939*	*3,2*	*51*	*0,2*	*990*	*3,4*	*0*	*5,2%*	*1,9%*	*10,2%*	*28,5%*	*38,5%*	*4,2%*	*7,6%*	*3,9%*	*53,0%*	*30,2%*	*9,3%*	7,6%
2004	*1*	*> 69*	131.625	*465*	*3,5*	*27*	*0,2*	*492*	*3,7*	*0*	*5,5%*	*1,8%*	*7,7%*	*29,3%*	*39,8%*	*3,7%*	*8,7%*	*3,5%*	*56,8%*	*31,0%*	*6,0%*	6,2%
1990-1997	9	00-99	60.548.895	75.779	1,3	4.773	0,1	80.552	1,3	388	5,9%	1,8%	9,4%	32,7%	33,5%	4,0%	7,7%	5,0%	53,6%	35,4%	5,6%	5,4%
1998	9	00-99	7.758.289	10.225	1,3	860	0,1	11.085	1,4	54	7,8%	2,4%	10,5%	32,6%	33,4%	3,6%	6,8%	3,0%	51,7%	35,1%	7,8%	5,5%
1999	9	00-99	7.778.063	11.015	1,4	896	0,1	11.911	1,5	76	7,5%	2,3%	11,3%	33,6%	32,4%	3,5%	6,8%	2,6%	54,2%	36,3%	4,5%	5,0%
2000	*7*	*00-99*	*6.634.460*	*9.415*	*1,4*	*843*	*0,1*	*10.258*	*1,5*	*58*	*8,2%*	*2,5%*	*11,4%*	*35,0%*	*31,2%*	*3,4%*	*6,3%*	*2,0%*	*53,9%*	*37,5%*	*3,8%*	*4,9%*
2001	*7*	*00-99*	*6.703.421*	*9.877*	*1,5*	*888*	*0,1*	*10.765*	*1,6*	*54*	*8,2%*	*2,6%*	*11,1%*	*34,5%*	*32,1%*	*3,2%*	*5,9%*	*2,3%*	*52,2%*	*37,7%*	*5,2%*	*4,9%*
2002	*4*	*00-99*	*3.509.461*	*5.297*	*1,5*	*456*	*0,1*	*5.753*	*1,6*	*16*	*7,9%*	*2,5%*	*11,7%*	*35,1%*	*31,5%*	*3,3%*	*4,1%*	*3,9%*	*52,7%*	*39,3%*	*3,8%*	*4,2%*
2003	*3*	*00-99*	*2.376.873*	*3.439*	*1,4*	*276*	*0,1*	*3.715*	*1,6*	*7*	*7,4%*	*2,6%*	*12,5%*	*34,3%*	*32,9%*	*3,6%*	*4,1%*	*2,6%*	*55,3%*	*36,9%*	*3,7%*	*4,2%*
2004	*1*	*00-99*	*1.063.638*	*1.582*	*1,5*	*143*	*0,1*	*1.725*	*1,6*	*6*	*8,3%*	*2,0%*	*10,3%*	*35,2%*	*33,3%*	*4,5%*	*4,0%*	*2,4%*	*53,7%*	*38,7%*	*2,6%*	*5,0%*

Cursieve getallen: landelijk niet volledige gegevens
Numbers in italic: data not complete at national level

LCIS: lobulair carcinoma in situ (wordt als benigne aandoening beschouwd)
LCIS: lobular carcinoma in situ (not considerd a malignant tumour)

4.2		Primair borstsparende chirurgie (BST)						Primair mastectomie					Niet-chirurgische primaire therapie								Totaal
4.2		*Primary breast conserving therapy (BCT)*						*Primary mastectomy*					*Not surgical primary therapy*								*Total*
Jaar	Regio's	Leeftijd					Totaal					Totaal	Hormonale Th		RadioTh		ChemoTh		Anders		
Year	*Regions*	*Age*	RadioTh+		RadioTh-		*Total*	RadioTh+		RadioTh-		*Total*	*Hormonal Th*		*RadioTh*		*ChemoTh*		*Other*		
			N	%	N	%	%	N	%	N	%	%	N	%	N	%	N	%	N	%	N
1990-1997	9	<50	7.111	40,8%	586	3,4%	44,2%	3.292	18,9%	5.106	29,3%	48,2%	148	0,9%	130	0,7%	398	2,3%	640	3,7%	17.411
1998	9	<50	1.103	39,7%	163	5,9%	45,6%	446	16,1%	757	27,2%	43,3%	26	0,9%	1	0,0%	114	4,1%	168	6,0%	2.778
1999	9	<50	1.150	39,9%	191	6,6%	46,5%	508	17,6%	763	26,4%	44,1%	18	0,6%	2	0,1%	111	3,8%	142	4,9%	2.885
2000	*7*	<50	*945*	*41,7%*	*117*	*5,2%*	*46,9%*	*445*	*19,6%*	*583*	*25,7%*	*45,4%*	*20*	*0,9%*	*3*	*0,1%*	*95*	*4,2%*	*58*	*2,6%*	*2.266*
2001	*7*	<50	*1.013*	*41,8%*	*141*	*5,8%*	*47,6%*	*483*	*19,9%*	*625*	*25,8%*	*45,7%*	*14*	*0,6%*	*3*	*0,1%*	*89*	*3,7%*	*54*	*2,2%*	*2.422*
2002	*4*	<50	*596*	*43,3%*	*105*	*7,6%*	*50,9%*	*253*	*18,4%*	*319*	*23,2%*	*41,6%*	*9*	*0,7%*	*1*	*0,1%*	*52*	*3,8%*	*41*	*3,0%*	*1.376*
2003	*3*	<50	*422*	*45,1%*	*32*	*3,4%*	*48,5%*	*152*	*16,2%*	*267*	*28,5%*	*44,8%*	*4*	*0,4%*	*1*	*0,1%*	*25*	*2,7%*	*33*	*3,5%*	*936*
2004	*1*	<50	*206*	*50,4%*	*15*	*3,7%*	*54,0%*	*51*	*12,5%*	*107*	*26,2%*	*38,6%*	*2*	*0,5%*	*1*	*0,2%*	*24*	*5,9%*	*3*	*0,7%*	*409*
1990-1997	9	50-69	11.422	38,2%	916	3,1%	41,3%	5.151	17,2%	9.996	33,4%	50,6%	837	2,8%	236	0,8%	391	1,3%	957	3,2%	29.906
1998	9	50-69	1.899	43,3%	221	5,0%	48,3%	523	11,9%	1.344	30,6%	42,6%	77	1,8%	3	0,1%	90	2,1%	229	5,2%	4.386
1999	9	50-69	1.922	42,1%	285	6,2%	48,3%	596	13,1%	1.357	29,7%	42,8%	78	1,7%	5	0,1%	134	2,9%	188	4,1%	4.565
2000	*7*	50-69	2.008	48,1%	235	5,6%	53,7%	537	12,9%	1.168	28,0%	40,8%	59	1,4%	4	0,1%	101	2,4%	62	1,5%	4.174
2001	*7*	50-69	2.119	48,1%	237	5,4%	53,5%	638	14,5%	1.114	25,3%	39,8%	77	1,7%	5	0,1%	121	2,7%	95	2,2%	4.406
2002	*4*	50-69	1.296	52,6%	167	6,8%	59,4%	259	10,5%	568	23,1%	33,6%	33	1,3%	5	0,2%	70	2,8%	66	2,7%	2.464
2003	*3*	50-69	878	56,1%	48	3,1%	59,2%	153	9,8%	393	25,1%	34,9%	24	1,5%	4	0,3%	32	2,0%	32	2,0%	1.564
2004	*1*	50-69	412	58,2%	28	4,0%	62,1%	69	9,7%	154	21,8%	31,5%	16	2,3%	0	0,0%	23	3,2%	6	0,8%	708
1990-1997	9	>69	2.530	13,2%	901	4,7%	17,9%	2.870	15,0%	8.910	46,4%	61,4%	2.796	14,6%	219	1,1%	106	0,6%	855	4,5%	19.187
1998	9	>69	527	17,3%	152	5,0%	22,3%	383	12,6%	1.315	43,2%	55,8%	435	14,3%	11	0,4%	34	1,1%	188	6,2%	3.045
1999	9	>69	733	20,6%	236	6,6%	27,3%	387	10,9%	1.454	40,9%	51,8%	512	14,4%	16	0,5%	31	0,9%	184	5,2%	3.553
2000	*7*	>69	*701*	*24,2%*	*189*	*6,5%*	*30,7%*	*314*	*10,8%*	*1.153*	*39,8%*	*50,6%*	*388*	*13,4%*	*12*	*0,4%*	*26*	*0,9%*	*117*	*4,0%*	*2.900*
2001	*7*	>69	*649*	*22,2%*	*182*	*6,2%*	*28,4%*	*325*	*11,1%*	*1.218*	*41,7%*	*52,8%*	*405*	*13,9%*	*11*	*0,4%*	*25*	*0,9%*	*106*	*3,6%*	*2.921*
2002	*4*	>69	*334*	*22,9%*	*85*	*5,8%*	*28,8%*	*129*	*8,9%*	*587*	*40,3%*	*49,1%*	*233*	*16,0%*	*4*	*0,3%*	*14*	*1,0%*	*71*	*4,9%*	*1.457*
2003	*3*	>69	*195*	*20,8%*	*36*	*3,8%*	*24,6%*	*92*	*9,8%*	*381*	*40,6%*	*50,4%*	*167*	*17,8%*	*6*	*0,6%*	*7*	*0,7%*	*55*	*5,9%*	*939*
2004	*1*	>69	*125*	*26,9%*	*12*	*2,6%*	*29,5%*	*48*	*10,3%*	*166*	*35,7%*	*46,0%*	*96*	*20,6%*	*2*	*0,4%*	*5*	*1,1%*	*11*	*2,4%*	*465*
1990-1997	9	totaal	21.063	31,7%	2.403	3,6%	35,3%	11.313	17,0%	24.012	36,1%	53,1%	3.781	5,7%	585	0,9%	895	1,3%	2.452	3,7%	66.504
1998	9	totaal	3.529	34,6%	536	5,3%	39,8%	1.352	13,2%	3.416	33,5%	46,7%	538	5,3%	15	0,1%	238	2,3%	585	5,7%	10.209
1999	9	*total*	3.805	34,6%	712	6,5%	41,1%	1.491	13,6%	3.574	32,5%	46,0%	608	5,5%	23	0,2%	276	2,5%	514	4,7%	11.003
2000	*7*	totaal	*3.654*	*39,1%*	*541*	*5,8%*	*44,9%*	*1.296*	*13,9%*	*2.904*	*31,1%*	*45,0%*	*467*	*5,0%*	*19*	*0,2%*	*222*	*2,4%*	*237*	*2,5%*	*9.340*
2001	*7*	*total*	*3.781*	*38,8%*	*560*	*5,7%*	*44,5%*	*1.446*	*14,8%*	*2.957*	*30,3%*	*45,2%*	*496*	*5,1%*	*19*	*0,2%*	*235*	*2,4%*	*255*	*2,6%*	*9.749*
2002	*4*	totaal	*2.226*	*42,0%*	*357*	*6,7%*	*48,8%*	*641*	*12,1%*	*1.474*	*27,8%*	*39,9%*	*275*	*5,2%*	*10*	*0,2%*	*136*	*2,6%*	*178*	*3,4%*	*5.297*
2003	*3*	*total*	*1.495*	*43,5%*	*116*	*3,4%*	*46,8%*	*397*	*11,5%*	*1.041*	*30,3%*	*41,8%*	*195*	*5,7%*	*11*	*0,3%*	*64*	*1,9%*	*120*	*3,5%*	*3.439*
2004	*1*	totaal	*743*	*47,0%*	*55*	*3,5%*	*50,4%*	*168*	*10,6%*	*427*	*27,0%*	*37,6%*	*114*	*7,2%*	*3*	*0,2%*	*52*	*3,3%*	*20*	*1,3%*	*1.582*

Cursieve getallen: landelijk niet volledige gegevens

Numbers in italic: data not complete at national level

4.3 A Adjuvante therapie na primaire chirurgie
4.3 A Adjuvant therapy after primary surgery

Jaar / *Year*	Regio's / *Regions*	Leeftijd / *Age*	Totaal / *Total*	Hormonale th. / *Hormonal th.*		Chemotherapie / *Chemotherapy*		Horm+chemoth. / *Horm+chemoth.*		Tot. adjTh / *Tot. adjTh*
			N	N	%	N	%	N	%	%
1990-1997	9	<50	16.095	645	4,0%	5.374	33,4%	392	2,4%	39,8%
1998	9	<50	2.469	111	4,5%	993	40,2%	202	8,2%	52,9%
1999	9	<50	2.612	131	5,0%	1.061	40,6%	486	18,6%	64,2%
2000	*7*	*<50*	*2.090*	*88*	*4,2%*	*649*	*31,1%*	*603*	*28,9%*	*64,1%*
2001	*7*	*<50*	*2.262*	*103*	*4,6%*	*627*	*27,7%*	*690*	*30,5%*	*62,8%*
2002	*4*	*<50*	*1.273*	*41*	*3,2%*	*335*	*26,3%*	*374*	*29,4%*	*58,9%*
2003	*3*	*<50*	*873*	*23*	*2,6%*	*155*	*17,8%*	*256*	*29,3%*	*49,7%*
2004	*1*	*<50*	*379*	*11*	*2,9%*	*87*	*23,0%*	*176*	*46,4%*	*72,3%*
1990-1997	9	50-69	27.485	8.437	30,7%	1.076	3,9%	284	1,0%	35,6%
1998	9	50-69	3.987	1.137	28,5%	388	9,7%	142	3,6%	41,8%
1999	9	50-69	4.160	1.161	27,9%	648	15,6%	243	5,8%	49,3%
2000	*7*	*50-69*	*3.948*	*948*	*24,0%*	*525*	*13,3%*	*405*	*10,3%*	*47,6%*
2001	*7*	*50-69*	*4.108*	*945*	*23,0%*	*514*	*12,5%*	*478*	*11,6%*	*47,2%*
2002	*4*	*50-69*	*2.290*	*431*	*18,8%*	*290*	*12,7%*	*235*	*10,3%*	*41,7%*
2003	*3*	*50-69*	*1.472*	*141*	*9,6%*	*172*	*11,7%*	*201*	*13,7%*	*34,9%*
2004	*1*	*50-69*	*663*	*105*	*15,8%*	*94*	*14,2%*	*140*	*21,1%*	*51,1%*
1990-1997	9	>69	15.211	6.117	40,2%	63	0,4%	16	0,1%	40,7%
1998	9	>69	2.377	1.084	45,6%	13	0,5%	7	0,3%	46,4%
1999	9	>69	2.810	1.273	45,3%	21	0,7%	9	0,3%	46,4%
2000	*7*	*>69*	*2.357*	*968*	*41,1%*	*14*	*0,6%*	*4*	*0,2%*	*41,8%*
2001	*7*	*>69*	*2.374*	*957*	*40,3%*	*20*	*0,8%*	*10*	*0,4%*	*41,6%*
2002	*4*	*>69*	*1.135*	*426*	*37,5%*	*9*	*0,8%*	*3*	*0,3%*	*38,6%*
2003	*3*	*>69*	*704*	*240*	*34,1%*	*6*	*0,9%*	*2*	*0,3%*	*35,2%*
2004	*1*	*>69*	*351*	*143*	*40,7%*	*4*	*1,1%*	*4*	*1,1%*	*43,0%*
1990-1997	9	totaal	58.791	15.199	25,9%	6.513	11,1%	692	1,2%	38,1%
1998	9	*total*	*8.833*	2.332	26,4%	1.394	15,8%	351	4,0%	46,2%
1999	9	totaal	9.582	2.565	26,8%	1.730	18,1%	738	7,7%	52,5%
2000	*7*	*total*	*8.395*	*2.004*	*23,9%*	*1.188*	*14,2%*	*1.012*	*12,1%*	*50,1%*
2001	*7*	*totaal*	*8.744*	*2.005*	*22,9%*	*1.161*	*13,3%*	*1.178*	*13,5%*	*49,7%*
2002	*4*	*total*	*4.698*	*898*	*19,1%*	*634*	*13,5%*	*612*	*13,0%*	*45,6%*
2003	*3*	*totaal*	*3.049*	*404*	*13,3%*	*333*	*10,9%*	*459*	*15,1%*	*39,2%*
2004	*1*	*total*	*1.393*	*259*	*18,6%*	*185*	*13,3%*	*320*	*23,0%*	*54,8%*

Cursieve getallen: landelijk niet volledige gegevens
Numbers in italic: data not complete at national level

4.3 B Primaire behandeling DCIS
4.3 B Primary treatment DCIS

BST / RT- / *BCT / RT-*		BST / RT+ / *BCT / RT+*		Mastectomie / *Mastectomy*		Overig / *Other*		Totaal / *Total*
N	%	N	%	N	%	N	%	N
274	26,7%	156	15,2%	565	55,1%	31	3,0%	1.026
50	23,4%	39	18,2%	113	52,8%	12	5,6%	214
67	32,1%	39	18,7%	95	45,5%	8	3,8%	209
51	*30,0%*	*43*	*25,3%*	*73*	*42,9%*	*3*	*1,8%*	*170*
58	*27,9%*	*60*	*28,8%*	*87*	*41,8%*	*3*	*1,4%*	*208*
27	*29,7%*	*29*	*31,9%*	*31*	*34,1%*	*4*	*4,4%*	*91*
10	*17,5%*	*16*	*28,1%*	*31*	*54,4%*	*0*	*0,0%*	*57*
6	*22,2%*	*11*	*40,7%*	*10*	*37,0%*	*0*	*0,0%*	*27*
772	31,9%	367	15,2%	1.173	48,5%	105	4,3%	2.417
162	32,5%	140	28,1%	176	35,3%	20	4,0%	498
160	33,3%	113	23,5%	190	39,5%	18	3,7%	481
131	*26,8%*	*181*	*37,1%*	*170*	*34,8%*	*6*	*1,2%*	*488*
106	*21,3%*	*169*	*34,0%*	*212*	*42,7%*	*10*	*2,0%*	*497*
62	*23,1%*	*111*	*41,4%*	*88*	*32,8%*	*7*	*2,6%*	*268*
20	*11,9%*	*82*	*48,8%*	*62*	*36,9%*	*4*	*2,4%*	*168*
8	*9,0%*	*45*	*50,6%*	*35*	*39,3%*	*1*	*1,1%*	*89*
200	30,5%	45	6,9%	364	55,6%	46	7,0%	655
49	32,9%	20	13,4%	65	43,6%	15	10,1%	149
73	35,4%	33	16,0%	89	43,2%	11	5,3%	206
63	*34,8%*	*40*	*22,1%*	*71*	*39,2%*	*7*	*3,9%*	*181*
46	*26,3%*	*41*	*23,4%*	*80*	*45,7%*	*8*	*4,6%*	*175*
29	*29,9%*	*28*	*28,9%*	*35*	*36,1%*	*5*	*5,2%*	*97*
9	*17,6%*	*14*	*27,5%*	*23*	*45,1%*	*5*	*9,8%*	*51*
9	*33,3%*	*10*	*37,0%*	*8*	*29,6%*	*0*	*0,0%*	*27*
1.246	30,4%	568	13,9%	2.102	51,3%	182	4,4%	4.098
261	30,3%	199	23,1%	354	41,1%	47	5,5%	861
300	33,5%	185	20,6%	374	41,7%	37	4,1%	896
245	*29,2%*	*264*	*31,5%*	*314*	*37,4%*	*16*	*1,9%*	*839*
210	*23,9%*	*270*	*30,7%*	*379*	*43,1%*	*21*	*2,4%*	*880*
118	*25,9%*	*168*	*36,8%*	*154*	*33,8%*	*16*	*3,5%*	*456*
39	*14,1%*	*112*	*40,6%*	*116*	*42,0%*	*9*	*3,3%*	*276*
23	*16,1%*	*66*	*46,2%*	*53*	*37,1%*	*1*	*0,7%*	*143*

Evaluation tables and glossary

Evaluation tables

Aggregated annual results (evaluation tables) from the 9 regional screening organisations were used for the national evaluation of the screening programme. After checking for completeness and consistency, the National Evaluation Team for Breast cancer screening (NETB) combines the tables for further analysis.

The A-tables contain regional data on the organisation of screening, the target population, the numbers of invitations with attendance and non-participation. The A-tables are based on the *invitations for the screening examinations scheduled for the year in question.* The A-tables distinguish between initial and subsequent screening rounds, with the subsequent screening rounds referring to women who have been invited to take part in the screening programme two or more times, regardless of possible previous participation.

The B-tables are based on the *actual number of examinations conducted by the regions in the year in question* and the screening results produced (referrals, detailed diagnosis, size and lymph-node status of the detected cancers). The screening examinations are subdivided into *initial examinations* (independent of the number of previous invitations) and *subsequent examinations* which are those that succeed the previous examination by no more than 2.5 years, or are subsequent examinations at an interval of 2.5 years or longer.

Definition of age and target group

The national evaluation maintains the age distribution used by Statistics Netherlands, which takes the age on 1 January of a certain year at 00:00. Until 1997, the *target group* was defined as women who *turned* at least 50 and at most 69 during the year in question. In 1998, women who turned 70-75 were added (three screening rounds). The current target group contains all women aged '50-75', i.e. women who *are* at least 49 or at most 74 at the start of the year in question – the age that is used for evaluation purposes. Because screening is not strictly synchronised with the calendar year and women are allowed to postpone their appointments, it is also fairly common for 75-year old women to receive screening.

Attendance percentage

The number of invitations sent (excluding reminders, i.e. only the original invitations) is used as the basis for calculating the participation rate (the attendance percentage). In the first screening round, this number is the same as the number of women in the target group, with the exception of a few women whose invitations were not sent because it had been made known beforehand that they had died. In the following rounds (screening round 2 or higher), relatively fewer women received an invitation –

women who indicated during the first round that they were not willing to participate further for various reasons, and depending on the regional invitation policy, also women with a screening or interval carcinoma.

This means that the number of women actually invited for a subsequent examination is smaller than the target group, and that attendance is distorted to appear higher when compared to the invitations sent for an initial screening examination.

Tracing interval cancers

Each year, according to a protocol, the screening organisations link the database of the women screened in a certain year to the database of the Regional Cancer Registration Centre *(Regionale Kankerregistratie, RKR).* Because of the official 2-year screening interval, this link cannot be made until the third year after the end of the screening year in question. If linked records show a positive match, checks are carried out to establish whether they do in fact concern the same woman, and whether an interval carcinoma or a screen-detected carcinoma is at play. The relevant mamma carcinoma is then coded in the RKR database with an 'I' or an 'S' respectively. In cases of interval carcinoma, the period in months since the previous screening examination is also recorded.

Data from women whose breast cancer was diagnosed outside the field of the screening region cannot be linked. For this reason, account must be taken of consistent underreporting of interval cancers, which will generally be greater for central regions and those in the *Randstad* area (Western and more urbanised part of the Netherlands) than in the remaining regions. This can be partially compensated for by not linking women whose diagnosis and treatment takes place to a large extent outside the region; yet this is not possible for individual patients who receive treatment elsewhere.

For this reason, the regions have also been asked to report the number of screen-detected carcinomas for the group of screened women affected by interval cancers, as this will allow a new detection rate to be

calculated. If this rate is lower than that of the previous result calculated for the corresponding year, this can be an indication of possible underreporting of interval carcinoma.
In the future, the link will be made with a national database from the cancer register, which will also allow women to be traced whose interval cancer was diagnosed in another region.

Evaluation tables of breast-cancer incidence and therapy

Each year, with assistance from the regional screening organisations, the regional cancer registers complete separate evaluation tables using data from the cancer register. These C-tables, as they are called, present the new cases of breast cancer *(incidence)* in the entire female population according to age and any possible relationship to the screening programme *(screening relationship)*. The D-tables show primary and adjuvant mamma carcinoma therapy, according to age and screening relationship. Linking the screening programme database with that of the cancer register is necessary in order to assess whether the registered breast cancer was detected by the screening or was diagnosed in a woman who had been screened at some point (interval cancer – see also 'interval cancers').
Given that the linking was originally intended to trace interval cancers, and that a screening interval of 2 years (at least) must be taken into account, the C and D tables can not be fully completed until approximately three years after the year in question.
Unlike the cancer register, the national evaluation is not based on the age at the time of diagnosis (the 'incidence date' in the cancer register), but on the age of a woman on 1 January at 00:00, analogous to the other evaluation tables. The definition of mamma carcinoma used by the NETB can also vary slightly from that used by the national cancer register regarding several rare morphological types.

The Dutch nation-wide breast cancer screening programme

The screening programme is co-ordinated by the Centre for Population Screening of the National Institute for Public Health and the Environment *(Rijksinstituut voor Volksgezondheid en Milieu, RIVM)* and financed by the Ministry of Health, Welfare and Sport. Quality control and ongoing monitoring have been entrusted respectively to the National Expert and Training Centre for Breast cancer screening (NETCB) and the National Evaluation Team for Breast cancer screening (NETB). The nine screening regions, collaborations between a Comprehensive Cancer Centre and the area health services, are responsible for actually performing the screens. Each region boasts 1 to 5 central units where the films are read that have been made in the screening units.
The programme for women aged 50-69 years has been gradually implemented in the Netherlands during 1989-1997 and during 1998-2001 extended up to the age of 75. The personal data of the eligible women are provided by the municipal population registers (since 1996 fully computerised). Every two years, they get a personal invitation letter with a fixed appointment for a screen examination in one of the approx. 60, mostly mobile, screening units. Non-responding women are issued a reminder after two or three months. An initial screen consists of two-view mammography; in subsequent rounds, oblique views are standard while additional craniocaudal views are taken only on indication (an estimated 30% of all subsequent screen examinations). The radiographer checks the films on the spot; if necessary, repeat or additional mammograms are made. All films are independently read by two radiologists, who must reach consensus to refer the woman for further clinical assessment. All the women examined receive the result of the screening in writing; in the event of a positive result, the general practitioner is informed in advance.

Evaluation data
The NETB annually collects regional tabulated data on invitations, attendance, screen examinations, referrals, assessment and screen-detected breast cancers including tumour stage. Data on interval cancers and breast cancer incidence and therapy are obtained after linking the regional files of screened women to the files of the regional cancer registry. Due to an inevitable delay in the cancer registry and because of the screening interval of 2 years, records of women screened in a certain calendar year cannot be linked to cancer registry records earlier than in the third year after screening. For technical reasons the linkage procedure is carried out at regional level which may lead to some underreporting of interval cancers in women diagnosed and treated in another region than where screening took place. Statistics Netherlands provides data on breast cancer mortality annually.

Definitions

- *Age*
  Women are eligible for the first time in the year when they will reach the age of 50, and for the last time when they will become 75. For the evaluation we generally use the age at January 1st of a given year, corresponding with ages 49 through 74 years.

- *Screening round and attendance*
  The screening round corresponds with the number of invitations for screening of the individual woman regardless of her attendance at the previous round(s). The attendance rate is the proportion of women invited for screening who attended the programme as a result of this invitation.

- *Initial and subsequent screening examinations*
  An initial screen is the first examination of the woman within the screening programme. Subsequent screens are broken down into examinations performed within 2.5 years of the previous screen (regular subsequent screen) and examinations after an interval of 2.5 years or longer.

- *Referral and detection rate*
  Screen results are based on screen examinations performed in a certain time period, irrespective of the year of invitation. The referral rate is the proportion of screened women (per 1000) who get a recommendation for further clinical assessment. The detection rate is the number of referred women (per 1000 women screened) in whom breast cancer histologically has been confirmed, or who have been regarded and treated by the surgeon as having breast cancer.

- *Breast cancer, screen-detected and interval cancer*
  Breast cancer is defined as primary malignant epithelial disorder of the mammary gland tissue,

including ductal carcinoma in situ; lobular carcinomas in situ are regarded as benign lesions. In case of a second breast cancer only the one with the worst prognosis (when simultaneously diagnosed) or the first one (when consecutively diagnosed) is taken into account. Tumour size and lymph node status are classified in accordance with the UICC guidelines. Per cent distribution of breast cancer size is based on all breast cancers, thus including ductal carcinoma in-situ and unclassified cancers.
Screen-detected carcinomas are breast cancers diagnosed as a result of a screening examination. Interval cancers refer to breast cancers diagnosed in screened women during the interval between two screening rounds and where the diagnosis does not follow from the screening examination. Interval cancer incidence rates are presented per 1000 woman-years follow-up of screened women, calculated from the date of the last screen to the date of diagnosis of interval cancer, to the date of the following screen or to the date of eventual death or departure from the region.

- *Expected results*
  Expected results are based on outcomes of the MISCAN microsimulation model, serving as reference values for the national evaluation. The model simulates individual life histories in the absence of screening and calculates the changes after introduction of a screening programme in terms of mortality, life-years gained and cost-effectiveness.

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