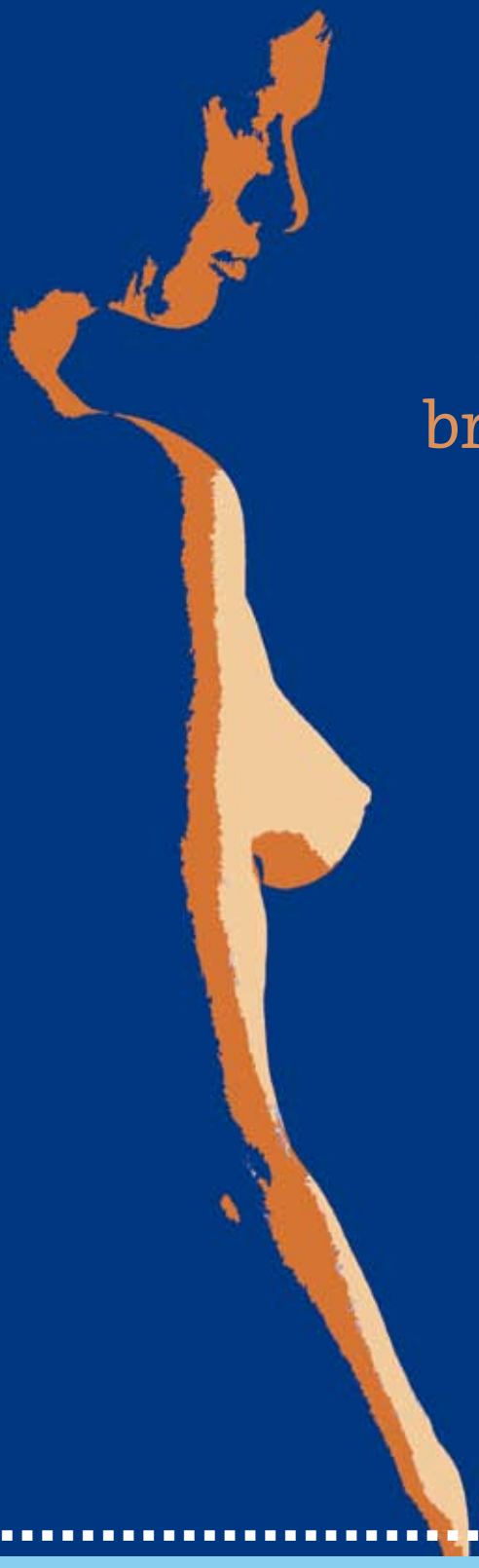

National evaluation of breast cancer screening in the Netherlands 1990 - 2011/2012

NETB XIII

National Evaluation Team for Breast cancer screening

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Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland 1990 – 2011/2012

2014 (XIII)

Thirteenth evaluation report
Het dertiende evaluatierapport

August 2014

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

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Table of contents

1

Introduction

This thirteenth evaluation report by the National Evaluation Team for Breast Cancer Screening in the Netherlands (NETB) gives details of monitoring and evaluation results relating primarily to the period from 2008 to 2011. Accordingly, this report complements the previous comprehensive report (the twelfth, published in 2009), which presented the results obtained up until 2007. In 2011 and 2012, two limited reports were published in folder form, together with the main monitoring results and some brief evaluation topics.

In the period from 2008 to 2011, the breast cancer screening programme in the Netherlands underwent some major changes:

- In 2010, as part of the organisational restructuring, the original nine regional organisations for breast cancer screening were reduced to five.
- The new regional organisations for cancer screening are also responsible for executing cervical cancer screening and, from 2014, colorectal cancer screening.
- The number of reading units (i.e. radiologists' groups that read the screening mammograms) was reduced from 28 to 16 in 2012.
- The entire transition to digital screening mammography took place in the period from 2008 to 2010. Since June 2010, all of the mammograms produced for the screening programme have been digital images.

Despite these far-reaching changes, which also involved a number of staff changes, the screening programme carried on as usual, without any detectable loss of activity or quality (confirmation was provided by the 2011 and 2012 NETB reports). This was made possible by thorough preparation, involving targeted training, support from all levels and national coordination by the National Institute for Public Health and the Environment (RIVM).

The breast cancer screening programme is monitored on an annual basis. This involves an assessment of such key quality indicators of breast cancer screening as participation rate, referral rate, detection rate, false-positive rate, tumour stage distribution of screen-detected cancers, breast cancer incidence and breast cancer mortality. The results are then submitted to the Centre for Population Screening in the form of a report. These results are based on regional screening data that is submitted annually (in aggregate form) to the NETB by the screening organisations. Monitoring data is not only used to assess the progress and quality of current population screening programmes. It is also used to regularly update the information materials given to women in the target population.

There are also evaluation activities, involving in-depth analyses of monitoring data, as well as additional studies into various aspects of the screening programme, many of which cover periods of several years. These activities have a range of different objectives. One is to determine the extent to which the screening programme has contributed to the observed decline in breast cancer mortality (by providing evidence). Other objectives are to establish the extent of adverse side effects (such as overdiagnosis, and false-positive screening results) and to identify points of reference for further quality improvements. Another goal is to estimate the potential impact of upcoming developments in the diagnosis and treatment of breast cancer. In addition to empirical research, this also involves studies based on microsimulation models.

All of the evaluation topics presented in this report have been fully completed. This is not yet the case with regard to the cost effectiveness of screening in women below the age of 50, for which further analyses are needed. To obtain a reliable impression of regional and sub-regional screening outcomes, data on interval cancers must first be added. Unfortunately, it is still not possible to present updated results on the incidence and treatment of breast cancer, as the data on recent years is not yet available.

The current national screening programme was introduced in 1989-1990, on the basis of evidence available at that time regarding the beneficial effects of screening on breast cancer mortality (given a favourable balance of pros and cons). Nevertheless, it is essential that this balance be continuously reviewed in the light of national and international developments. This is particularly relevant in the light of the ongoing debate in the medical literature, about breast cancer screening. This debate is not primarily about the Dutch breast cancer screening programme, instead it focuses on the most correct interpretation of the results obtained in mammographic screening trials during the 1970s and 1980s, versus the results of current observational studies (including the Dutch evaluation outcomes). Nevertheless, this debate could well reflect poorly on the Dutch screening programme. It is, therefore, important to retain the capacity to effectively assess the pros and cons of breast cancer screening in the Netherlands in 2011. The authors trust that this report will make a useful contribution to this endeavour.

Contents of the report

Chapter 2 presents data about the target population, about the invitations and about participation in the screening programme. Because this data becomes available relatively soon after the end of a reporting year, the report also covers 2012. Since 2008, there has been a moderate decline in participation rates. This is an added incentive to lose no time in analysing the data on participation. The section concludes by listing possible causes for the observed changes in participation rates.

Chapter 3 presents the national screening outcomes for 1990 to 2011 in terms of referral rates, detection rates and tumour stages in screen-detected breast cancer cases.

The Dutch screening programme's transition to digital screening mammography was fully completed in 2010. *Chapter 4* supplements the previous section by comparing analogue and digital techniques in terms of the main screening results obtained.

There was a long wait until recent data on interval cancers became available, but in 2012 the national link-up between screening and the Cancer Registry was finally established. In 2013, data became available on interval cancers (detected in the first two years after screening) in the entire group of women screened in the period from 2004 to 2009. These results are presented in *Chapter 5*.

Chapter 6 describes the changes in breast cancer mortality over the past 40 years. It also summarises the findings of some recent Dutch studies into the relationship breast cancer mortality (which is in decline) and the screening programme.

Chapter 7 lists the costs incurred by the screening programme for the period from 2008 to 2013, divided into regional and national costs.

Overdiagnosis is considered to be one of the major harms of mammographic screening. However, this is often (quite wrongly) equated to the temporary increase in breast cancer incidence resulting from mammographic screening. *Chapter 8* shows the best way to calculate the extent of overdiagnosis. It also gives best estimate for overdiagnosis in the Dutch screening programme.

Chapter 9 deals with the outcomes of mammographic screening tests at three levels: the entire population being screened, subgroups, and individual participants. Longitudinal data from the Nijmegen screening programme was used for this purpose.

Chapter 10 is both a discussion and a summary. The main findings presented in this evaluation report are reviewed, then correlated with one another.

2

Target population, invitations and participation 1990 – 2012

2.1 Target population

On 1 January 2012, the Netherlands had a total of 2,598,747 women in the 49 to 74 age group. This corresponded to 30.8% of the entire Dutch female population (source: Statistics Netherlands). In 1998, the first year in which women aged 69 to 74 also became eligible for screening, this overall share was just 25.8%. The size of the target population increased continuously from the 1990s onwards. Accordingly, in 2012, it was 27.3% higher than in 1998, while the total female population increased by 6.7% in the same period (ageing of the population).

Figure 2.1 shows the age distribution of the female population in the Netherlands for 1990, 2000 and 2012. The ages of the target groups are shown between the horizontal grey lines. Based on the figure, it can be deduced that the size of the target group will stabilise over the next ten years. From then on it will decline as the subsequent, smaller birth-year cohorts become eligible for the screening programme.
Figure 2.2 shows the numbers of women in the target population (for each individual age in this range) for the period from 2007 to 2012. The peak in the plots corresponds to women born in the second half of the 1940s, who are now around 65 years of age. Despite

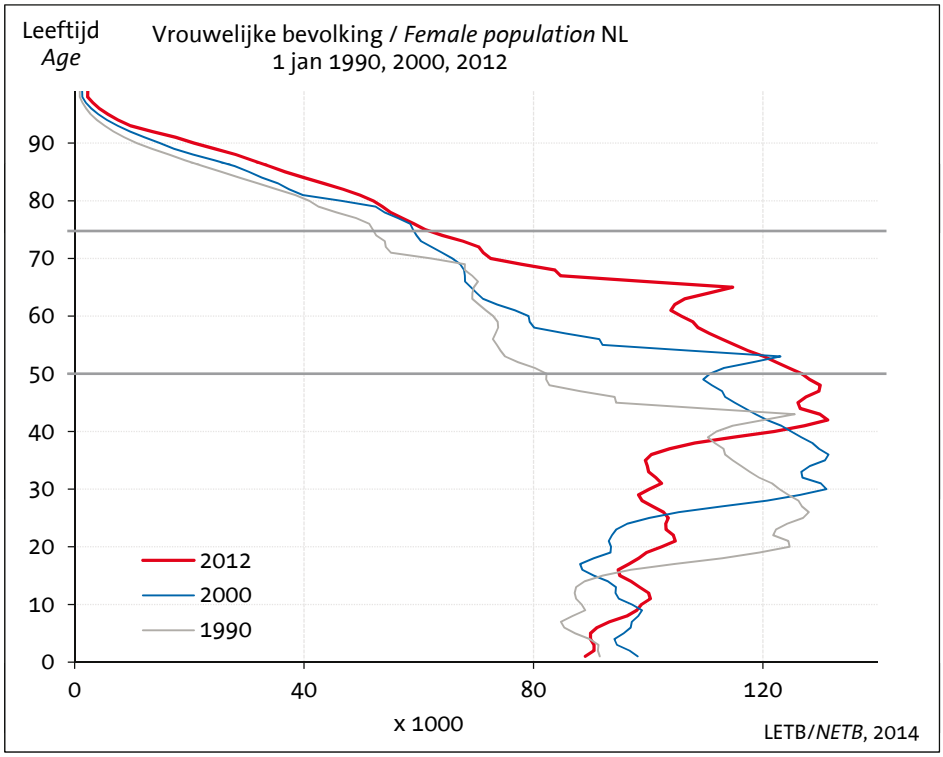

Figure 2.1
Age-distribution of the female population in the Netherlands in 1990, 2000 and 2012, between gray horizontal lines targeted ages (Source: Statistics Netherlands)

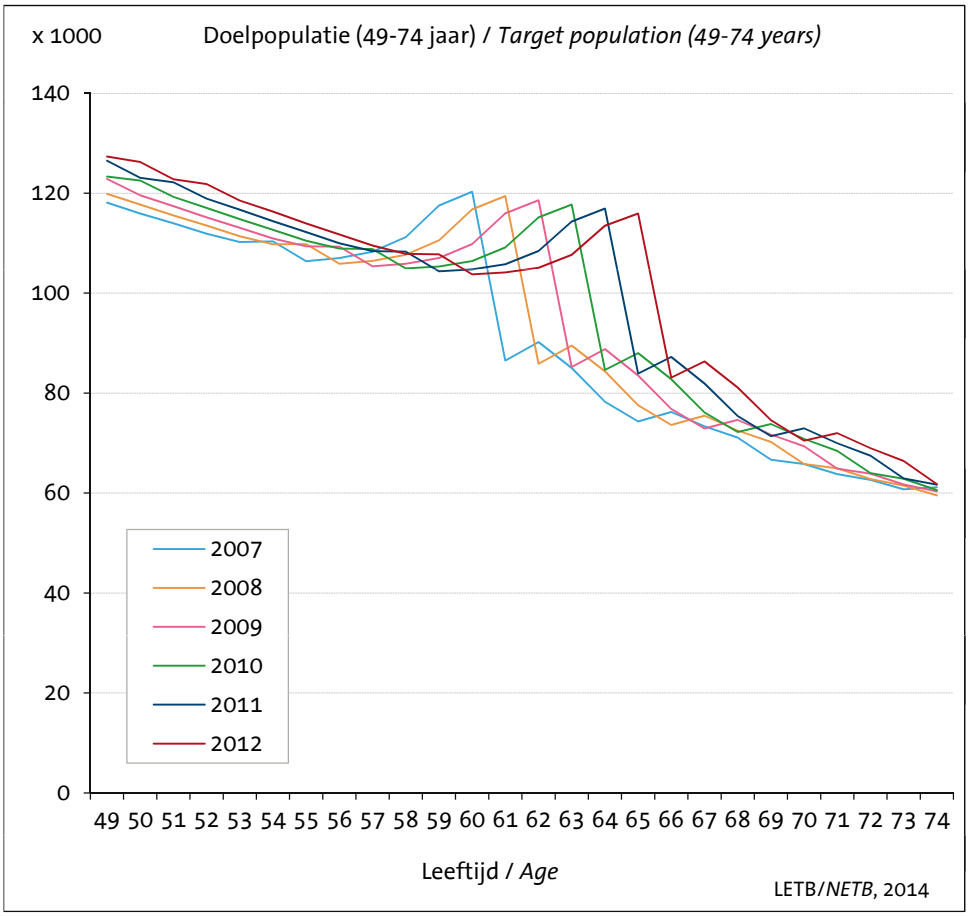

Figure 2.2
Age-specific target population 2007-2012

this striking peak, the average age of the women in the target population (between 59.8 and 60.1 years of age) has remained virtually constant since 1998.

2.2 Invitations

Definitive non-participation

In any given year, initial invitations are sent to all those women who have just joined the target group for the first time. Since about the year 2000, these are mainly women who, in the year in question (depending on the screening schedule for their place of residence), will reach the age of 50 or 51. Invitations are also sent to a number of older women who have only recently taken up residence in the Netherlands.

Some women respond to the initial invitation (or a subsequent invitation) by indicating that they do not wish to participate in the screening programme. In subsequent screening rounds, no further invitations are sent to these women (definitive non-participation). If they change their minds at a later date, they can always re-register. They will then be sent an invitation when it is time for the next screening examination. In addition, no further invitations are sent to any women who report either that they are being treated for breast cancer or that they are still having clinical check-ups. Invitations will only be sent when the women in question have re-registered for the screening programme. This means that subsequent invitations will not be sent to every woman who, at that point in time, is a member of the target group in question. Since 1997 (the first year in which definitive non-participation was measured) the overall share ranged from 2% to 7% of the target group, per year (Figure 2.3). This overall share tripled when the breast cancer screening programme was expanded to cover women of up to 75 years of age. It subsequently fell to 4%, but increased again after 2006, reaching nearly 6% in 2012. This is partly due to the increasing number of women with breast cancer (either screen-detected cancer or interval cancer) in the target population. The status of "no further invitations" can only be requested by the woman in question. Accordingly, regions tend to vary in terms of the level of detail that they record.

Calculation of the participation rate

The participation rate ("attendance rate") is calculated simply by dividing the number of women who respond to the invitation by the total number of women invited. Unlike subsequent invitations, however, initial invitations also include in the 'invited' category those women who later definitively withdraw from the screening programme. When subsequent invitations are issued these women are no longer included,

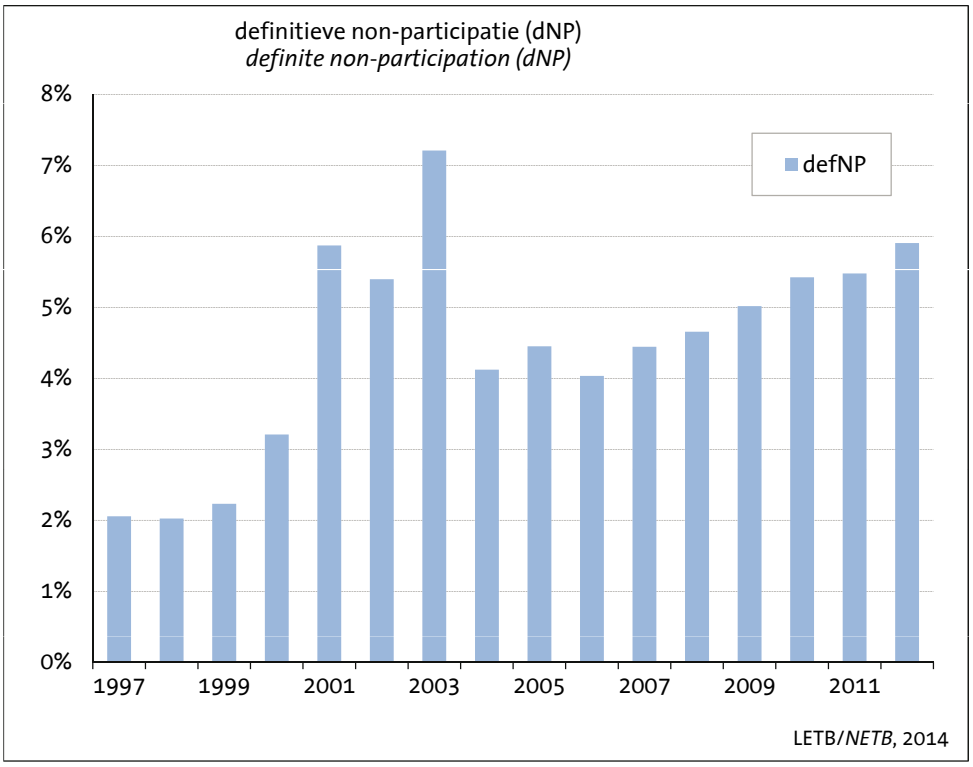

Figure 2.3
Proportion (%) of definite non-participation (defNP) 1997-2007

so the denominator (the number of women invited) is, relatively, slightly smaller than is the case with initial invitations, resulting in a slightly more favourable participation rate.

Invitation interval

Women are invited by groups, per postcode area (or areas). Invitations for the next round of screening must be issued within 24 + 2 months of this date. It is not always possible to achieve this, however, due to changes in local authorities' invitation schedules. Such changes may result from a lack of capacity or from the commissioning of a new, additional screening unit. At the individual level, this means that some women will not receive subsequent invitations within the prescribed period of 24 + 2 months (Figure 2.4). In addition, those women who move to another local authority area (postcode area) may re-

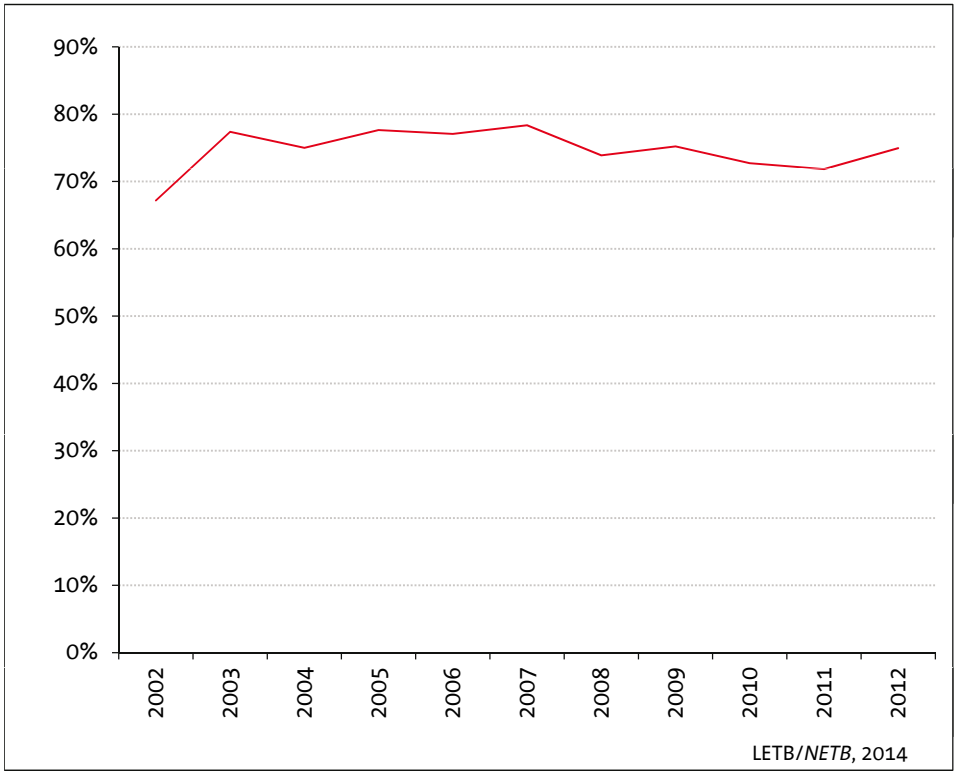

Figure 2.4
Proportion (%) of women re-invited within 22-26 months after the previous invitation, 2002-2012

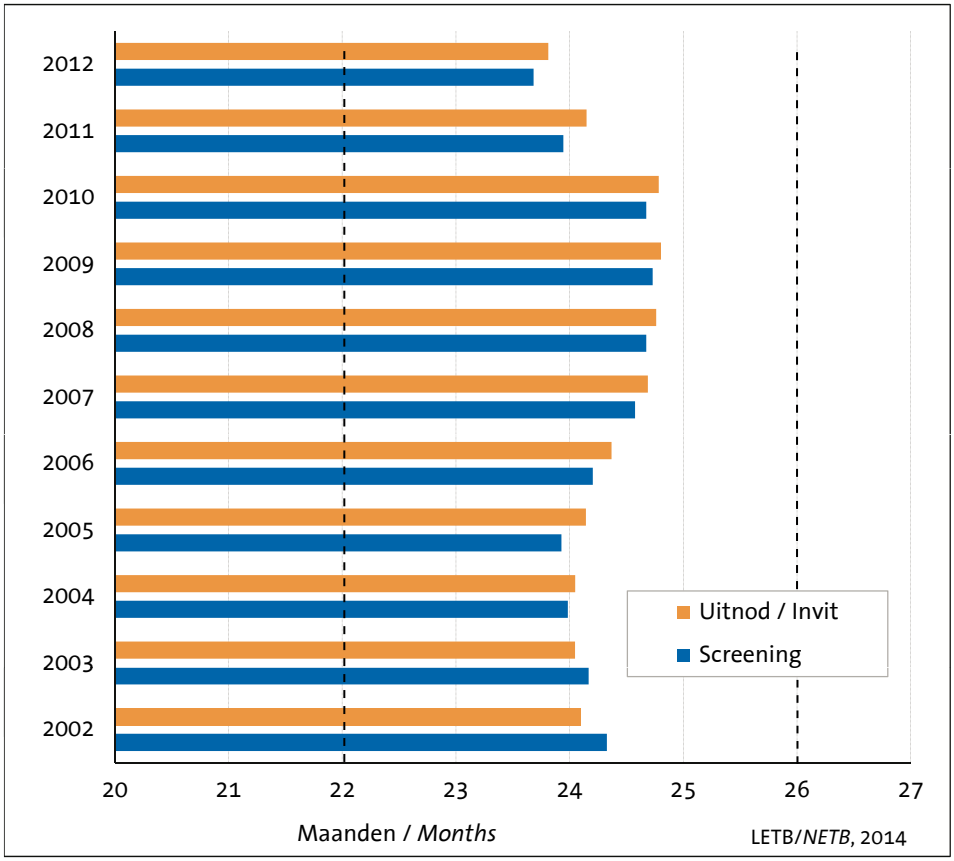

Figure 2.5
Mean individual invitational (Invit) and screening interval in months, 2002-2012

ceive their subsequent invitations either before or after this deadline. Over the past decade, about 75% of those women being invited to participate in their next screening test actually received the subsequent invitation on time.

In terms of being able to guarantee an average screening interval of about two years, the most important factor is that the women in question receive their invitation to the next round of screening in good time. Figure 2.5 shows that the average individual screening interval for subsequent screening tests is equal to the average individual invitation interval. There are slight differences between the sets of aggregated data underpinning calculations of these average intervals (two-monthly periods in the case of the invitation interval compared to three-monthly periods for the screening interval). As a result, they are not entirely comparable. In addition, the average invitation interval may be slightly longer than the average screening interval. Nevertheless, after 2010, there

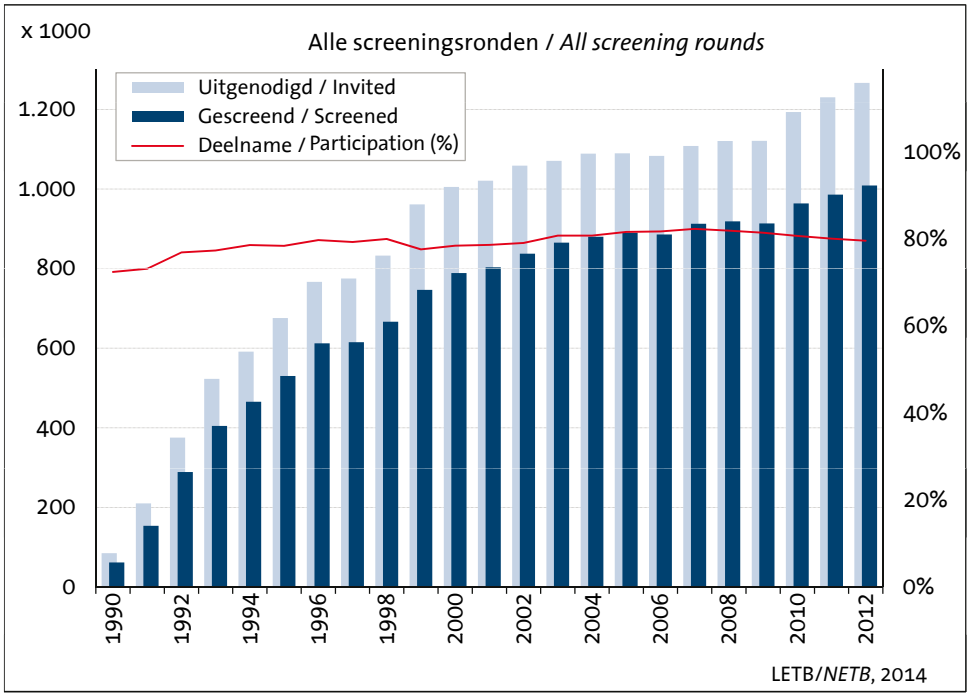

Figure 2.6
Number of invited and screened women, and participation rate (%) by year (1990-1997: 50-69 years; 1998-2012: 50-75 years)

was a further, clear reduction in the average invitation interval. In 2012, it even fell below the two-year mark, leading to a reduction in the average individual screening interval.

2.3 Participation

A new record was set in the year 2000, when invitations were sent to more than one million women. This rising trend continued, and in 2012 the total number of invitations reached 1,266,559 (Figure 2.6). The participation rate rose gradually from 72.5% in 1990 to 80.1% in 1998. However, it fell back slightly around the year 2000, when the screening programme was expanded to cover women of up to 75 years of age. From 2003 onwards it began to rise again, reaching a maximum of 82.4% in 2007. Since 2008, there has been a slight decrease of about 0.5% per year, resulting in a figure of 79.6% in 2012.

The slight decline in participation rate was seen in all age groups. This involved both initial and subsequent invitations, as well as the majority of sub-regions (the area covered by a reading unit). Another factor was an increase in the percentage of women who did not participate in the last two rounds of screening (Figure 2.7).

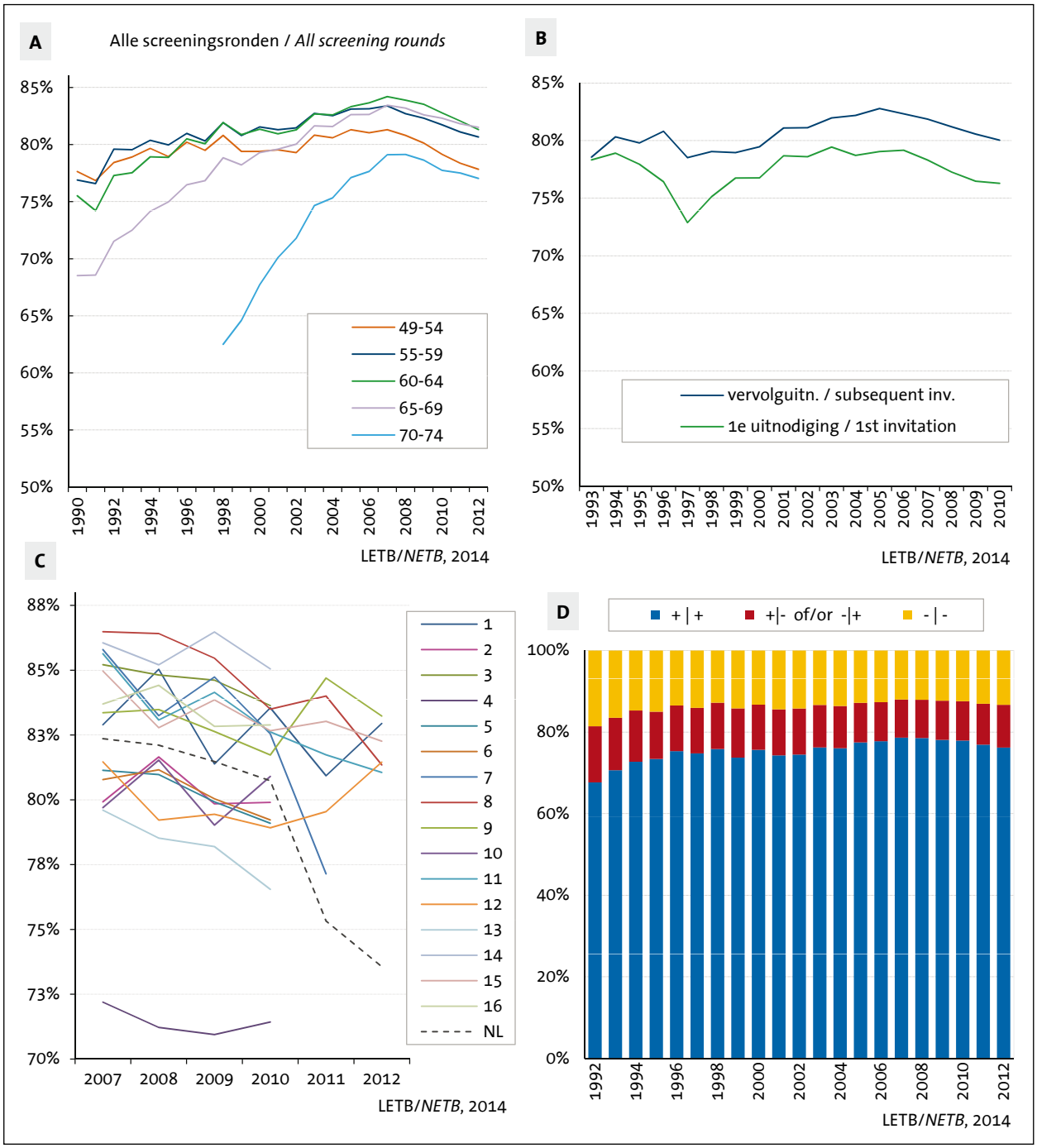

Figure 2.7 Participation rate (%) **A:** by age group, 1990-2012; **B:** 1st and subsequent invitations (all ages), 1993-2012; **C:** by subregional areas, 2007-2012; **D:** per cent distribution of (non-)participation in two successive screening rounds, 1992-2012 (+: participation; -: non-participation)

Table 2.1 Participation 2007-2012 first and subsequent invitations

Alle uitnodigingen / *All invitations*	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
Oorspronkelijke uitnodigingen *Initial invitations*	1.108.163	1.120.828	1.121.185	1.193.347	1.230.577	1.266.559
- deelname oorspronk. uitnodiging - *participation initial invitations*	80,9%	80,5%	80,0%	79,2%	78,4%	77,9%
Herinneringsuitnodiging *Reminder invitation*	111.298	102.813	95.152	109.519	119.462	123.110
- deelname herinneringsuitnodiging - *participation reminder*	15,0%	16,2%	17,0%	17,2%	18,0%	18,3%
Totaal onderzocht / *Total screened*	912.679	918.885	913.483	963.740	985.805	1.008.644
Totale deelname (%) / *Total participation (%)*	82,4%	82,0%	81,5%	80,8%	80,1%	79,6%
Gestandaard. deelname 49-74 jaar *Age-adjusted participation 49-74 years*	**82,25%**	**81,86%**	**81,35%**	**80,61%**	**79,97%**	**79,50%**
95% C.I.	(82,18%, 82,33%)	(81,79%, 81,94%)	(81,28%, 81,42%)	(80,54%, 80,68%)	(79,90%, 80,04%)	(79,43%, 79,57%)
Vervolguitnodigingen *Subsequent invitations*	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
Oorspronkelijke uitnodigingen *Initial invitations*	984.217	999.155	999.641	1.061.833	1.101.074	1.132.885
- deelname oorspronk. uitnodiging - *participation initial invitations*	81,4%	80,9%	80,5%	79,7%	79,0%	78,5%
Herinneringsuitnodiging *Reminder invitation*	93.848	85.244	77.511	88.350	96.209	98.221
- deelname herinneringuitnodiging - *participation reminder*	14,7%	16,2%	17,2%	17,5%	17,9%	17,8%
Totaal onderzocht / *Total screened*	814.705	822.570	818.304	862.130	887.043	906.666
Totale deelname (%) / *Total participation (%)*	82,8%	82,3%	81,9%	81,2%	80,6%	80,0%
Gestandaard. deelname 50-74 jaar *Age-adjusted participation 50-74 years*	**82,64%**	**82,17%**	**81,68%**	**80,97%**	**80,35%**	**79,80%**
95% C.I.	(82,56%, 82,71%)	(82,09%, 82,24%)	(81,60%, 81,76%)	(80,89%, 81,04%)	(80,28%, 80,43%)	(79,72%, 79,87%)
Eerste uitnodigingen / *First invitations*	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
Oorspronkelijke uitnodigingen *Initial invitations*	123.946	121.673	121.544	131.514	129.503	133.674
- deelname oorspronk. uitnodiging - *participation initial invitations*	76,8%	76,8%	76,0%	74,6%	73,1%	72,5%
Herinneringsuitnodiging *Reminder invitation*	17.450	17.569	17.641	21.169	23.253	24.889
- deelname herinneringuitnodiging - *participation reminder*	16,2%	16,4%	16,2%	16,3%	18,8%	20,4%
Totaal onderzocht / *Total screened*	97.974	96.315	95.179	101.610	99.028	101.978
Totale deelname (%) / *Total participation (%)*	79,0%	79,2%	78,3%	77,3%	76,5%	76,3%
Gestandaard. deelname 49-54 jaar *Age-adjusted participation 49-54 years*	**79,74%**	**79,23%**	**78,73%**	**77,81%**	**76,78%**	**76,94%**
95% C.I.	(79,51%, 79,97%)	(79,00%, 79,46%)	(78,50%, 78,96%)	(77,58%, 78,04%)	(76,55%, 77,01%)	(76,71%, 77,17%)
Instromers 1e screeningsronde *Newcomers 1st screening round*	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
Deelname 49-50 jaar (ruw) *Participation 49-50 years (crude)*	80,3%	79,8%	79,0%	78,1%	77,3%	77,1%
Deelname 49-50 (gestandaard.) *Participation 49-50 (age-adjusted)*	**80,3%**	**79,8%**	**79,1%**	**78,1%**	**77,3%**	**77,2%**
95% C.I.	(80,09%, 80,55%)	(79,54%, 80,00%)	(78,83%, 79,30%)	(77,88%, 78,34%)	(77,09%, 77,56%)	(76,96%, 77,42%)
Deelname 49-51 jaar (ruw) *Participation 49-51 years (crude)*	80,1%	79,7%	78,9%	77,9%	77,1%	77,0%
Deelname 49-51 (gestandaard.) *Participation 49-51 (age-adjusted)*	**79,0%**	**79,0%**	**77,9%**	**77,2%**	**75,9%**	**75,8%**
95% C.I.	(78,78%, 79,25%)	(78,81%, 79,27%)	(77,64%, 78,11%)	(76,99%, 77,45%)	(75,63%, 76,10%)	(75,55%, 76,02%)

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A number of sub-regions for which data was not available for the entire period were not included in Figure 2.7, C. Furthermore, no 2011-2012 data is shown for sub-regions whose boundaries were re-drawn after 2011.
Seventy six percent of the women who were invited to participate in the 2010 and 2012 screening tests actually took part on both occasions. A further 11% participated in just one of the two screening rounds, and 13% did not take part on either of these occasions. Since 2007, the overall share of consistent participants has decreased slightly, while the proportions of non-participants and irregular participants have increased slightly.

2.4 Further analysis of participation data

When the initial results of the 2009 reporting year showed a slight decline in participation rate for the second consecutive year, it was suspected that this might be an emerging trend. From then on, successive batches of participation data were retrieved at an earlier stage and analysed. In 2012, the NETB reported to the Centre for Population Screening/RIVM on factors that might have influenced participation rates in the period from 2007 to 2011 (NETB, 2012). The question was whether, based on NETB data and supplementary data from the screening database, there was any evidence that the trend change affecting participation was more pronounced than average in a given subgroup. Firstly a few parts of this report will be updated here, then the report's main findings will be summarised.

Participation by screening round and age
Table 2.1 shows that the decline involves all types of invitations, as well as the number of 49-50 year olds who are enrolling in the programme for the first time. Based on the age-adjusted ("standardised") participation rates, this year-on-year decline in all invitations and in the invitations for subsequent screening tests is statistically significant (bold numbers).
In the case of initial invitations, on the other hand, the 2012 decline was not the start of a trend. Furthermore, the standardised participation rate of 76.94% was slightly higher than in 2011 (76.78%), although this difference is not significant. In the case of initial invitations (which can be for women of any age), standardised participation can also be distorted by the presence of a few older women who are being invited for the first time. This is because their participation rate often differs from that of younger women. In 2007, 6,603 women above the age of 54 were invited for the first time (5.3%). After 2007 this overall share fell sharply. In 2008 there were 1,256 (1.0%) invitees, followed by 1,337 (1.1%) in 2009, 1,527 (1.2%) in 2010, 1,483 (1.1%) in 2011, and 1,603 (1.2%) in 2012.
Purely in terms of the initial invitations issued to women in the 49-50 or 49-51 age groups who were enrolling in the screening system for the first time, the participation rate in 2012 was not significantly different from that observed in 2011. This is all the more remarkable given that, in the preceding years, this age group's participation rate had declined much more than the participation rate for invitations to subsequent screening tests. Figure 2.8 shows that the participation rate associated with initial invitations is mainly determined by individuals aged 49 and 50. Together, women of these ages made up nearly 95%

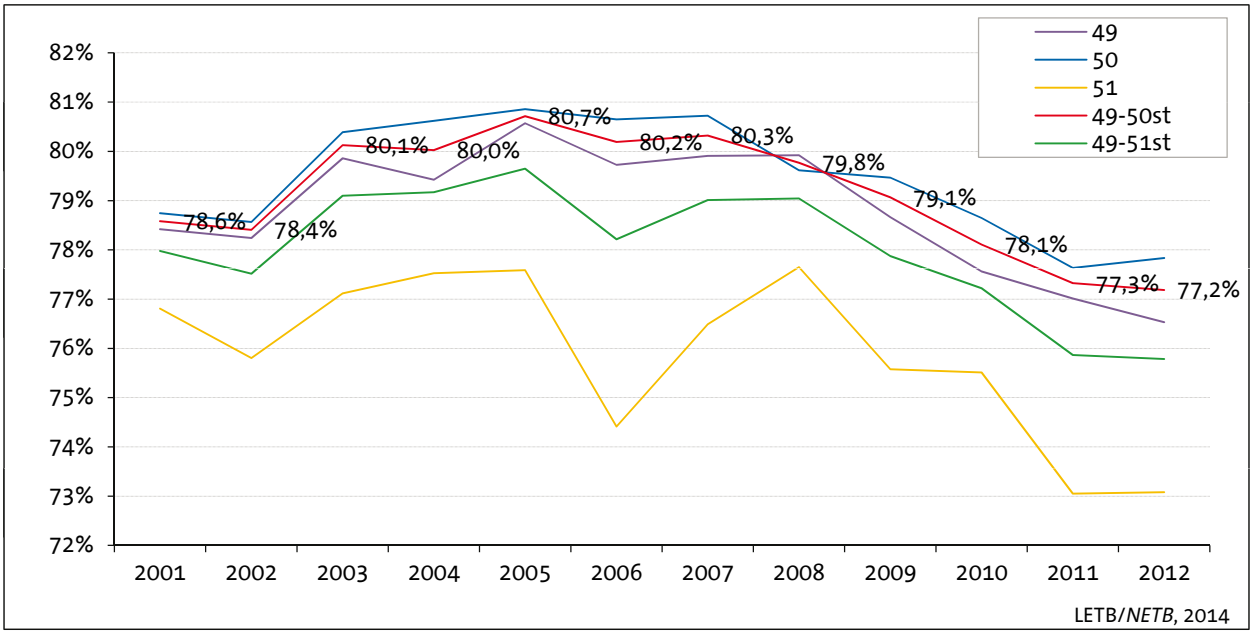


Figure 2.8 Participation of newly invited young women ("newcomers", first invitation) aged 49, 50 and 51 years, 2001-2012

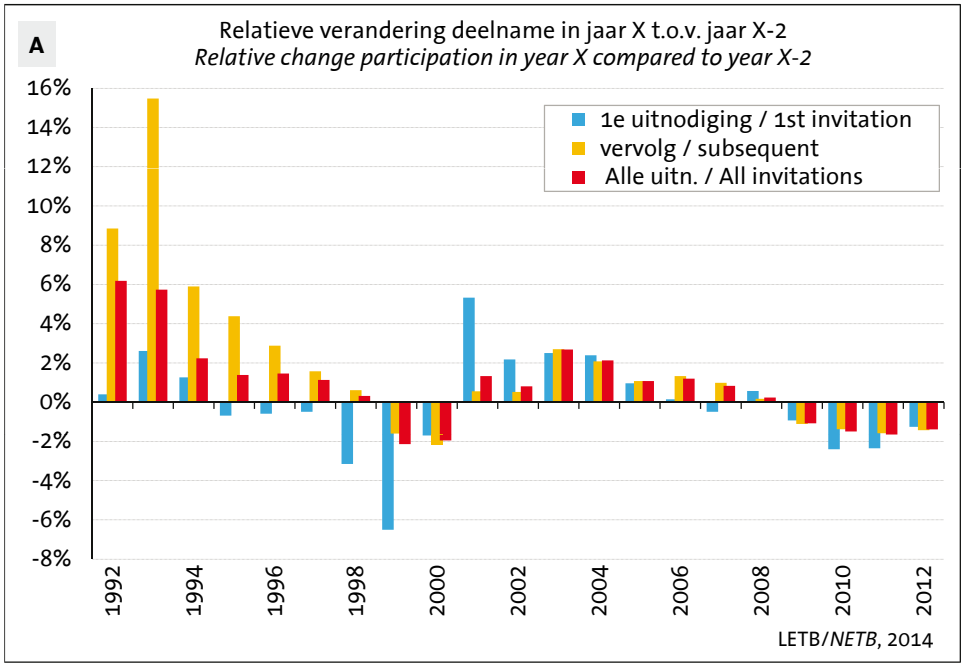
of all initial invitees. Women aged 51 accounted for only 3-4% of all initial invitations.

Alternate year participation rate

As a large proportion of the women invited in any given year will also have been invited two years previously, it makes sense to examine trends in participation rates for that year as well. In Figure 2.9, the change in participation rate relative to that recorded two years previously is presented by screening round or type of invitation (A) and age (B).

For instance, total participation fell by 2% in both 1999 and 2000, relative to 1997 and 1998. Indeed, in 1999, participation in response to initial invitations was a full 6% lower than it had been in 1997 (the actual figures were 72.9% and 77.9%; Figure 2.9, A). At the time, that temporary decline was mainly attributed to the expansion of the screening programme to cover women of up to 75 years of age. From 1998 onwards, that change boosted the overall share of older invitees with lower average participation rates. In recent years, the decline compared to the situation two years previously peaked at over 2% in 2010 (compared to 2008) and in 2011 (compared to 2009). By 2012, it had fallen to 1.5% less participation than in 2010.

In 2010 and 2011, initial invitations showed the greatest decline in alternate year participation rates. Over the past ten years, however, initial invitations have mainly involved young women who had not been eligible for an invitation two years previously. Accordingly, the greatest decline was seen in the 49-54 age



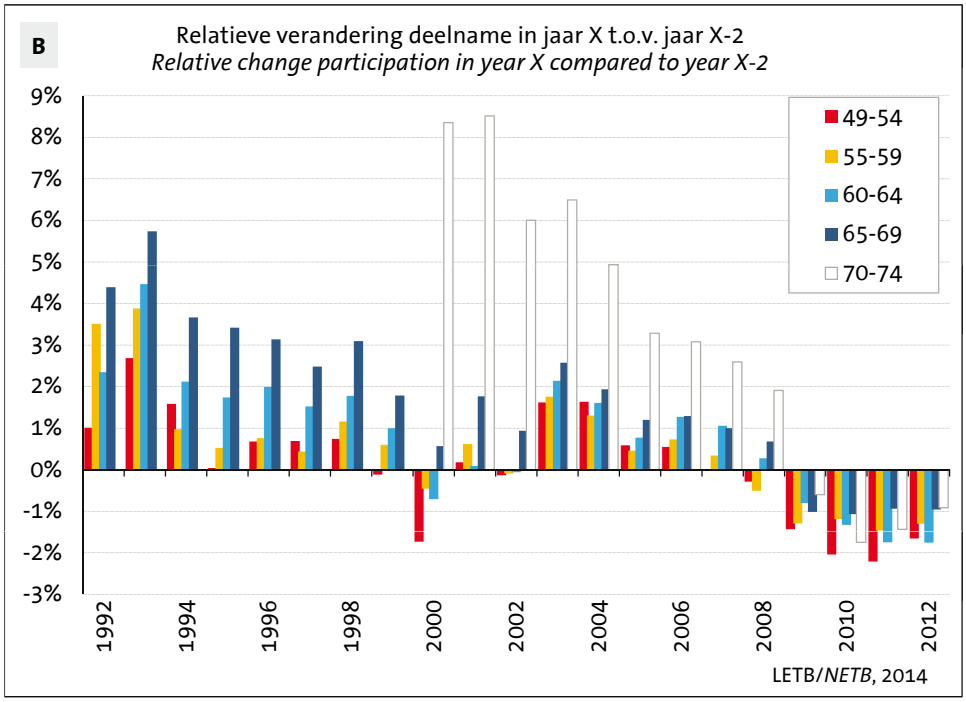


Figure 2.9
Per cent change of participation rate in given year ("year X") compared with two years before ("year X-2"), 1992-2012
A: by screening round (first, subsequent or all invitations)
B: by age group

group (Figure 2.9, B). This indicates a change in participation behaviour that cannot have been influenced by previous experiences with the screening programme.

Reminder invitations

Women who fail to respond to an invitation ('original invitation') are sent a reminder letter a few weeks later. Some of the women in question respond to this reminder by taking part in the screening programme. It has traditionally been the case that where the original invitation resulted in a relatively low participation rate, the reminder invitation makes a relatively greater contribution to the overall participation percentage, and vice versa.

Since 1993, reminder invitations made annual contributions of between 1.5% and 2.1% to the overall participation percentage (Figure 2.10, A). With regard to invitations for subsequent screening tests, this percentage was slightly lower. Conversely, in the case of initial invitations, the contribution made by reminder invitations was consistently in excess of 2%, even rising to as much as 3.8% in recent years.

Over the years, the levels of participation generated by reminder invitations have varied from 10% to 20% (Figure 2.10, B). Since 2003, the participation rate in response to all types of invitations (including invitations for subsequent screening tests) has increased. The opposite is true of initial invitations over the same period, until 2010. From 2011 onwards, however, participation in response to a reminder following an initial invitation increased again, reaching 20.4% (the highest level ever) in 2012.

Since the early years of the twenty-first century, initial invitations have mainly involved relatively young women around the age of 50. Reminder invitations are particularly important for this group. Its members tend to lead busy lives, so invitations to fixed appointments can be rather inconvenient. In recent years, screening organisations have been experimenting with reminder invitations, for instance by no longer offering a fixed examination date and location. The women involved can then make appointments for a time and location that suits them best. The rise in annual participation rates over the past few years, in response to reminder invitations, may indicate that the modified invitation policy is bearing fruit in this regard. From a different viewpoint, it is valid to ask whether the previous more 'directive' reminder invitation policy (fixed date and loca-

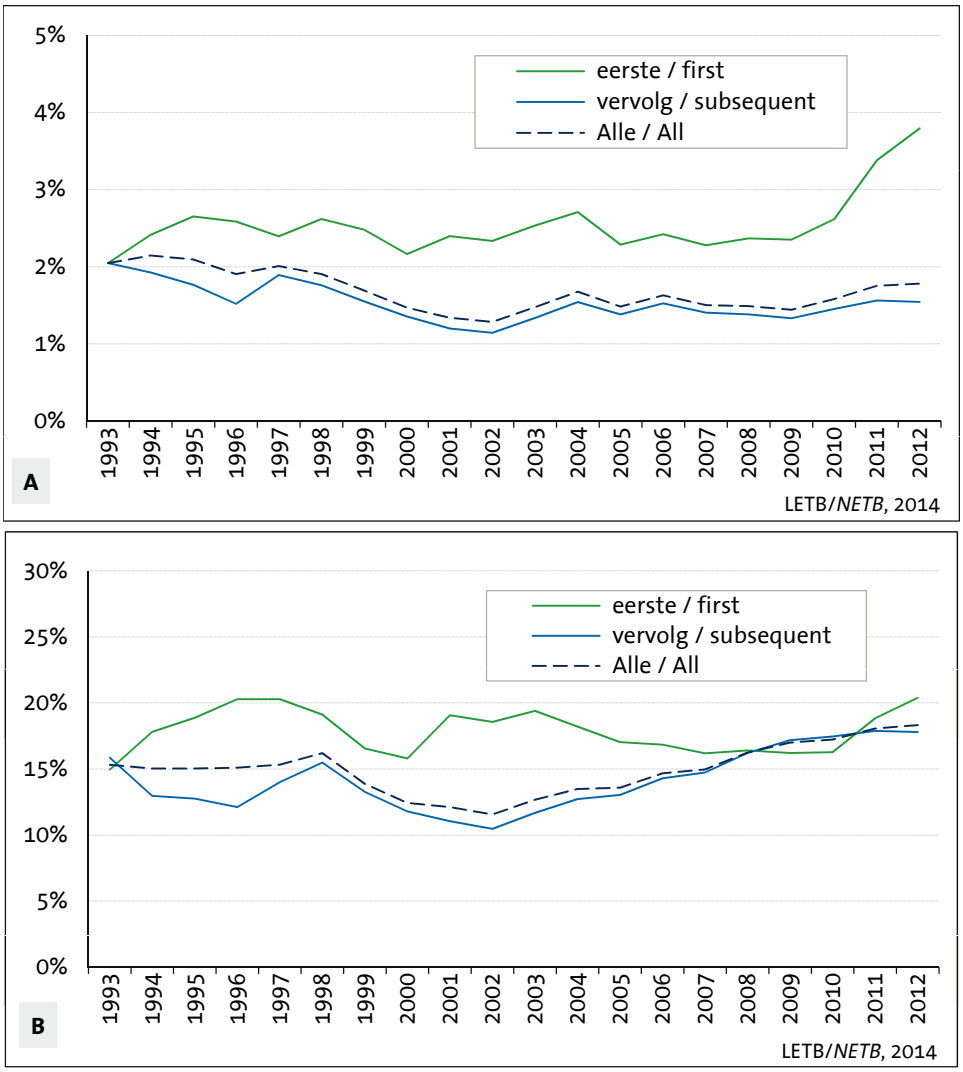


Figure 2.10
Participation (%) due to reminder invitation:
A: contribution to the overall participation rate, and
B: participation following the reminder invitation

tion) adversely affected participation rates. However, this question cannot be answered on the basis of the NETB data alone.

Number of women who participate less

After 2007, there was a year-on-year decline in participation rates of 0.4% to 0.7%. That equates to around 1% over a period of two calendar years. In a population of around 1.2 million invitees, this amounts to about 10,000 extra women who do not participate in any given year.

In spite of increased breast-cancer detection rates, the continual rise in referral rates since 1996 has led to an increase in the number of women with false-positive screening results. In the last few years, this has affected about ten to fifteen thousand women per year. Women with a false-positive result do not always return to the screening programme. Some undergo regular hospital check-ups for many years, which also involve clinical mammography. Others are disappointed or dissatisfied with the programme, due to this 'false alarm'. If the majority of women with false-positive results stopped participating in screening programmes, this might account for the declining participation rate.

For this reason, the subsequent participation behaviour of women with a false-positive result has been studied since 2002. This work is supported by the Regional Screening Organisation South-West and FSB (a foundation for general and technical cooperative support in the screening programme). On average, 70% to 80% of these women are invited to participate in the next round of testing. In 2010, for example, invitations were sent to 8,536 (75%) of the 11,415 women who had a false-positive result in 2008. If every woman with a false-positive result failed to respond when invited to participate again two years later, then the participation rate would be about 1% lower than the observed value (Figure 2.11).

However, an examination of the actual participation behaviour of women who obtained a false-positive result in the previous round, reveals an entirely different picture (Figure 2.12). It appears that three out of four women with a false-positive result still participate in the next round of screening when invited to do so. Indeed, such participation shows a rising trend over the course of time.

For many years, women with true-negative results ("other") in the previous round have shown a participation rate of around 95% (Figure 2.12). Each year, invitations are also issued to around 1,000 to 2,000 women with a true-positive (TP, screen-detected cancer) or false-negative (FN, interval cancer). Most of these individuals are probably women with an interval cancer of which the screening organisation was unaware when it issued the subsequent invitation. Such women participate only to a minimal extent, which has an adverse impact on the overall participation rate. However, the numbers involved are so small that the actual effect is negligible.

Figure 2.12 also shows that the level of participation by women who did not get a true-negative result ("other") in the previous round has always been low, even in the period when participation rates were increasing almost continuously. It is indeed remarkable that, during the very years in which overall participation rates begin to decline, these rates started to rise in women with false-positive (FP), true-positive (TP) or false-negative (FN) results. A similar trend was also observed by the South-Western Screening Organisation during a study into the determinants of participation. If these women had participated at the same level as the national average, then the national participation rate since 2004 (and probably even

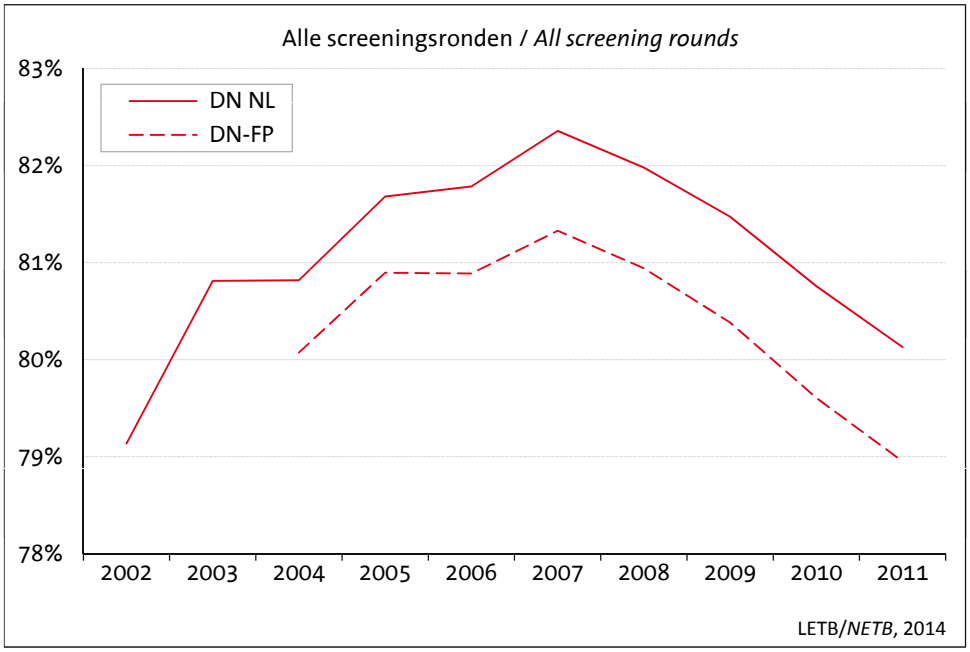


Figure 2.11
Observed (DN-NL) and expected (DN-FP) participation rate (%) if all women with a previous false-positive screening result would not participate

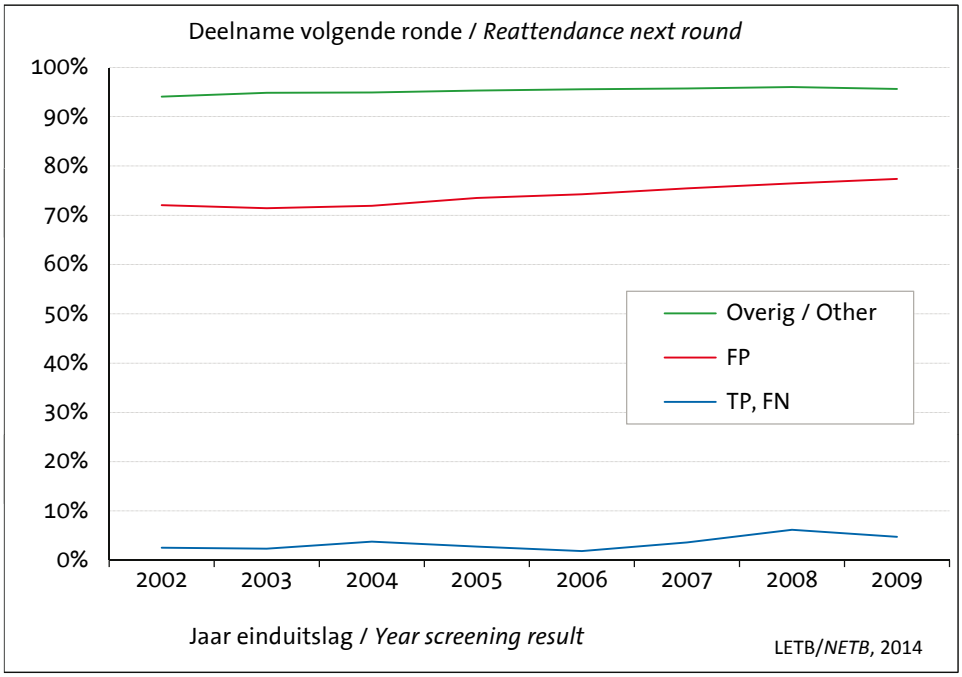


Figure 2.12
Reattendance (%) depending on screening result in preceding round; FP= false-positive; TP=true-positive; FN= false-negative

before that) would have been 0.1% to 0.2% higher. Accordingly, the recent fall in the participation rate cannot be ascribed to women with a false-positive result.

2.5 Possible reasons for the decline in participation

The slight decrease in participation may have been caused by the screening programme itself or by the target group, but external factors may also be involved (NETB, 2012).

As far as the screening programme is concerned, it is certain that neither a re-drawing of screening region boundaries (with all of the associated changes in the computerised information system) nor the recent increase in the number of women with false-positive screening results has contributed to the decline in participation. It is difficult to identify any effects generated by organisational issues (possible problems with the location of the mobile screening units, changes to invitation policy) or by the revised and more balanced information material that has been available since 2007. However, there is insufficient evidence that these factors have contributed to the observed decline (Intomart-GfK, 2012). Increasing numbers of younger women with a familial predisposition to breast cancer have been traced after screening detected breast cancer in their mothers and aunts. One effect of this might be that, after years of clinical check-ups, fewer of these women tend to enrol in the programme. How many women this involves remains to be investigated. Whether digital mammography leads to higher levels of perceived pain is still debated, but if so, then this should mainly be limited to those invited to return for a subsequent screening test.

An increasing proportion of women in the target group are being definitively excluded from the regular invitation process (definitive non-participants), partly as a result of the detection of breast cancer during screening. The level of definitive non-participation is highest among older women. This group makes up a shrinking proportion of the overall target population, due to screening take-up in recent years by the numerically superior baby boom generation. A study has been carried out into determinants related to non-response in the breast cancer and cervical cancer screening programmes conducted by the South-Western Regional screening Organisation. The findings showed that women living in highly urbanised areas, who were either born outside the Netherlands or who are non-Western nationals, were proportionally more likely to drop out between the 2007/2008 and 2009/2010 screening rounds (Blauw-Research, 2012). However, unless this factor was significantly different in the past (when participation was still rising) it would not wholly account for (or contribute to) the declining participation rate. Data obtained by the National Evaluation Team for Breast Cancer Screening in the Netherlands (NETB) in the 1990s showed that, even then, the participation percentage was inversely proportional to the level of urbanisation. Around 20,000 to 25,000 Turkish and Moroccan women become eligible for screening each year. The available data suggests that this group has always had a significantly lower participation rate (50% or less). Accordingly, only complete non-participation by this group of women would substantially reduce the overall participation rate (by about 0.9%).

Women in their forties, in particular, make use of mammography outside the context of screening programmes, in what is known as opportunistic screening. If these individuals opt to continue with regular clinical check-ups beyond the age of fifty, this could adversely affect participation rates, especially among those being invited to attend their initial screening test. However, virtually nothing is known about the extent of opportunistic screening in the Netherlands. Since the year 2000, the incidence of breast cancer in women between the ages of 46 and 48 has been rising. This, together with the proportionally greater increase in the incidence of in situ cancers, might indicate increased screening activity in this age group.
Since the year 2000, screening programmes have been the subject of persistent criticism in medical journals and the lay media. This has allegedly led to a change in attitude towards screening among general practitioners and specialists. However, a survey commissioned by the Centre for screening (part of the National Institute for Public Health and the Environment) has shown that GPs play no significant part in determining whether to take part in screening or not. Nothing is known about the extent to which women in the target group allow themselves to be influenced by critical voices in the media. Nor is it known whether the increased focus on breast cancer care (partly fuelled by interest in prominent breast cancer patients) has reduced the perceived threat from breast cancer and, as a result, the perceived necessity of screening. This also applies to possible 'competition' from the upcoming screening programme for colorectal cancer.
The last remaining possibility is that the slight decline may be due to a favourable development, namely that women in the target group are becoming increasingly better informed about the pros and cons of early detection and mammography screening. Research has shown that the best informed women in this regard are those who are now becoming eligible for the cervical cancer and breast cancer screening programmes (Van Agt, 2008). If this leads to nothing more than well-informed, non-participation then this can also be seen as a positive development.
In conclusion, it can be stated that no specific cause for the observed decline in participation rates can, as yet, be identified. The most likely explanation seems to be that this is due to a combination of several different factors. The main recommendation is that an assessment should be made of the level of opportunistic screening and of clinical check-ups in women with a familial predisposition. An investigation should also be carried out into whether a prolonged sequence of clinical check-ups does indeed deter women from enrolling in the screening programme.

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3

Screening results from 1990 to 2011

This section presents the national results obtained by the breast cancer screening programme over time, mainly through the use of figures. Appendix II presents the key results in a summary table; detailed figures per year and type of screening test can be found in Appendix IV.

3.1 Screening tests

In the period from 2007 to 2009, the number of screening tests appeared to have stabilised, at around 915,000. In 2011, however, there was a further sharp increase, to 986,885 (Figure 3.1). In total, nearly 15.2 million tests have been performed since 1990, 20% of which were initial screening tests and 80% subsequent screening tests. In recent years, however, the overall share of initial screening tests has dropped to between 11% and 12%. Since 2003, the overall share of subsequent screening tests at intervals of 2.5 years or more has remained at about 4.5%. After 2008, the overall share of digital mammography rose sharply, reaching 42% in 2009 and 94% in 2010. 2011 was the first year in which mammography was entirely digital.

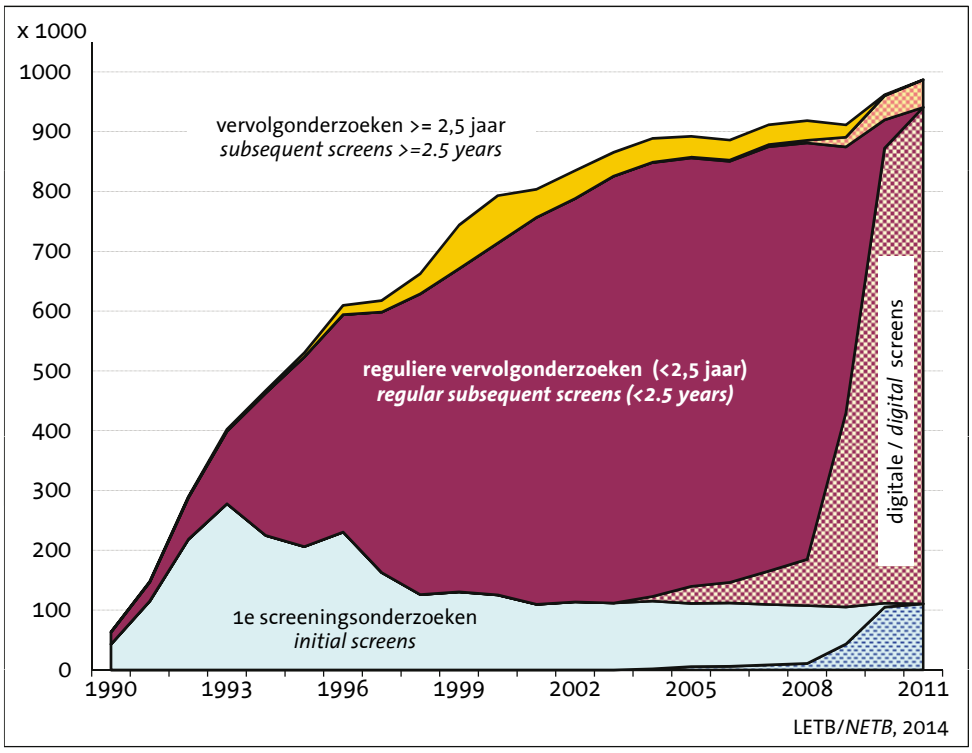


Figure 3.1
Number of initial screens, regular subsequent screens within 2.5 years, and subsequent screens >=2.5 years by year, 1990-2011 (shaded areas: digital screening exams)

For practical reasons, *regular subsequent screening* is defined as subsequent screening that is performed within a period of 2.5 years after the previous screening test. This seems to be a very wide margin, given that the formal screening interval is just two years. However, it is virtually impossible to guarantee this interval for large groups of women, even if invitations were to be issued at individual level. That would involve offering women a screening test date that is exactly two years later, moreover these individuals would preferably not be allowed to change this appointment. In reality, invitations to women to participate in the Dutch breast cancer screening programme are issued at group level (postcode areas). In the majority of cases, the date on the invitation is determined by the period in which the mobile screening unit can next be moved to the town or city in question. Moreover, these women have the option of choosing another screening test date, and it is estimated that 30% of them actually do so. Finally, if they move to another town or region, women can find themselves in a completely different screening schedule.

3.2 Screening interval

The length of the screening interval is primarily dependent on the time at which previously screened women receive their invitations to the next screening. About 75% of women will receive invitations to the subsequent screening test within a period of 24 months $\pm$ 2 months.

Figure 3.2 shows the percentage of invitations per period of time after the last screening, from 2005 to 2011. This shows that, in most years (with the exception of 2005 and 2011), the majority of women received invitations at 24 to 25 month intervals. In 2005 and 2011, the average individual screening interval was less than two years (23.9 months; Figure 3.3, bottom line on the x-axis).

Over the past ten years, the maximum difference in average interval length for regular subsequent screening tests was 0.8 months. While this may not seem much, it does mean that, within the 2.5 year period, more than 800,000 women are screened more than three weeks later, possibly generating a slight increase in the detection rate as a result.

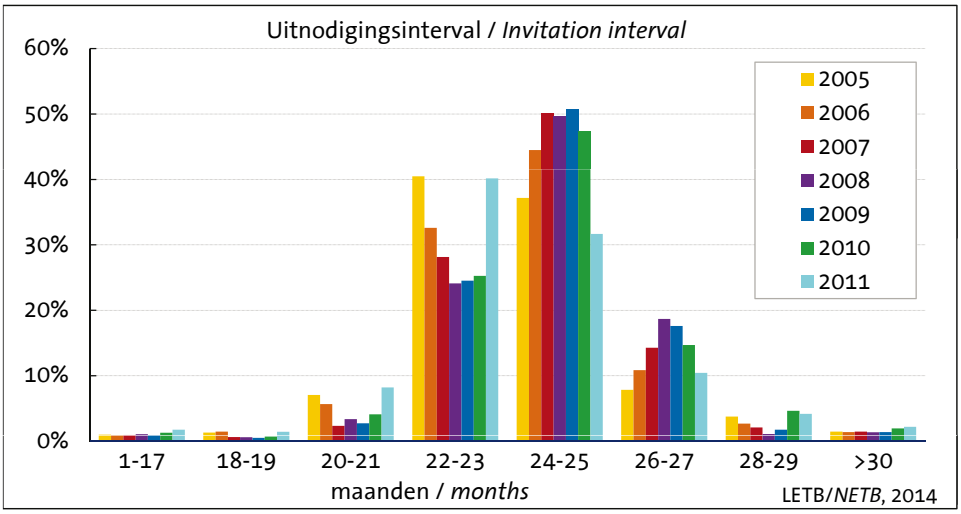


Figure 3.2
Per cent distribution of length of the mean individual invitational interval in months, 2005-2011

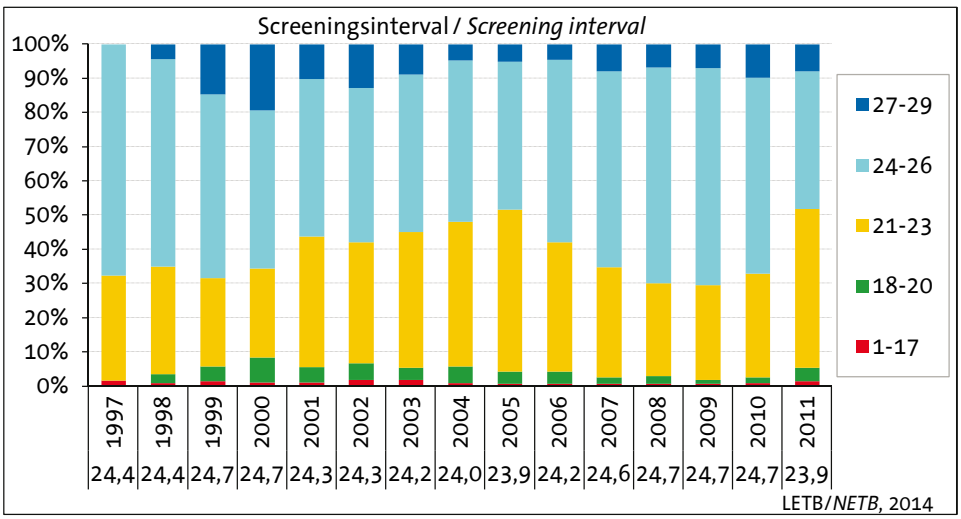


Figure 3.3
Per cent distribution of length of the mean individual screening interval in months, 1997-2011

3.3 Recommendations for referral

For the first time, more than 20,000 tested women were referred to hospital for further tests in 2011. The actual figure involved was 21,129, or 21.4 per 1,000 screened individuals. As Figure 3.4 shows, referral rates have risen continuously since 1996 (when the breast cancer screening programme was first fully implemented), more than doubling in the intervening period.

The referral rate is dependent on factors such as the type of screening test (initial or subsequent screening test) and the age distribution of the group of women being tested. In Figure 3.5, the progression of the referral rate over time (from Figure 3.4) is superimposed over the number of screening tests (from Figure 3.1). This shows that, from 1994 onwards, the majority of screening tests performed were subsequent screening tests (in which relatively fewer women were recommended for referral). At the same time, there was a fall in the average age of women attending their initial screening test. This is because, from the second screening round onwards, in any given town or city, all of the women receiving their initial invitation will be aged around 50 (at which age they are less likely to be referred). These developments account, to some extent, for the initial decline in the referral rate up to 1996.

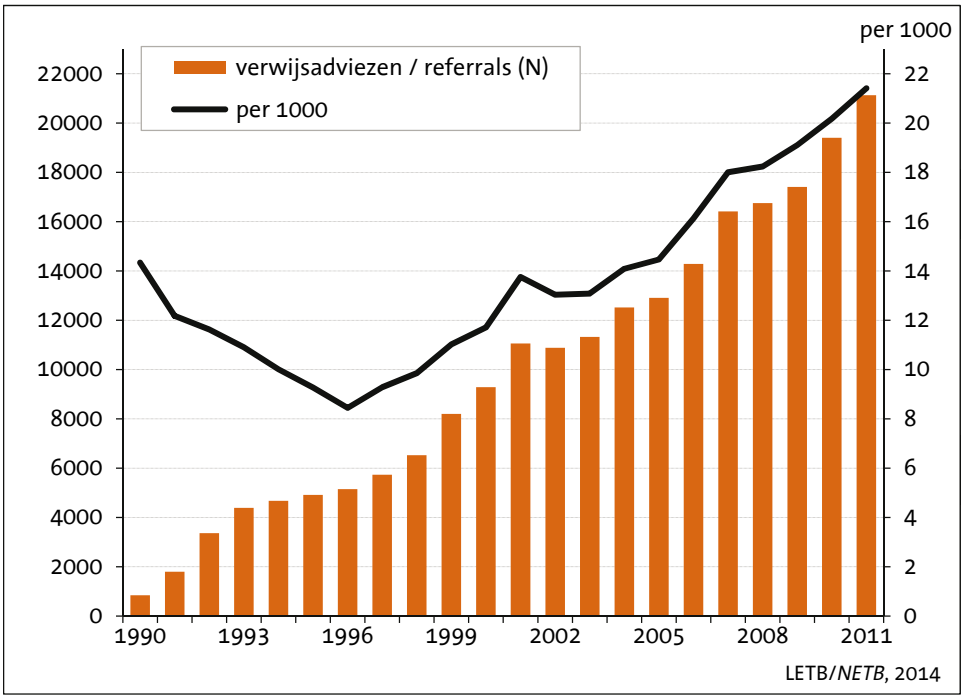


Figure 3.4
Number of referral recommendations and crude referral rate per 1000 by year, 1990-2011

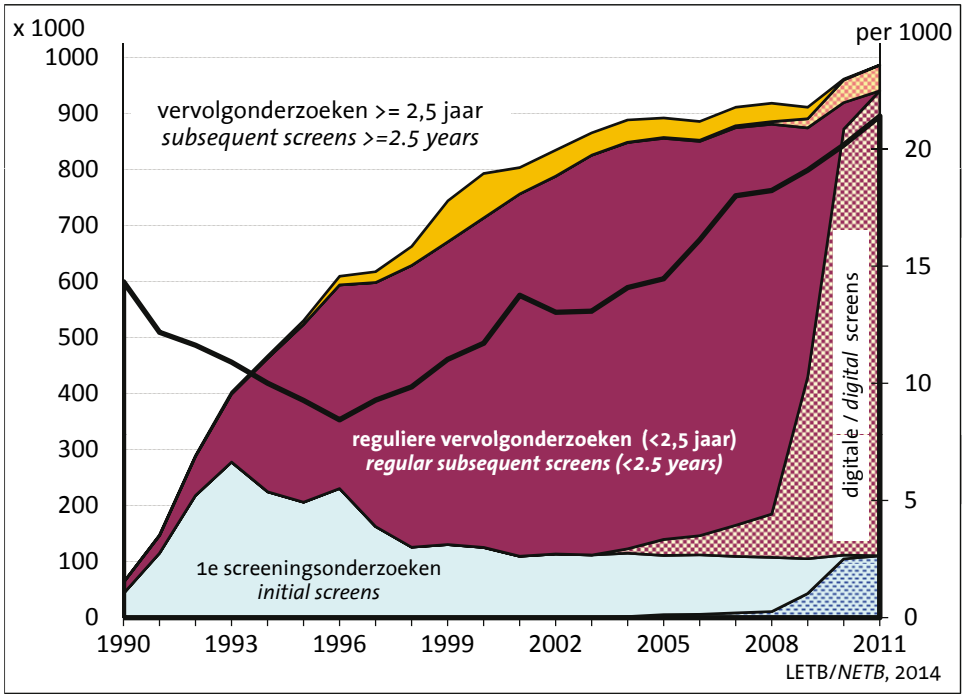


Figure 3.5
Number of screening examinations and referral rate per 1000, 1990-2011

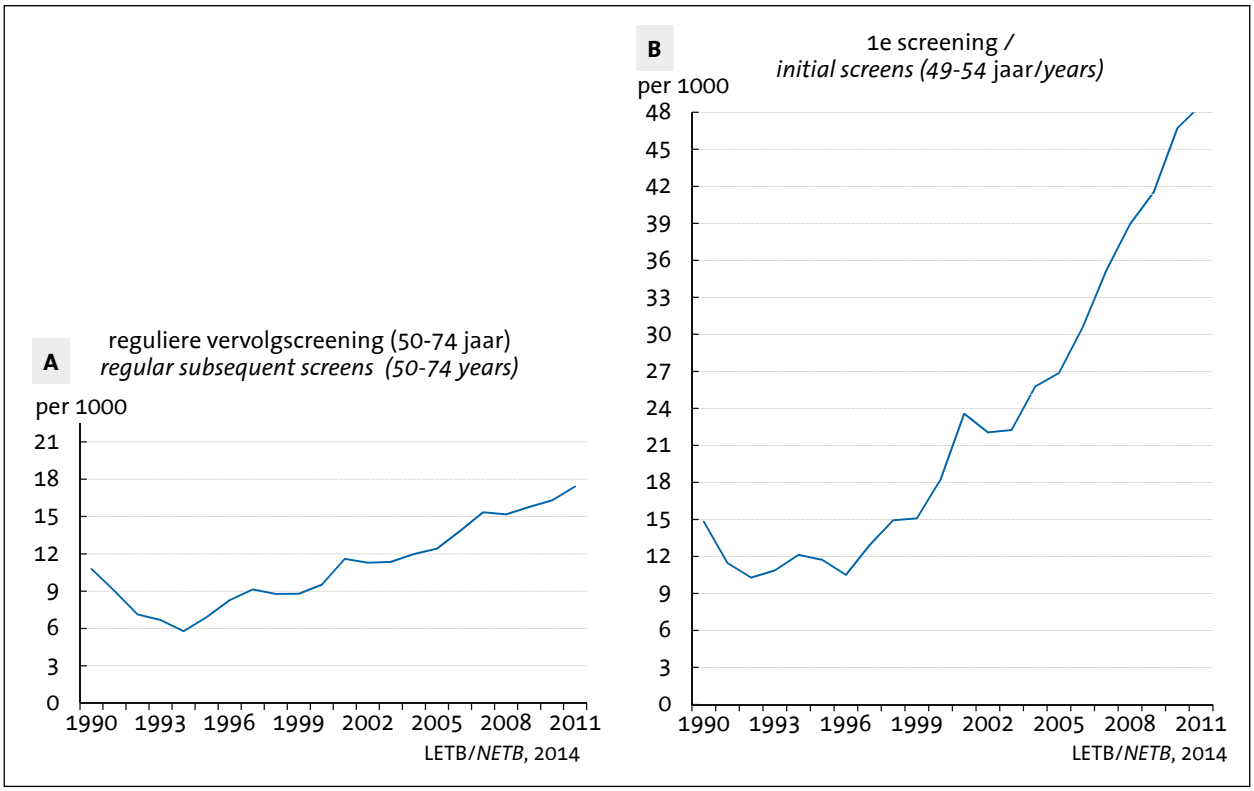


Figure 3.6 Age-adjusted referral rate per 1000 for **A:** regular subsequent screens in women aged 50-74 years, 1990-2011, and **B:** initial screens in women aged 49-54 years

However, when the referral rates for initial and regular subsequent screening tests (interval < 2.5 years) are examined separately, then the referral rate for subsequent screening tests in the early 1990s also appears to have declined (Figure 3.6, A). It should be noted that, in the interests of comparability over a protracted period of time, the data in question was adjusted for possible differences in age structure. In the mid 1990s, the number of cases of breast cancer detected by screening was considered to be too low (see Section 3.4), so screening radiologists were encouraged to boost the number of referrals. As a result, from 1997 onwards, referral rates began to rise again. The expansion of the screening programme to cover women of up to 75 years of age led, from 2000 to 2001, to a temporary further increase. This was due to the enrolment of a number of older, previously unscreened women (prevalence screening). From 2008 onwards, the ever increasing use of digital screening tests helped to boost the referral rate still further.

In 2011, the referral rate for initial screening tests was 48.8 per 1,000, so it had more than tripled since the 1990s. In the same period, the referral rate for regular subsequent screening tests approximately doubled, reaching 17.4 per 1,000 in 2011.

The increase in referral rate can be observed across all age groups, in both initial and subsequent screening tests (Figure 3.7). Remarkably, in subsequent screening tests from 2001 onwards, the referral rate for women aged 50-54 (the youngest age group) is higher than that for women aged 55-59 (Figure 3.7, A). This is probably due to the fact that the average density of breast tissue is higher in younger women. With regard to the initial screening tests, the post-1997 referral rates for women aged 55 and above are based on small numbers (around 4,000 per year), which accounts for the large fluctuations seen.

Women referred for follow-up

The screening organisations routinely submit their monitoring data on 1 October of the year following the reporting year. Usually, on that date, there are still some regions that do not have sufficient full follow-up data for those women who have been referred. In recent years, the increasing number of recommendations for referral has made it difficult to obtain and process all follow-up details in good time.

The NETB has set a target of at least 95 percent definitive screening results, to enable it to draw reliable conclusions about the progress of the screening programme. In general, this requires that screening data be updated in the spring of the second year after the reporting year in question.

Figure 3.8 shows the degree of completeness of the data on which this report is based, for the year in question. With the sole exception of 1990, this percentage for the national total (red bars) has consistently exceeded 97.5%. The dark grey bars represent the region with the lowest percentage of follow-up data for the year in question. In the past, it was quite common for regions to present follow-up data that

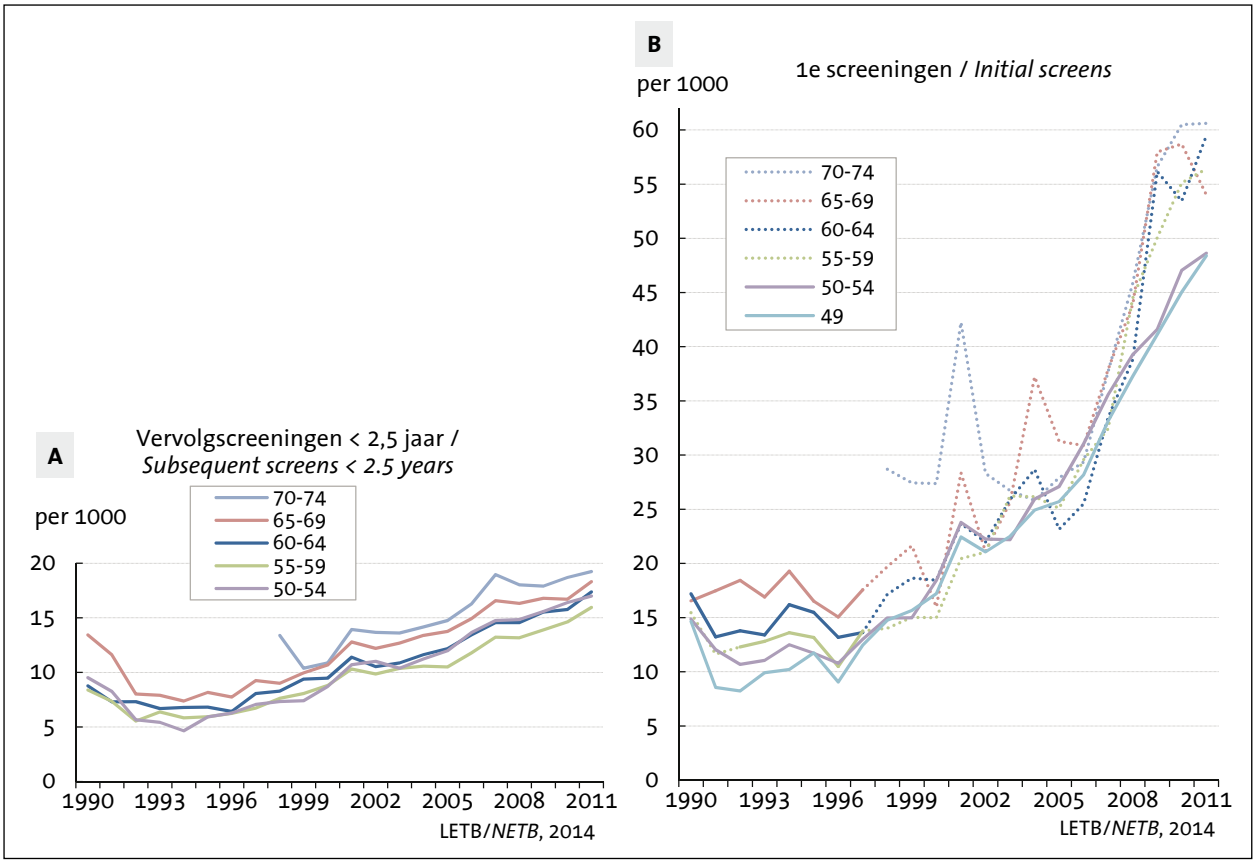


Figure 3.7 Age-specific referral rates per 1000 for **A:** regular subsequent, and **B:** initial screen examinations, 1990-2011

was less than 95% complete. In a few cases, this figure even slipped below 90%. Since 2008, however, all of the screening regions have been compliant with the 95% standard.

In some cases, further diagnostic testing does not yield a definitive screening result. Since 2002, this has involved an average of 81 women each year, or about 0.5% of all those who received a recommendation for referral (Table 3.1).

In addition, account should also be taken of those women who have lodged an objection to the recording and/or exchange of their data for evaluation purposes. This has occurred on about 4,300 occasions since the screening programme was first launched, which is equivalent to 0.026% of all the women screened. Over the past three years (2009-2011), however, this amounted to just 0.015% (approx. 150 per year) of the women screened. It is unlikely that all of

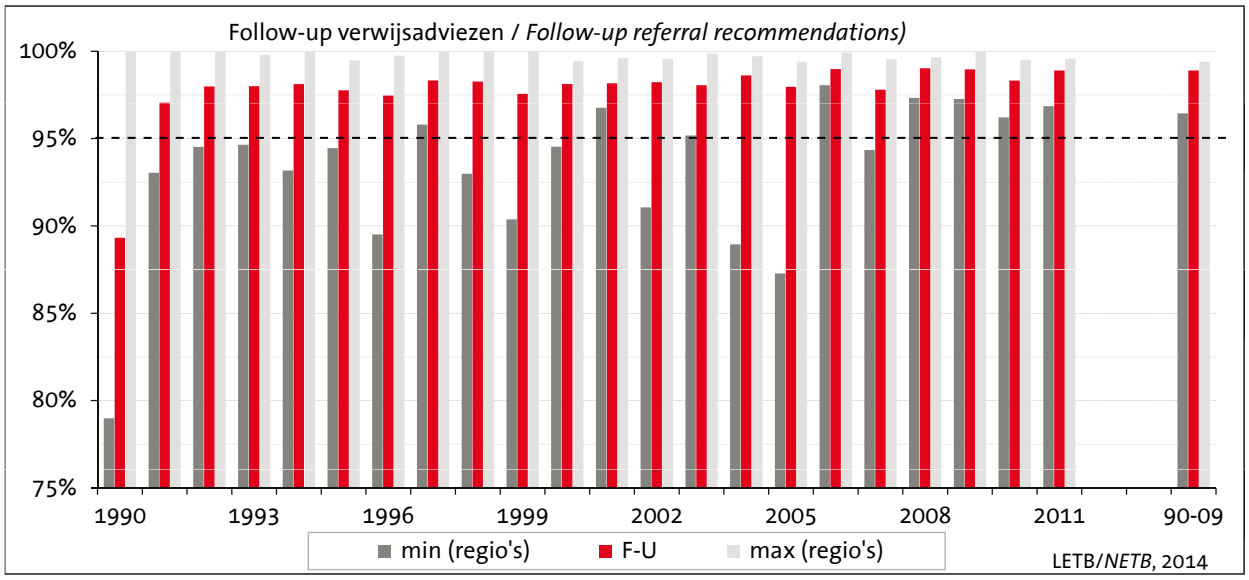


Figure 3.8 Annual percentage of complete follow-up (F-U) of referral recommendations in the Netherlands, and the regional minimum (min) and maximum (max) percentage of complete follow-up, 1990-2011

Table 3.1 Average number and percentage of referral recommendations per year without a final diagnosis, period 2002-2011

Verwijsadviezen / *Referral recommendations*	153.047	
Geen einddiagnose / *Final diagnosis missing*	809	
Reden geen einddiagnose *Reason for missing final diagnosis*	Gemiddeld per jaar (2002-2011) *Annual mean (2002-2011)*	
	N	%
overleden vóór einddiagnose / *deceased before final diagnosis*	5,5	0,04%
vertrokken / *moving to another place*	8,4	0,05%
client ziet af van nader onderzoek / *diagnostic assessment not desired*	17,8	0,12%
ingevuld bezwaarschrijft / *no permission for follow-up*	1,4	0,01%
onvolledige follow-up / *incomplete follow-up*	11,3	0,07%
niet verwezen of verder onderzocht / *not referred or no diagnostic assessment*	14,7	0,10%
geen reden / onbekend *no reason / unknown*	21,8	0,14%
Totaal / *Total*	80,9	0,53%

LETB/*NETB*, 2014

these women received a recommendation for referral, but this can occasionally be the case. Accordingly, the number of women for whom no final diagnosis is obtained would then be slightly larger than the figure indicated in Table 3.1.

3.4 False-positive and true-positive screening results

False-positive results

The increase in the referral rate from 1998 onwards has boosted the number of true-positive results (TP, the breast cancer detection rate). It has also led to a proportionately much larger increase in false-positive results (FP) (Figure 3.9). In the case of regular subsequent screening tests, the detection rate increased from 3.8 per 1,000 in 1998 to 5.9 per 1,000 in 2011. The corresponding increase for initial screening tests was from 5.3 per 1,000 in 1998 to 7.2 per 1,000 in 2011. At the same time, however, the false-positive rate for initial screening tests quadrupled, and the rate for subsequent screening tests doubled.

Figure 3.10 shows, however, that the increase in false-positive results is mainly due to cases in which the diagnosis is based on non-invasive diagnostic (imaging) methods. Around the year 2000, half of all false-positive results were still based on invasive di-

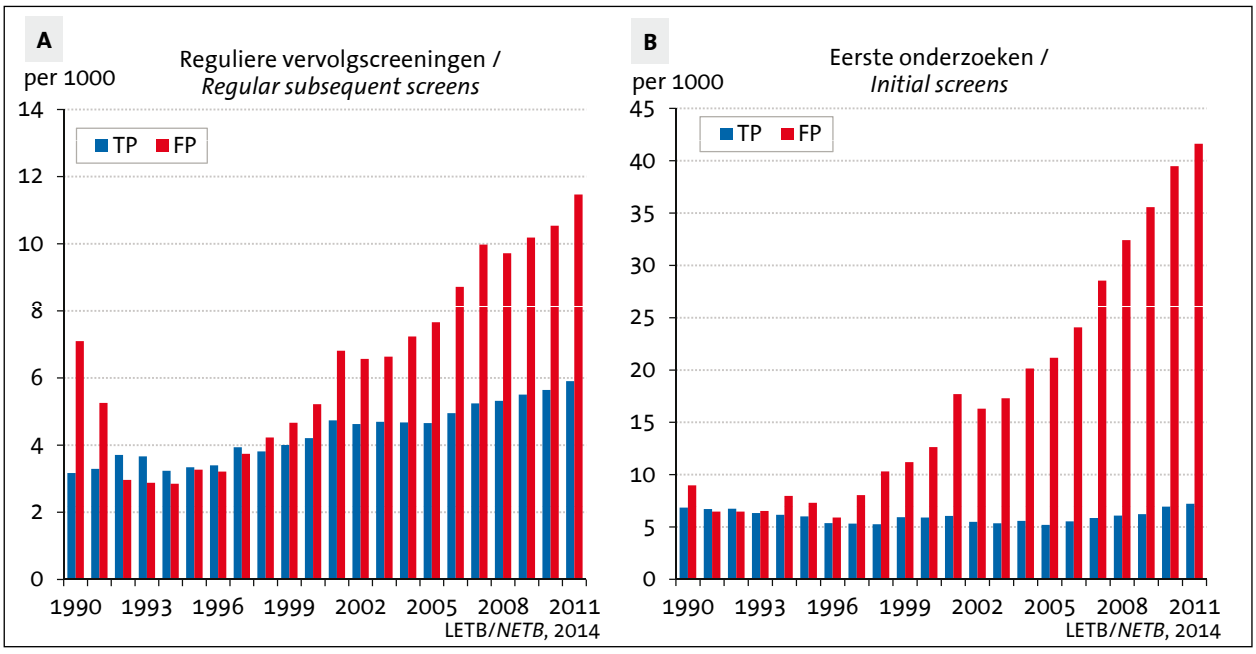


Figure 3.9 True-positive (TP) and false-positive (FP) screen results per 1000 women screened for **A:** regular subsequent, and **B:** initial screens, 1990-2011

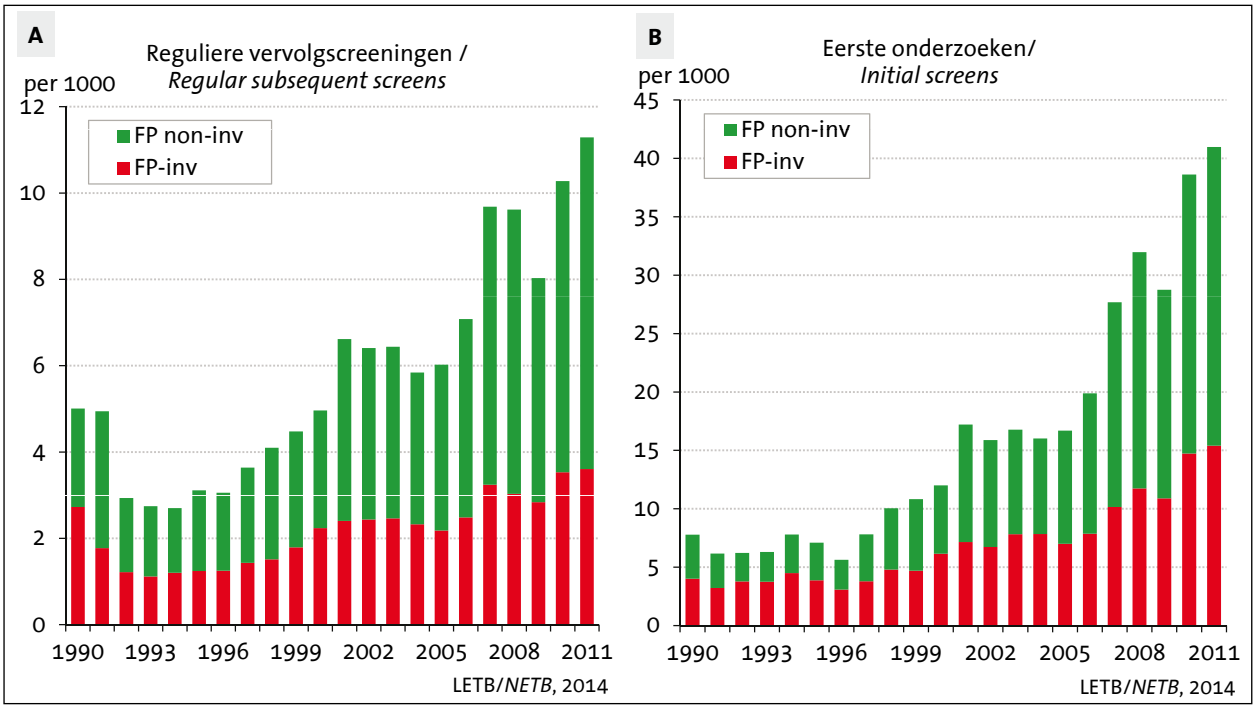


Figure 3.10 Distribution of false-positive screen results per 1000 women screened by invasive (needle biopsy, FP-inv) and non-invasive (additional imaging only, FP non-inv) assessment for **A:** regular subsequent, and **B:** initial screens, 1990-2011

agnostics (mostly needle biopsies). By around 2010, however, just a third of the women who received what, with hindsight, proved to be an unnecessary recommendation for referral underwent minimally invasive diagnostic procedures.

Positive predictive value of the recommendation for referral

Over the years, there has been a decline in the positive predictive value of referral, reflecting the increasing percentage of false-positive screening results (Figure 3.11, standardised values). The results for subsequent screening tests peaked at 56% in 1992, triggering a gradual decline in the positive predictive value. By 2007, this value had fallen to 33%, and it subsequently stabilised at around this level. The positive predictive value of initial screening tests fell by 30% to 40% in the 1990s, reaching a level of 14% in 2011.

True-positive screening results - detection rate

In 2011, the breast cancer screening programme detected just over 6,000 breast cancers. The combined detection rate for invasive and in situ breast cancers was 6.2 per 1,000 women screened (Figure 3.12).

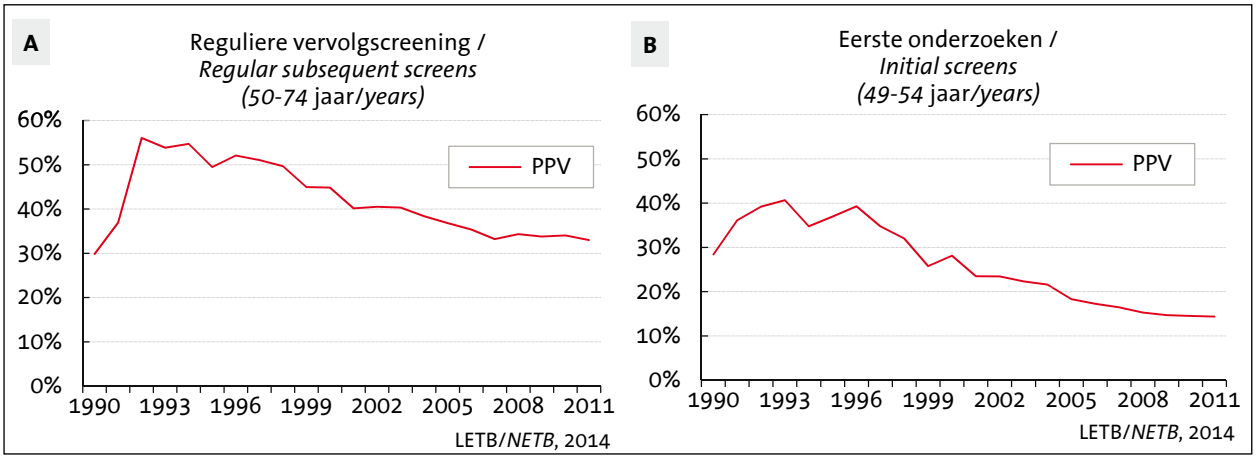
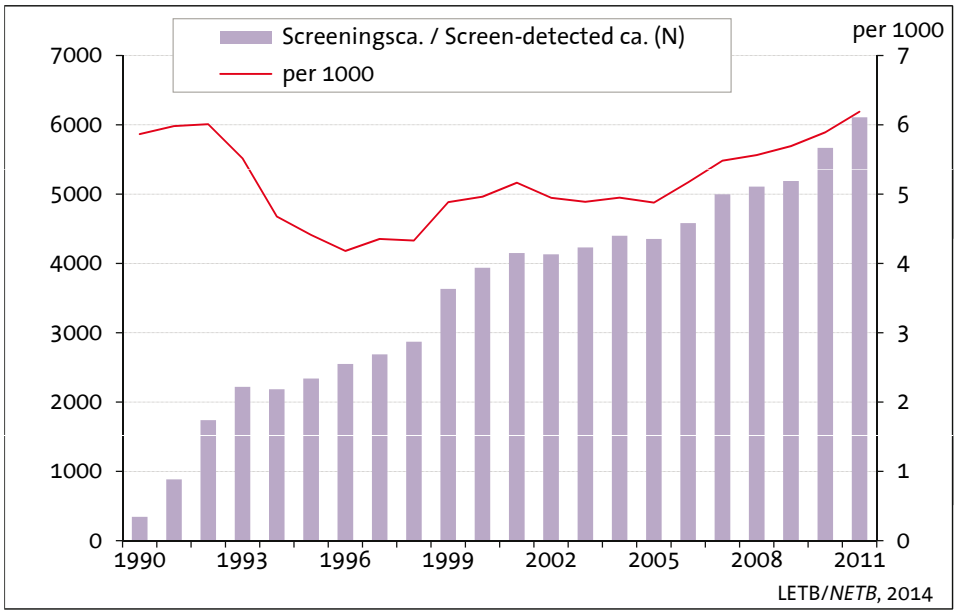


Figure 3.11 Age-adjusted positive predictive value (PPV) of recall recommendation for **A:** regular subsequent, and **B:** initial screens, 1990-2011

Figure 3.12
Number of screen-detected (invasive and in-situ) breast cancers and crude detection rate per 1000 by year, 1990-2011



Never before, since the beginning of the programme, had the detection rate exceeded 6.0 per 1,000 (in 1990 and 1991 prevalence screening had boosted this rate to 6.0). The declining percentage of initial screening tests in the first half of the 1990s cut the overall detection rate to a minimum of 4.2 per 1,000. It then rose to about 5 per 1,000 in the first five years of the 21st century. This was due to the rising referral rate and to the expansion of the screening programme to cover women of up to 75 years of age. This figure rose continuously from 2005 to 2011. Indeed, the crude detection rate at the end of this period was more than 20% higher than it had been at the beginning.

In 2011, regular subsequent screening tests detected 5.9 breast cancers per 1,000 women. The corresponding figure for initial screening tests in that year was 7.2 per 1,000. This detection rate was the highest value ever recorded, for both types of screening test. Given that, in 2011, the average screening interval for regular subsequent screening tests was significantly

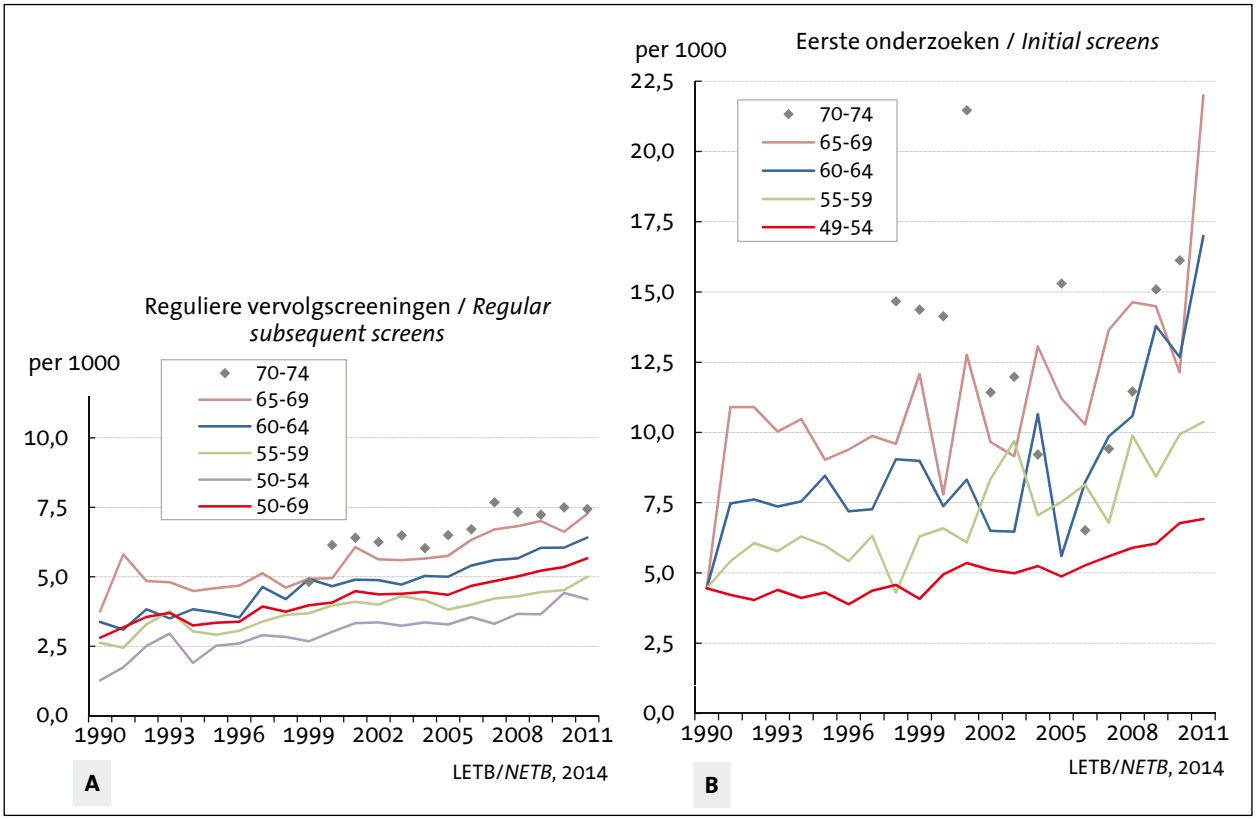


Figure 3.13 Age-specific breast cancer detection rate per 1000 for **A:** regular subsequent, and **B:** initial screens, 1990-2011

shorter than in previous years (23.9 months versus 24.7 months, see Section 3.2), the breast cancer detection rate was significantly higher. This increased detection rate is seen in all age groups. In the case of subsequent screening tests, in particular, it exhibits clear age dependency (as opposed to the referral rate which, in recent years, was higher in the 50-54 age group than in the 55-59 age group) (Figure 3.13). The annual figure for initial screening tests, since 2007, is just 4,000 to 6,000 screened women aged 55 and above, in whom 40-50 breast cancers were detected. This accounts for the erratic fluctuations in detection rates in the older age groups (Figure 3.13, right panel).

To better estimate the extent to which the detection rate has risen over the years, the detection rates in Figures 3.14 and 3.15 were confined to those ages that were eligible for screening throughout the entire period of the screening programme (50-69 for subsequent screening tests and 49-54 for initial screening tests). In addition, these figures were adjusted to compensate for differences in age distribution. Figure 3.14 shows that the detection rate for both initial and subsequent screening tests has indeed increased. This was a two-stage process. The initial increase, which occurred in the years preceding and following the year 2000, was due to the Optimisation Study, after which the detection rate stabilised at a higher level until 2005. This was followed by a second stage, which involved a continuous increase from 2006 onwards.

Figure 3.15 shows the progression of the detection rate for various tumour stages, for subsequent screening tests (Figure 3.15, A) and for initial screening tests (Figure 3.15, B). The 1990s mainly showed a rising trend in the detection of more large, invasive breast cancers (> 20 mm [T2] at initial screening tests and >10 mm [T1c and T2] at subsequent screening tests). In subsequent screening tests, the increasing detection of T1c tumours (11-20 mm in diameter) stabilised for the first time in 2002-2005. Following a further slight increase, it then stabilised for a second time from 2009 onwards.
Since 2008, the increase in detection mainly involved ductal carcinoma in situ (DCIS) and small invasive T1a (<= 5 mm) and T1b (6-10 mm) tumours. As far as DCIS is concerned, this undoubtedly resulted from the introduction of digital mammographic screening. The same may also be true of the small invasive tumours, as international evaluations of digital screening programmes have found similar results. However, these results should be treated with caution, in connection with the increasing use of neo-adjuvant therapy from 2005 to 2010. This form of therapy commences with systemic treatment to reduce the volume of the tumour, which is then removed surgically. This results in a situation where the histopathological cross-section of the excised tumour is smaller than the cross-section seen on the preceding mammogram. To some extent, therefore, the increased detection of T1a and T1b tumours may be an artefact. This might also account for sudden stabilisation of the long-term increase in the detection rate for T1c tumours (especially in subsequent screening tests) in the same recent period.

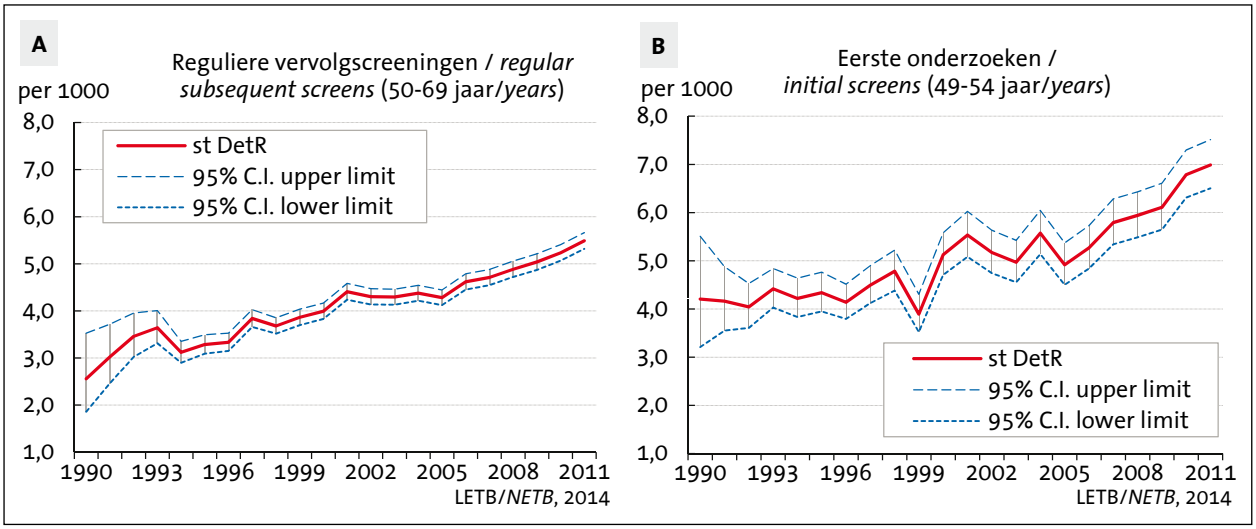


Figure 3.14 Age-adjusted overall (invasive and in-situ) breast cancer detection rate (stDR) per 1000 with 95% confidence interval (95% C.I.) for **A:** regular subsequent screens in women aged 50-69 years, and **B:** initial screens in women aged 49-54 years, 1990-2011

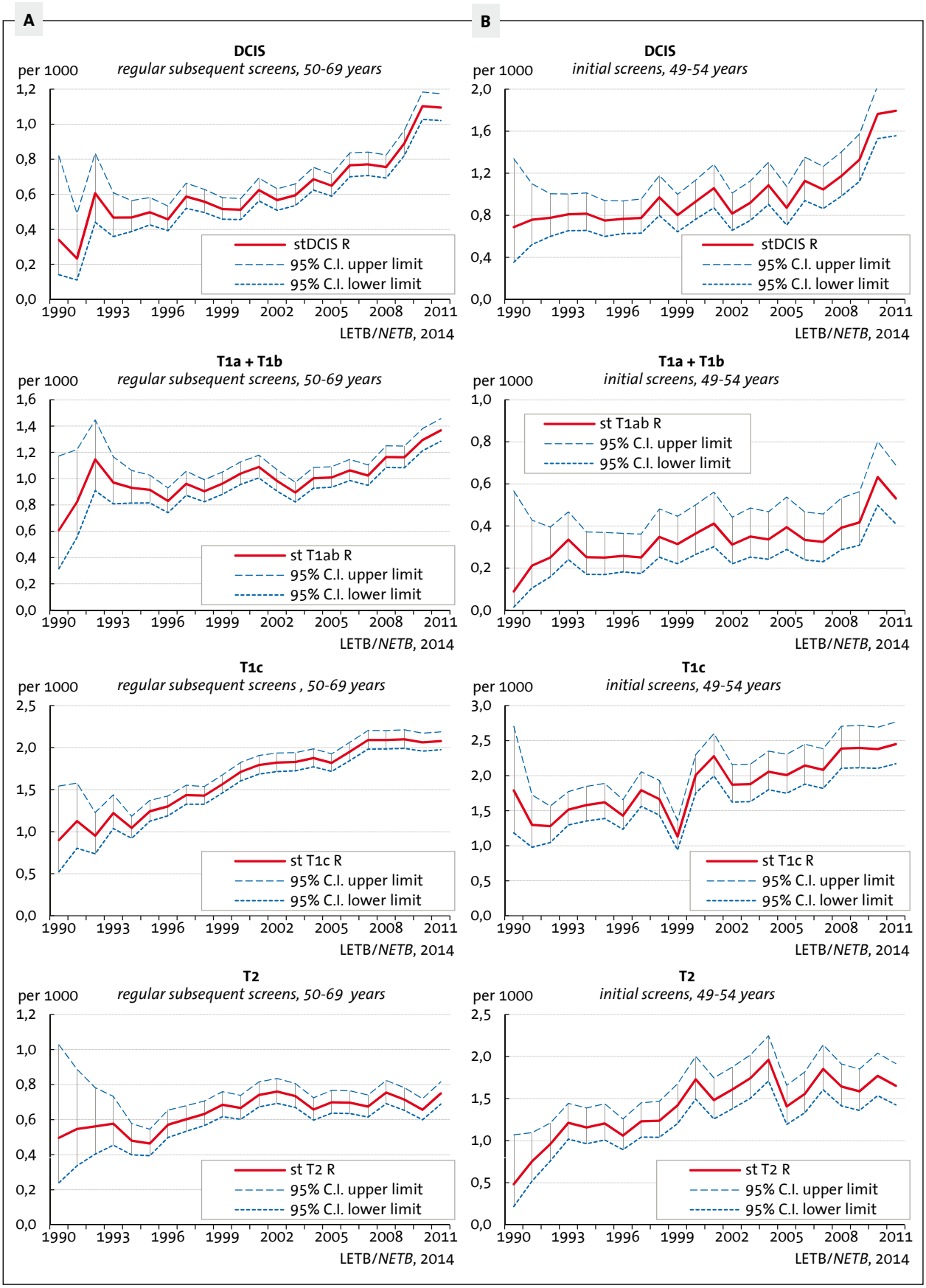


Figure 3.15 Age-adjusted cancer detection rates per 1000 with 95% confidence interval (95% C.I.) of **DCIS,** invasive **T1a+T1b** tumours (<= 10 mm), **T1c** tumours (11-20 mm) and **T2** tumours (>20 mm), for **A:** regular subsequent screens (50-69 years), and **B:** initial screens (49-54 years), 1990-2011

Percentage distribution in stages of screen-detected cancers

For the sake of completeness, details of the percentage distribution of tumour stages are also given here. However, this measure is less rigorous where there are substantial shifts in the percentages of individual fractions over time, as this creates the impression that a particular tumour stage is being detected either more frequently or less frequently. Rates, on the other hand, provide insight into genuine increases or decreases in the detection rate for a given tumour stage.

From 1990 to 2011, a total of almost 78,500 breast cancers were detected by the screening programme. The actual stage involved was known in 97% of these cases. Of these subjects, 15.4% had a DCIS. This percentage remained fairly constant until 2008 (13%-15%), but it then increased to 17.4% in 2009, 20.4% in 2010 and 19.5% in 2011 (Figure 3.16; see also Section 4 and Appendices II and IV). In initial screening tests, the level of DCIS was always 2-5 percentage points higher. In 2010 and 2011, one quarter of all screen-detected cancers involved a DCIS.

Seventy-nine percent of all breast cancers detected involve either a DCIS or a small invasive tumour 20 mm or less in diameter (T1). The remainder are mostly invasive T2 tumours (21-50 mm in diameter). T3 and T4 tumours are relatively rare, jointly accounting for around 1% of all screen-detected cancers.

Although it clearly involves smaller numbers of screen-detected cancers, the percentage of screen-detected cancers that have not been classified according to tumour size and tumour stage (TX) in the initial screening test is about twice as large as for subsequent screening tests (4-5% versus 2-3%). It is not clear what might be causing this. The subjects in question are mainly younger women, who have a relatively high chance of being given neo-adjuvant therapy. As a result, some of these tumours may disappear completely, which makes it difficult to determine the original size of the tumour.

Lymph node status associated with screen-detected cancers

Figure 3.17 shows a striking difference between the detection rates for lymph node positive and lymph node negative invasive breast cancers. The former group is characterised by a marked increase until 2000, followed by a period of stabilisation from 2001 onwards. The latter group exhibited a more gradual increase up to the end of 2011.

The late 1990s saw the introduction of the sentinel node procedure. It is suspected that this may have artificially boosted the number of lymph node positive breast cancers. The reason is that, unlike the earlier, conventional axillary lymph node dissection, only a few lymph nodes can be tested using the sentinel node procedure. Moreover, the use of increasingly sophisticated techniques means that these nodes can now be more extensively examined than ever before. As a result, there is now a greater chance that metastasising tumour cells will be found in the lymph

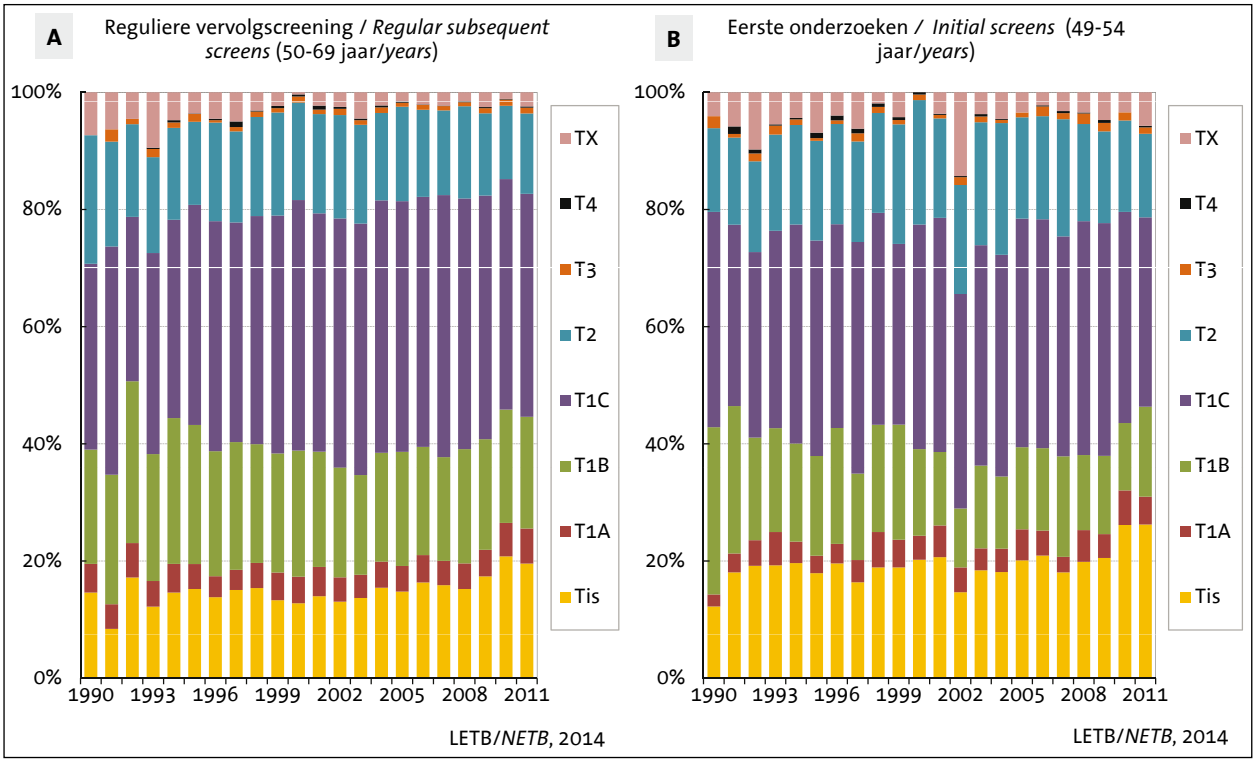


Figure 3.16 Per cent tumour size distribution of breast cancers detected at **A:** regular subsequent screens in women aged 50-69 years, and **B:** initial screens in women aged 49-54 years, 1990-2011

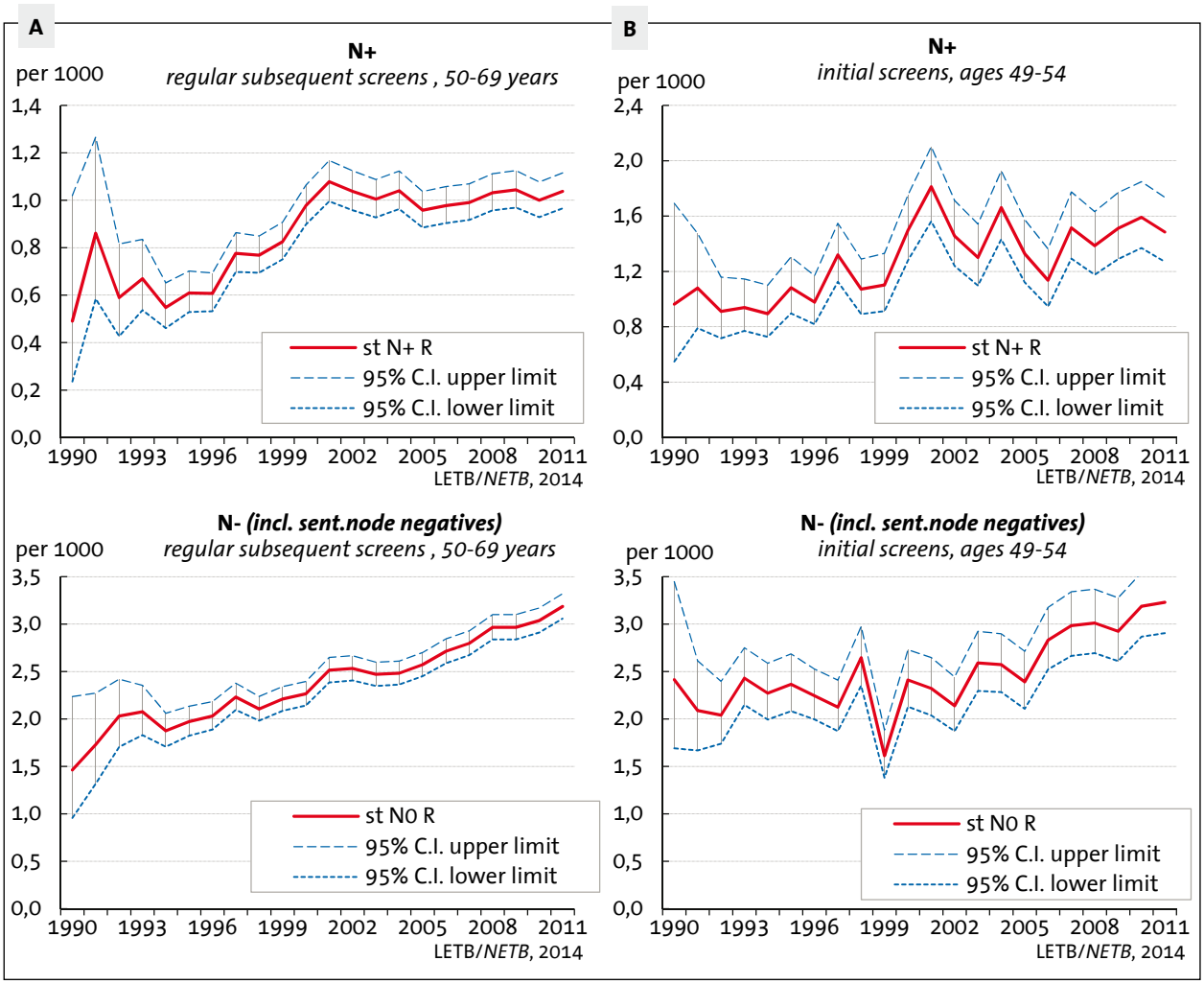


Figure 3.17 Age-adjusted lymph node positive (N+) and lymph node negative (N-) invasive breast cancer detection rates per 1000 women screened with 95% confidence interval (95% C.I.) for **A:** regular subsequent (50-69 years), and **B:** initial screens (49-54 years), 1990-2011

nodes. In 1996, the International Union Against Cancer (UICC) modified the international classification of mammary carcinomas, introducing new codes for microinvasion and isolated tumour cells. The post-2001 stabilisation of the detection rate for lymph node positive mammary carcinomas indicates that the increase seen in the preceding years can indeed be ascribed to the introduction of the sentinel node procedure.

A more difficult question to answer is why the detection rate for lymph node negative breast cancers is increasing. This may be due to the disproportionate improvement in the detection rate for small invasive tumours, which are predominantly lymph node negative. It may also be evidence of an increasing background incidence of breast cancer.

The authorities responsible for monitoring screening for breast cancer in the Netherlands did not take account of the sentinel node procedure until around the year 2000. At that point, the screening regions were asked to separately register any lymph node negative breast cancers that were detected purely by sentinel node procedures. Within a few years, it emerged that sentinel node procedures had been performed in more than half of all screen-detected cancers (Nsn, Figure 3.18).

Of the screen-detected cancers found in recent years, 75% were lymph node negative and about 25% were lymph node positive. At around 30%, there were slightly more lymph node positive carcinomas in the initial screening tests. Two thirds were lymph node negative (Figure 3.18, A). In four out of five lymph node negative breast cancers, lymph node status was determined solely on the basis of a sentinel node procedure.

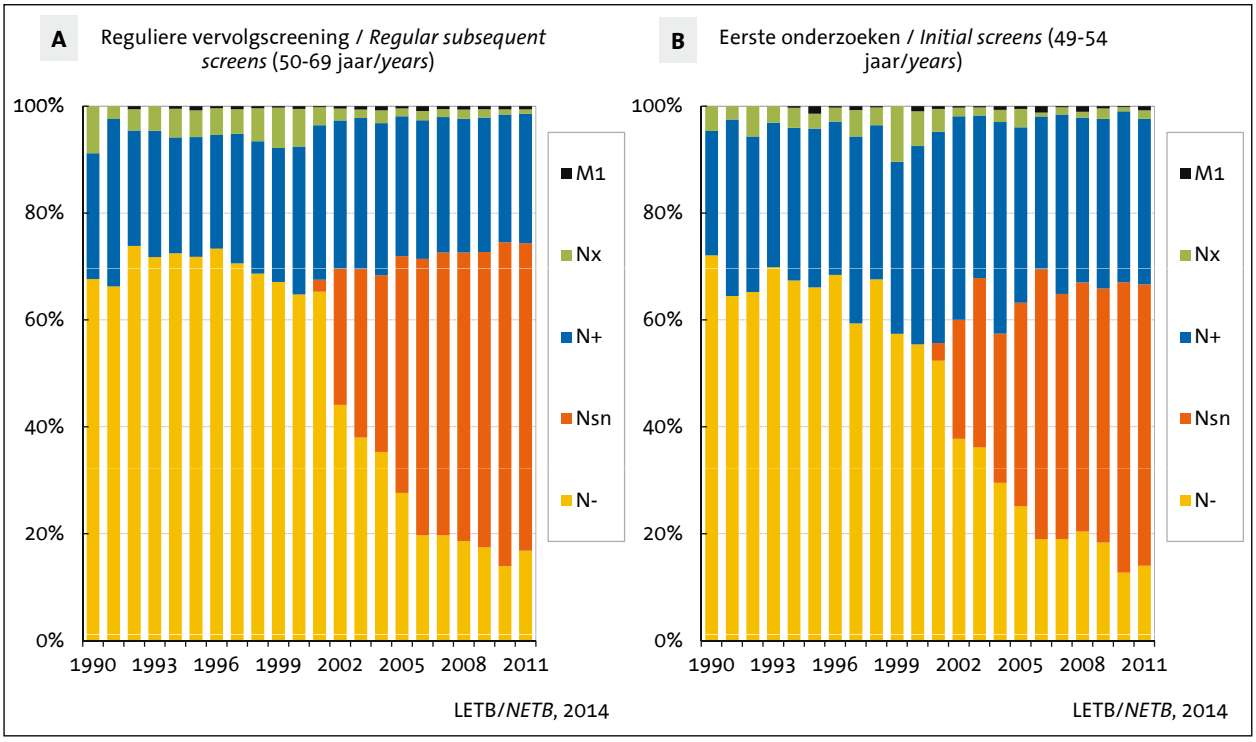


Figure 3.18 Per cent distribution of lymph node status (Nsn = negative sentinel node) and distant metastases of invasive screen-detected breast cancers at **A:** regular subsequent screens in women aged 50-69 years, and **B:** initial screens in women aged 49-54 years, 1990-2011

3.5 Regional (and sub-regional) differences in screening results

In the past, the NETB also regularly included regional screening results in its reports. However, organisational restructuring towards the end of the first decade of the 21st century made it impossible to reliably reconstruct the regions' screening results for protracted periods of time. Moreover, it seemed to be more useful to examine and compare screening results by reading unit (RU) rather than by region.

A start was made in 2013, with an analysis of results by RU for the period from 2002 to 2011. The first results were presented to a Focus Group that had been called in by the Executive Board. One preliminary finding was that the referral rate, false-positive rate, and positive predictive value of RUs' recommendations for referral per year often deviate significantly from the national average for the same year, while this is not usually the case with the detection rate. Additionally, the RUs' results over the years seem to fluctuate inconsistently, so it is difficult to assess an RU on the basis of a single year's data. When assessing an RU over a protracted period, however, account must again be taken of the organisational and personnel changes that have occurred over time. Similarly, reducing the number of RUs from 28 to 16 has, in some cases, resulted in major changes to the composition of the radiologist groups in the remaining RUs.

Given that the analyses in question have yet to be concluded, it would be inappropriate to include a more extensive presentation of results per RU at this point. The example shown below (Figure 3.19) indicates how the results per RU can be compared. This approach also facilitates coordination with findings presented in the quality reports issued by the National Expert and Training Centre for Breast Cancer Screening (LRCB).

The figure depicts age-adjusted referral and detection rates over a 10-year period (2002-2011), by RU, with 95% confidence intervals (vertical bars) for regular subsequent screening tests (Figure 3.19, A and C) and for initial screening tests (Figure 3.19, B and D). The red line shows the national average with a 95% confidence interval (red dotted line) for the same period. If the confidence interval around an RU value does not overlap with that of the national average, this would represent a significantly anomalous result. It can be concluded from the figure that RUs' referral rates often deviate significantly from the national average referral rate. Yet this only occurs sporadically with detection rates.

However, it is important to make some observations at this point. For instance, some RUs do not have comprehensive data for the entire 10-year period, as it was not always possible to disaggregate regional screening data by RU, and because some RUs had not been operating throughout the entire period. In addition, the geographical areas screened by specific

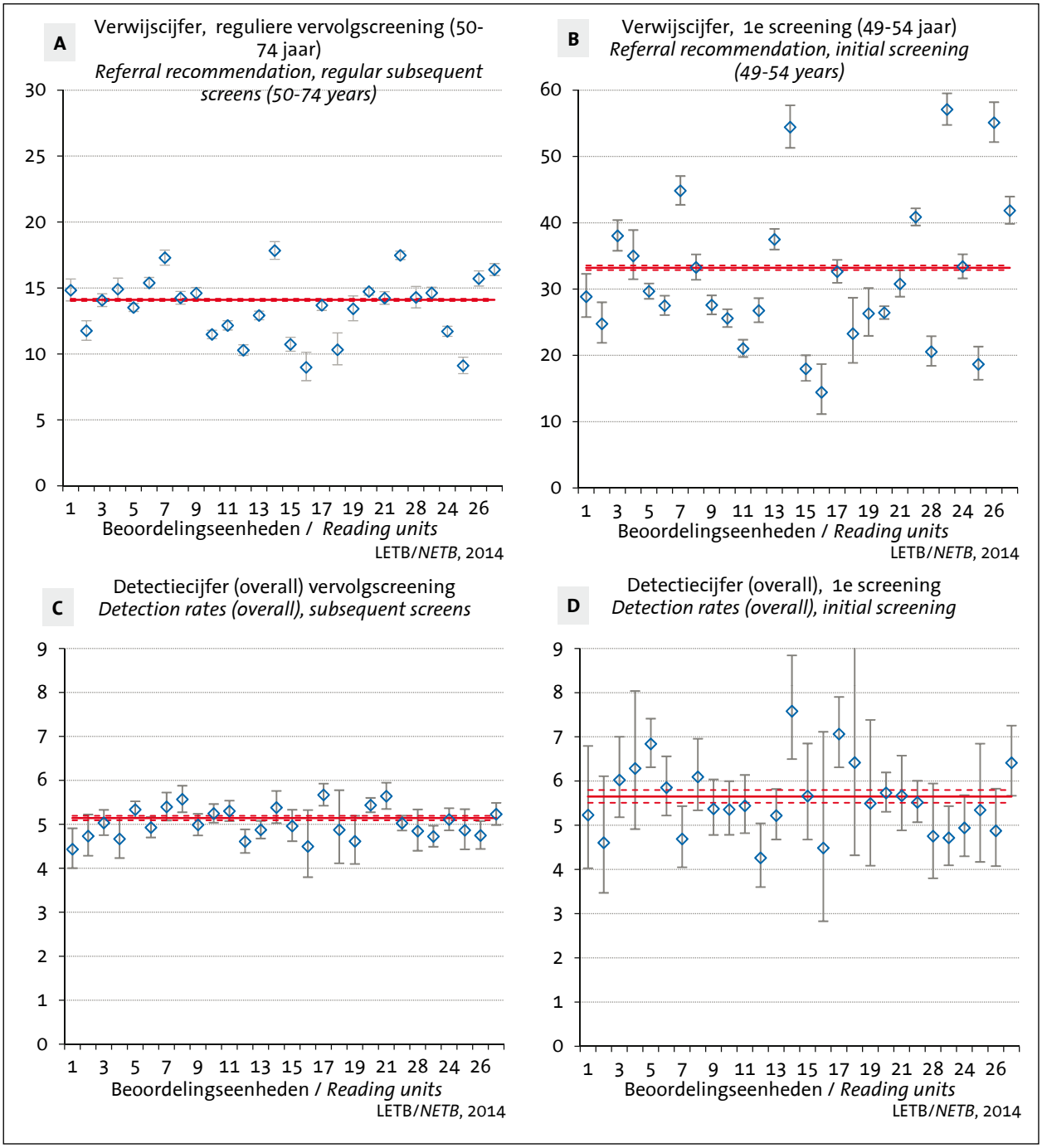


Figure 3.19 Age-adjusted referral recommendation **(A, B)** and (invasive + in-situ) breast cancer detection rate **(C, D)** per 1000 2002-2011 with 95% confidence interval by reading unit (n=28) for **A, C:** regular subsequent screens in women aged 50-74 years, and **B, D:** initial screens in women aged 49-54 years.
Red lines: national mean value 2002-2011 with confidence interval.

RUs have changed. Also, there have been personnel changes within the radiological staff. These factors need to be taken into account when interpreting the results. It may be more useful to examine the results over a shorter period of time, for example, four years (two to three screening rounds). The interval cancers should also be involved in the analysis, to obtain a reliable impression of the RUs' performance.

4

Transition to digital screening

In the period from 2004 to 2010, all of the screening organisations switched to digital mammography. This Chapter evaluates the performance of the screening programme in this period of transition – in terms of referral rate, detection rate, and positive predictive value (PPV) – by comparing the figures from the various reading units. A single reading unit assesses the tests from various screening units. Depending on the extent to which digitisation has been adopted, the screening tests submitted to a reading unit will either be purely analogue, a mixture of analogue and digital, or purely digital (once all of the units involved have completed the transition).
It is this consideration that underpins the comparison between reading units. The screening tests are classified into the following three groups: 1. Digital (DM), 2. Analogue from a reading unit that also assesses digital (SFM), 3. Analogue from a reading unit that still only assesses analogue (SFM only). The analyses are stratified by age (49-54 and 55-74) and screening round (initial screening test and regular subsequent screening test).

Table 4.1 Point estimates of recall recommendation (referral), detection rate and positive predictive value by study group (2004-2010) with 95% confidence interval (95% C.I.)

	DM-group			SFM-group			SFM-only-group		
Verwijscijfer / *Recall rate*									
	N	per 1000	95% C.I.	N	per 1000	95% C.I.	N	per 1000	95% C.I.
2004	332	3,39	(3.05; 3.77)	2.659	1,50	(1.45; 1.56)	8.208	1,28	(1.25; 1.31)
2005	742	2,23	(2.08; 2.40)	2.248	1,41	(1.35; 1.47)	8.656	1,35	(1.33; 1.38)
2006	852	2,13	(2.00; 2.28)	2.165	1,42	(1.36; 1.48)	9.902	1,56	(1.53; 1.59)
2007	1.397	2,24	(2.13; 2.36)	2.714	1,57	(1.51; 1.63)	10.806	1,75	(1.72; 1.79)
2008	1.740	2,00	(1.91; 2.09)	5.764	1,59	(1.55; 1.63)	7.841	1,88	(1.84; 1.92)
2009	7.319	2,02	(1.97; 2.07)	6.448	1,73	(1.69; 1.77)	2.270	1,83	(1.75; 1.90)
2010	16.981	1,99	(1.96; 2.02)	801	1,50	(1.40; 1.61)			
Detectiecijfer / *Detection rate*									
	N	per 1000	95% C.I.	N	per 1000	95% C.I.	N	per 1000	95% C.I.
2004	60	6,53	(5.07; 8.40)	877	4,98	(4.66; 5.32)	2.981	4,67	(4.51; 4.84)
2005	174	5,43	(4.68; 6.30)	706	4,46	(4.14; 4.80)	3.042	4,77	(4.61; 4.95)
2006	211	5,41	(4.73; 6.19)	686	4,47	(4.15; 4.82)	3.254	5,15	(4.98; 5.33)
2007	398	6,38	(5.78; 7.03)	876	5,05	(4.73; 5.39)	3.274	5,31	(5.13; 5.50)
2008	475	5,47	(5.00; 5.99)	1.965	5,42	(5.18; 5.66)	2.243	5,39	(5.17; 5.61)
2009	2.121	5,82	(5.57; 6.07)	2.077	5,54	(5.31; 5.78)	613	4,92	(4.54; 5.32)
2010	5.035	5,89	(5.73; 6.06)	195	3,67	(3.19; 4.22)			
Positief voorspellende waarde / *Positive predictive value*									
		%	(95% C.I.		%	(95% C.I.		%	(95% C.I.
2004		18%	(0.15; 0.23)		35%	(0.33; 0.37)		38%	(0.37; 0.39)
2005		26%	(0.23; 0.30)		34%	(0.32; 0.36)		36%	(0.35; 0.37)
2006		27%	(0.24; 0.30)		33%	(0.31; 0.35)		35%	(0.34; 0.36)
2007		30%	(0.28; 0.33)		34%	(0.32; 0.35)		32%	(0.31; 0.33)
2008		29%	(0.27; 0.32)		35%	(0.34; 0.37)		31%	(0.30; 0.33)
2009		31%	(0.30; 0.32)		35%	(0.34; 0.36)		29%	(0.28; 0.31)
2010		32%	(0.32; 0.33)		27%	(0.24; 0.30)		-	-

LETB/NETB, 2014

While there was an initial sharp rise in the digital group's referral rate, in subsequent years this tailed off to a level just above that of the analogue groups. The final referral rate was 20 per 1,000 screening tests. Throughout the period of the study, the detection rate in the digital group exceeded that of the analogue groups, reaching a level of 6 per 1,000 screening tests in 2010. The low initial value of the PPV was a direct result of a high referral rate and a stable detection rate. A falling referral rate boosted the PPV to 32% in 2010 (Table 4.1).

Significantly more cases of ductal carcinoma in situ (DCIS) were detected in the digital group, regardless of age or screening round. Significantly fewer T1c and T2+ tumours were detected in older women (Figure 4.1). The results varied from one region to another. This variation was not constant, nor did it diminish during the study period.
The initial rise in the referral rate had also been observed in previous studies (Bluekens et al, 2012; Nederend at al, 2012; Karssemeijer et al, 2009; Bluekens et al, 2010). The rapid fading of this effect is a direct result of the extra training on digital screening provided by the National Expert and Training Centre for Breast Cancer Screening (LRCB). Ultimately, the referral rate and detection rate obtained with digital screening were higher at the end of the study period, but – in international terms – the referral rate for a two-yearly screening programme is still quite low (Otten et al, 2005; Vigeland et al, 2008; Hambly et al, 2009; Vinnicombe et al, 2009; Del Turco et al, 2007; Domingo et al, 2011; Van Ongeval, 2007, Sala et al, 2009; Skaane & Skjennald, 2004). The LRCB's advice to reading units is that they should aim for a referral rate of 20 per 1,000 screening tests.
The detection and treatment of DCIS prevents (at least, in part) the detection and prevention of invasive tumours later in life. This is confirmed by the smaller number of T1c and T2+ tumours found in older women. The full effect of early detection may not yet have been achieved. On the other hand, there is a risk that some cases diagnosed as DCIS will have been wrongly detected and treated (or over-treated). The additional instances of DCIS detection might also result from the detection of biologically indolent tumours that would never have been discovered without screening (Gelder et al, 2011). All in all, digital screening performs at least as well as analogue screening, and it seems to offer the prospect of detecting significant numbers of smaller tumours.

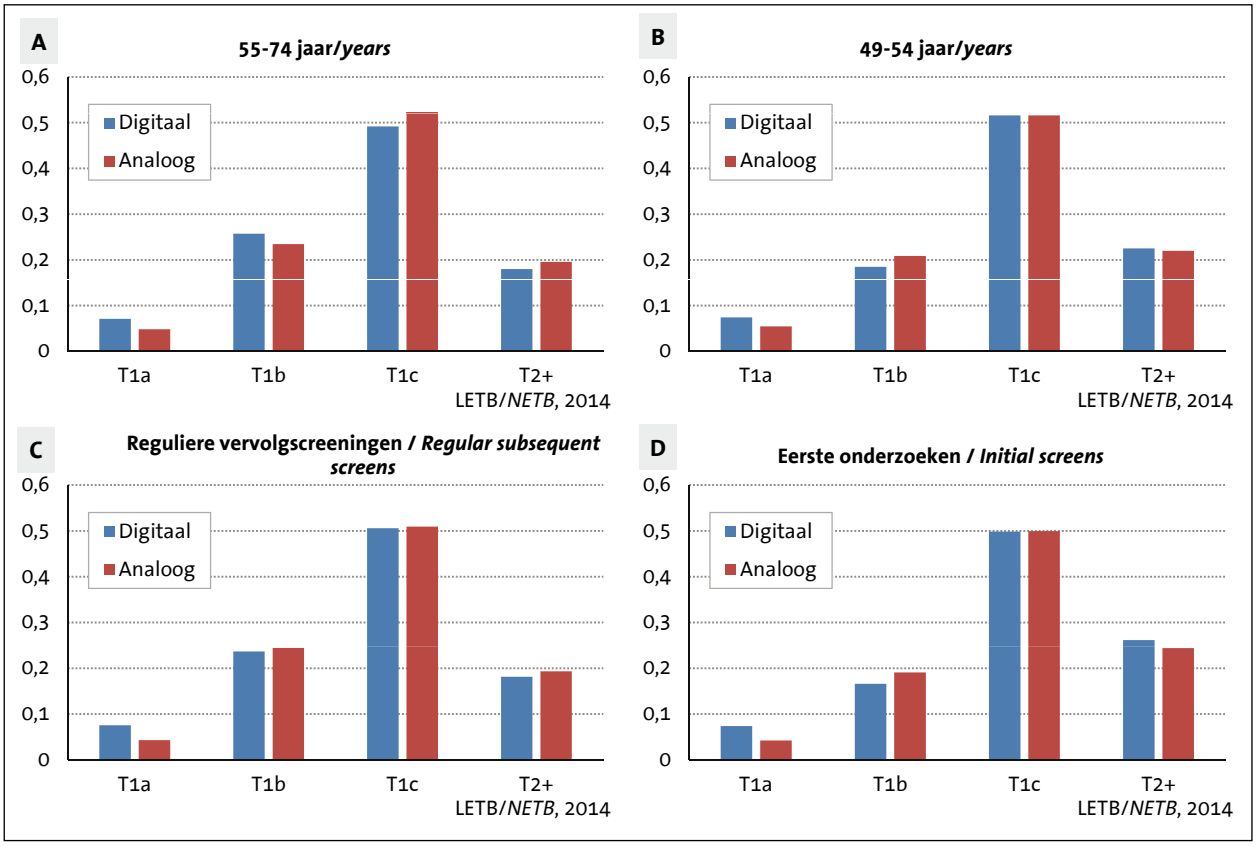


Figure 4.1 Tumour stage distribution (%) by age group **(A,B)** and by screening round **(C,D).** Tumour classes: T1a = tumour size 0-5 mm; T1b = 6-10 mm; T1c = 11-20 mm; T2+ >20 mm

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5

Interval cancers

In 2012, the first successful national link-up was established between a screening database (of women who were tested in 2004) and the Netherlands Cancer Registry's database, for the purpose of tracing interval cancers. In the last six months of 2012, once it had been established that the results of this link-up presented a realistic picture of the incidence of interval cancers, a link was established with a database containing the details of women screened from 2005 to 2009. In May 2013, the joint screening organisations submitted to the NETB databases containing the comprehensive screening results for 2004 to 2009. These databases contain details of all the interval cancers diagnosed within a minimum period of two years following the most recent screening test.

In the past, such link-ups were periodically established at regional level between the screening organisations and the corresponding regional Comprehensive Cancer Centre. However, details of the interval cancers for all of the regions (of which there were nine at that time) were limited to the 1990 to 1993 screening years. For the 1994 to 1999 screening period, details were available of interval cancers in eight of the nine regions. For the period from 2000 to 2001, this fell to seven regions, in 2002 there were just six, and in 2003 only five. From 2007 onwards, in anticipation of an upcoming nationwide link-up, more and more regions abandoned the idea of a link-up at regional level.

This means that, to date, it has generally been necessary to impose restrictions on the interpretation of interval cancer results, as these were not complete at national level. For instance, the possibility of selection bias had to be taken into account. Now that national data on interval cancers is complete, past results can be assessed for the presence of such bias, and there is reason to be confident that future link-ups will be implemented effectively.

This section starts by presenting the 'interval cancer results for 2004 to 2009'. This should be read as interval cancers diagnosed in women within a period of at least two years after a screening test carried out in the period from 2004 to 2009. The results for 2004 to 2009 will be compared to those from the preceding period (1990 to 2003) of the screening programme.

Discrepancies with data from Section 3 (Screening results)

As the data on interval cancers was not selected from the screening organisation's database until many (4 to 7) years later, some of the figures do not fully match the screening results presented in Section 3. The latter are based on the monitoring data which, at that time, were supplied from one year to eighteen months after the end of the reporting year in question. Until 2009, this data was obtained from individual regional databases.

In about 2009, the various regional screening databases were merged into a single national database. However, the regional screening organisations continue to administer their own records. This merger has led to a slight shift from initial invitations and initial screening tests to subsequent invitations and subsequent screening tests. This is because, in the past, regional screening organisations were not always aware whether or not a woman had previously been invited and/or screened in another region. Once the regional files had been merged, cases of this kind were detected and classified as subsequent invitations or subsequent screening tests. As a result, the national database contains about 5-7% fewer initial invitations and initial screening tests and 1-2%

more subsequent invitations or subsequent screening tests.
From 2009 onwards, the national database also supplied monitoring data, and there were only minimal differences in the number of screening tests compared to the 2013 interval cancer data. The differences in question result from the regular cleansing of databases. In addition, both the longer follow-up period after screening and the link-up itself have brought extra screen-detected cancers to light. On an annual basis, this amounts to about 3% more screen-detected cancers, or an increase in the detection rate of about 0.2 per 1,000 women screened.

Table 5.1 Crude screening results including interval cancers by type of screening examination, time period 2004-2009

A. Alle screeningsonderzoeken / *All screening examinations*

2004-2009	Borstkanker + *Breast cancer +*	Borstkanker - *Breast cancer -*	Gescreend *Screened*	PVW (%) *PPV (%)*	32,7%
Screen +	29.530	60.772	90.302	Verwijscijfer /1000 *Referral rate /1000*	16,7
Screen --	11.855	5.306.582	5.318.437	Fout-positief /1000 *False-positive /1000*	11,2
	41.385	5.367.354	5.408.739	Detectiecijfer /1000 *Detection rate /1000*	5,5
	Programma-sensitiviteit	*Programme specificity*		Intervalkankers /1000 *Interval cancers /1000*	2,2
LETB/*NETB*, 2014	71,4%	98,9%		Prevalentie *Prevalence*	7,7

B. Eerste screeningsonderzoeken / *Initial screens*

2004-2009	Borstkanker + *Breast cancer +*	Borstkanker - *Breast cancer -*	Gescreend *Screened*	PVW (%) *PPV (%)*	17,9%
Screen +	3.784	17.331	21.115	Verwijscijfer /1000 *Referral rate /1000*	32,9
Screen --	1.636	618.506	620.142	Fout-positief /1000 *False-positive /1000*	27,0
	5.420	635.837	641.257	Detectiecijfer /1000 *Detection rate /1000*	5,9
	Programma-sensitiviteit	*Programme specificity*		Intervalkankers /1000 *Interval cancers /1000*	2,6
LETB/*NETB*, 2014	69,8%	97,3%			

C. Reguliere vervolgscreeningen / *Regular subsequent screens (<2.5 years)*

2004-2009	Borstkanker + *Breast cancer +*	Borstkanker - *Breast cancer -*	Gescreend *Screened*	PVW (%) *PPV (%)*	37,3%
Screen +	23.737	39.838	63.575	Verwijscijfer /1000 *Referral rate /1000*	14,0
Screen --	9.620	4.465.779	4.475.399	Fout-positief /1000 *False-positive /1000*	8,8
	33.357	4.505.617	4.538.974	Detectiecijfer /1000 *Detection rate /1000*	5,2
	Programma-sensitiviteit	*Programme specificity*		Intervalkankers /1000 *Interval cancers /1000*	2,1
LETB/*NETB*, 2014	71,2%	99,1%			

D. Vervolgscreeningen >=2,5 jaar / Subsequent screens >=2.5 years

2004-2009	Borstkanker + *Breast cancer +*	Borstkanker - *Breast cancer -*	Gescreend *Screened*	PVW (%) *PPV (%)*	35,8%
Screen +	2.009	3.603	5.612	Verwijscijfer /1000 *Referral rate /1000*	24,6
Screen --	599	222.297	222.896	Fout-positief /1000 *False-positive /1000*	15,8
	2.608	225.900	228.508	Detectiecijfer /1000 *Detection rate /1000*	8,8
	Programma-sensitiviteit	*Programme specificity*		Intervalkankers /1000 *Interval cancers /1000*	2,6
LETB/*NETB*, 2014	77,0%	98,4%			

PVW: positief voorspellende waarde
PPV: positive predictive value

5.1 Interval cancers in screened individuals from 2004 to 2009

Crude interval cancer rate in screened individuals 2004-2009

In the period from 2004 to 2009, a total of 5.4 million screening tests were carried out, which led to 90,302 (16.7 per 1,000) recommendations for referral and, ultimately, to the detection of 29,530 breast cancers (5.5 per 1,000; Table 5.1 A). This resulted in a predictive value of 32.7% and a false-positive rate of 11.2 per 1,000 women screened.

In addition, within the first two years after screening 11,855 interval cancers (invasive and in situ) were diagnosed, which amounts to 2.2 per 1,000 women screened. Programme sensitivity was 71.4% and programme specificity 98.9%. In the initial screening tests, the interval cancer rate was 2.6 per 1,000 (Table 5.1, B). Hence, despite the higher detection rate of 5.9 per 1,000, this is higher than in regular subsequent screening, where the interval cancer rate was 2.1 per 1,000 at a detection rate of 5.2 per 1,000 (Table 5.1, C). In accordance with this, both programme sensitivity and programme specificity were lower for initial screening tests than for regular subsequent screening tests (69.8% versus 71.2% and 97.3% versus 99.1%).

Nearly 230,000 subsequent screening tests (4.2% of all tests) were performed after an interval period of 2.5 years or more (Table 5.1, D). While this group probably consists largely of women who skipped a round of screening, its exact composition – in terms of the length of the interval period involved – is unknown. As breast cancers can grow for extended periods of time, the chance of detecting them (8.8 detected breast cancers per 1,000) is greater than the national average. The same is true of the probability of diagnosing an interval cancer in the first two years after screening (2.6 per 1,000). Nevertheless, this group has the highest programme sensitivity, at 77.0%. This group distorts the programme sensitivity of the whole range of screening tests, but in a moderately favourable way. In the period from 2004 to 2009, however, the annual percentage of subsequent screening tests at an interval of 2.5 years remained stable at 4.0% to 4.5%.

Figure 5.1 shows the progression of the detection rate, the interval cancer rate (including in situ cancers)

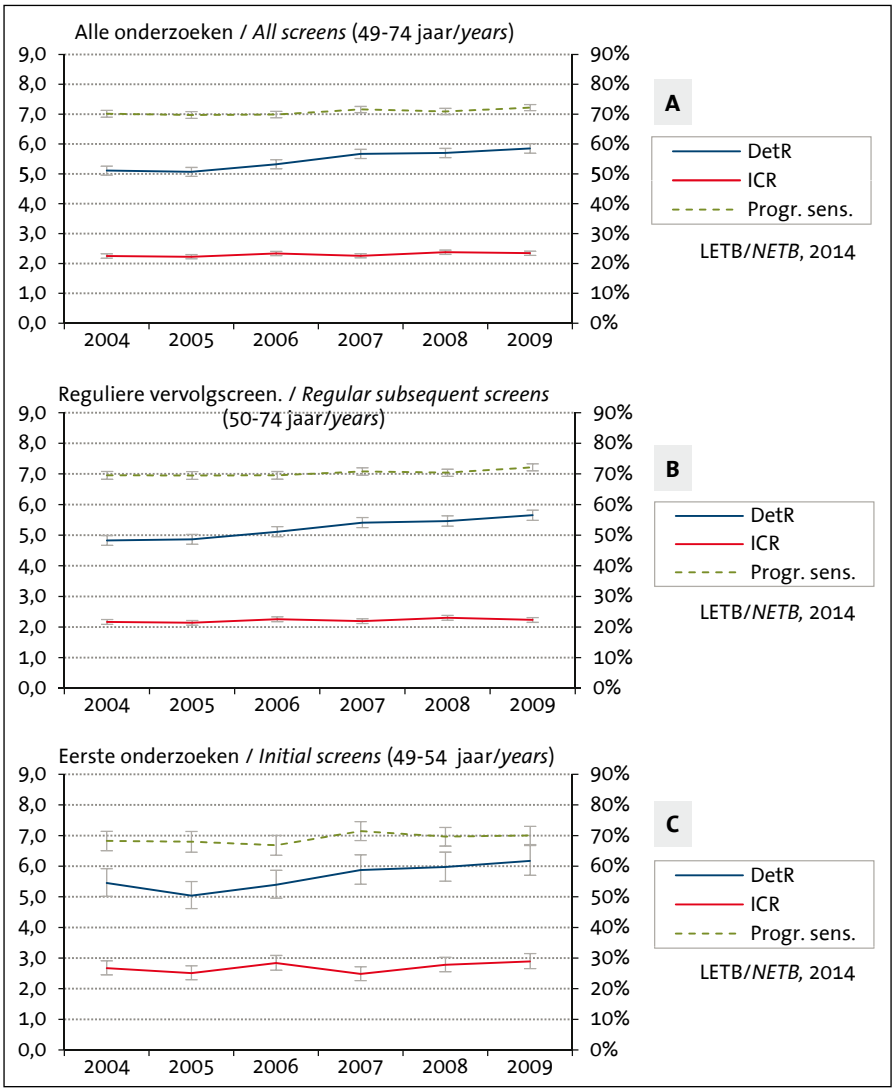

Figure 5.1
Age-adjusted detection rate per 1000 (DetR), interval cancer rate per 1000 (ICR) and programme sensitivity (%, Progr. sens.) with 95% confidence intervals for
A: all screens 2004-2009,
B: regular subsequent screens, and
C: initial screens

and programme sensitivity from 2004 to 2009, in the first two years after screening for all tests, for initial screening tests and for regular subsequent screening tests. These results have been adjusted for differences in the age distribution of women being screened over the years. As part of this adjustment, women aged 55 and above at the initial screening test were excluded from the analysis. This involves small numbers of older women per age group. These individuals have a disproportionately large effect on the standard adjustment for age, which can distort the results.

Figure 5.1 shows a clear increase in the detection rate. From 2007 onwards, it was higher (to a statistically significant extent) for all tests and regular subsequent screening tests than in 2004. The interval cancer rate, however, has remained the same for many years. The increasing detection of breast cancers by the screening programme is boosting programme sensitivity. In 2009, programme sensitivity for subsequent screening tests was significantly higher than it was in 2004 (Figure 5.1, B). However, this might result from the increased detection of in situ cancers (DCIS) by digital screening towards the end of the first decade of the 21st century (see also Sections 3 and 4). Up to the end of 2008, the use of digital screening tests was still limited, so any effect that this might have had on the incidence of interval cancers can be expected to be negligible.

A further study of interval cancers after analogue and digital screening will determine whether or not digital screening affected interval cancers from 2009 onwards. This study is still in progress. Nevertheless, a calculation of programme sensitivity based solely on invasive screen-detected cancers and interval cancers can give a useful indication in this regard. Figure 5.2 compares overall programme sensitivity (including in situ cancers) with sensitivity to invasive breast cancers alone. With regard to the latter, the increase in sensitivity from 2007 to 2009 was also higher. This suggests that digital screening did indeed have an effect on programme sensitivity.

Programme sensitivity was significantly higher in older women than in their younger counterparts, but age dependency is not always clearly evident between neighbouring age groups (Figure 5.3). For instance, sensitivity in women aged from 50 to 54 is generally lower than in 49-year-olds.

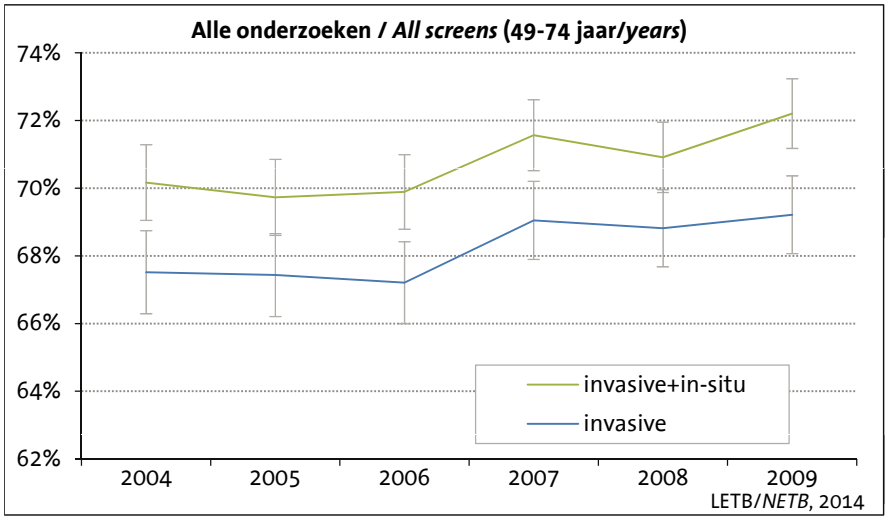

Figure 5.2
Age-adjusted overall (invasive and in-situ) and invasive programme sensitivity, all screens 2004-2009

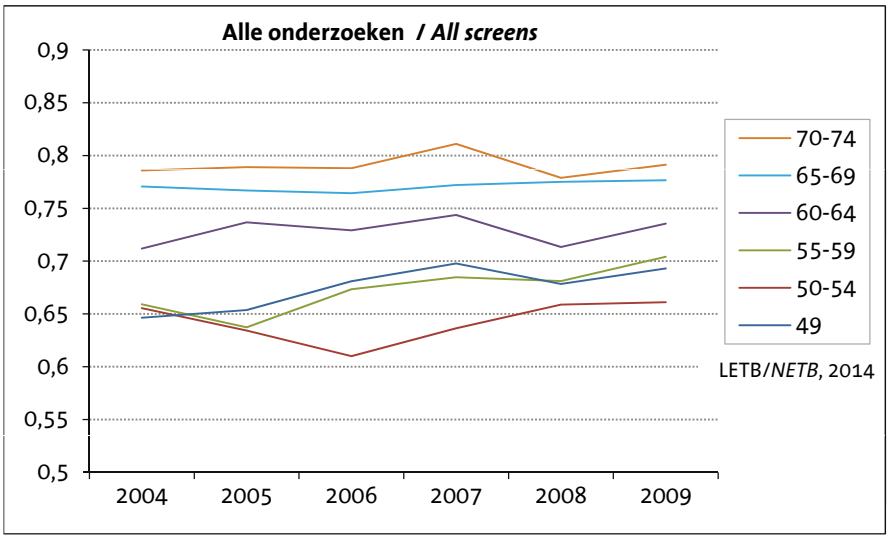

Figure 5.3
Age-specific programme sensitivity (first two years after screening), all screens 2004-2009

Calculation of the interval cancer rate

Interval cancer rates can be calculated in various ways. The standard approach is to use one of the following two methods:

a. *based on the number of women screened*
   This is the simplest method. Here, the number of interval cancers (numerator) in a given period after screening (e.g. two years) is divided by the number of women screened (denominator).

b. *based on the number of women screened with negative screening results*
   Here the numerator is the same as in method a., but the denominator only includes women with a negative screening result or referred women who are given a negative (benign) screening result after additional diagnostic procedures. Women with a true-positive result (screen-detected cancer) are excluded. As the denominator is slightly smaller than in a., the interval cancer rate is slightly higher.

The NETB prefers a more precise method of calculation, namely

c. *based on the number of woman-years at risk of developing an interval cancer*
   In this method of calculation, the numerator is identical to a. or b. The denominator, however, takes account of actual follow-up. Women are only counted during the period in which they are actually at risk of developing interval cancers. Women are no longer "at risk" if they already have cancer (screen-detected cancer or interval cancer), have died, have moved house such that no follow-up is possible (this currently mainly means moving abroad, whereas in the past it could also mean moving to a different region), or have been re-screened (which marks the start of a new period in which they are at risk of interval cancer).
   In this connection, the follow-up period is calculated per six-month period after screening. Each (screened) woman can contribute up to six months to a six-month period, if she did not have a screen-detected cancer (follow-up time = 0) and did not develop interval cancer in the six-month period in question, if she did not die, did not move house, and was not re-screened. If any of these situations apply then, for the woman in question, only the number of months up to the date of that event (diagnosis of interval cancer, death, moving house, next screening test) are counted. For those women who, on the basis of their age, will not receive a subsequent invitation, a period of up to 30 months can be taken into consideration, provided that no issues arise.

As Figure 5.4 shows, the lines of calculation methods a. and b. are virtually identical, so the difference between these two methods is negligible. In this example, the interval cancer rate based on screen-negative women (method b.) is up to 0.1 per 1,000 higher than that based on the number of women screened (method a). In the first year after screening, there is also only a slight difference between these methods and method c.

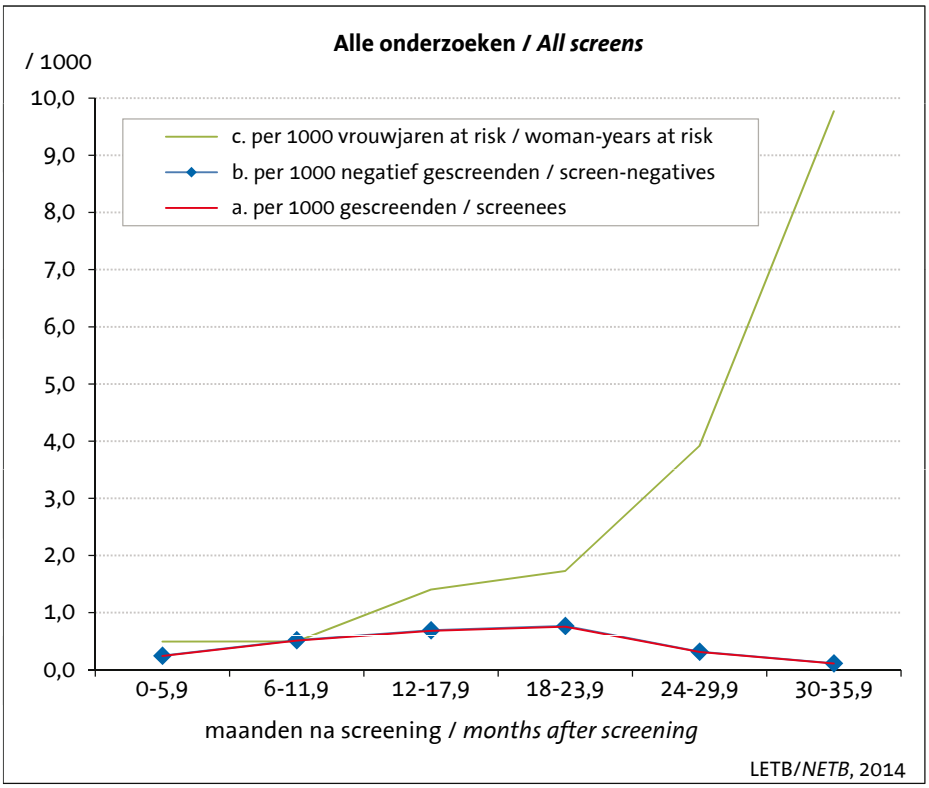

Figure 5.4
Interval cancer rates per 1000 by half year time period after screening and different calculation methods a-c, all screens 2004-2009

In the third and fourth six-month periods after screening, however, the interval cancer rate based on women-years of follow-up at-risk (method c.) starts to rise. This is because a number of women have already been re-screened, more women have moved or died, and more women have had a diagnosis of interval cancer. After two years, most women have been re-screened, so a relatively high number of interval cancers in this group in the third year after screening greatly reduces the denominator. Using the simplified calculation methods (a. and b.), however, the interval cancer rate seems to fall in the third year. This is because the denominator is still as large as it was at the start, while interval cancers are still only found in a small group of women.

Method c. provides the best picture of the development of interval cancers over time. The Dutch programme is the only major screening programme in the world where standard use can be made of this method. This is because the screening regions are linked to the computerised register of residents (municipal personal records database, GBA). The main drawback is that the results cannot be compared with those of other countries, precisely because most of them do not have programmes with this capability.

Programme sensitivity and mammographic sensitivity

Evaluations of population screening programmes generally involve a calculation of programme sensitivity. In order to calculate mammographic sensitivity (the actual sensitivity of the screening test), it would be necessary to know (immediately after the screening test) how many of those women who received no recommendation for referral nevertheless had a breast cancer which was detectable by mammography at that point in time. Theoretically, this could only be approximated by an objective systematic review of the screening mammograms. This is equally impossible.

It is often the case that breast cancers diagnosed at a later point in time (e.g. a year after screening) were not visible on the previous screening mammogram. Perhaps it was not until after the screening test that they reached a size at which they could be detected by mammography. At the time of screening, mammography was not sufficiently effective. Accordingly, these cancers cannot be classified as "missed at screening".

With regard to programme sensitivity, however, these breast cancers – which are still "invisible" at screening – are also counted as interval cancers. Accordingly, the denominator of the calculation (the sum of screen-detected cancers plus interval cancers) becomes larger, thereby reducing the calculated sensitivity percentage. In the medical literature, programme sensitivity in the first year or in the first 3-6 months after screening is often used as a proxy for mammographic sensitivity. From 2004 to 2009, in the Dutch programme, this averaged 87.9% (Table 5.2). Based on the systematic review of almost all interval cancers during independent quality inspections by reading units of the National Expert and Training Centre for Breast Cancer Screening (LRCB), no detectable abnormalities were found in about 52% of interval cancers. Excluding this from the 2-year sensitivity calculation gives a mammographic sensitivity for the Dutch situation of 84.0%.

At 98.9%, programme specificity is high compared to many programmes in other countries (Table 5.2). That means that nearly 99% of the women screened who did not have breast cancer received no recommendation for referral. In other words, they were quite properly not referred. Specificity is primarily dependent on the referral rate, i.e. the higher the referral rate the lower the specificity. Despite the sharp increase in referral rate seen in the Dutch breast cancer screening programme over the past few years, this is still relatively low in international terms. It also accounts for the high level of programme specificity.

Table 5.2 Programme sensitivity and specificity in the 1st, 2nd and the first two years after the screening examination

	Sensitiviteit / Sensitivity			Specificiteit / Specificity		
Onderzoeken 2004-2009 ***Screen examinations***	**1e jaar** ***1st year***	**2e jaar** ***2nd year***	**1e+2e** ***1st+2nd***	**1e jaar** ***1st year***	**2e jaar** ***2nd year***	**1e+2e** ***1st+2nd***
- eerste - *initial*	85,6%	79,1%	69,8%	97,28%	97,28%	97,27%
- reguliere vervolgscr. - *regular subsequent*	87,9%	78,9%	71,2%	99,12%	99,12%	99,12%
- vervolgscreening >=2,5 jaar - *subsequent screens >=2.5 years*	91,3%	83,1%	77,0%	98,41%	98,41%	98,41%
Alle onderzoeken *All screens*	87,9%	79,2%	71,4%	98,87%	98,87%	98,87%

LETB/*NETB,* 2014

Tumour stage of interval cancers

Half of all the interval cancers that are diagnosed in the first two years after screening are either in situ carcinomas (Tis) or small invasive tumours 2 cm or less in diameter (T1a, T1b and T1c) (Figure 5.5). This is a significantly smaller proportion than in screen-detected cancers (around 75%). Almost 40% are T2 tumours (21-50 mm in diameter). DCIS accounts for approximately 5%, although it peaked briefly at 7% in 2008.

Also, about half of all interval cancers are lymph node negative (Figure 5.6). In four out of five cases, lymph node negativity was established on the basis of a sentinel node procedure alone (Nsn). In 45% of interval cancers, metastases are found in the lymph nodes, while 4% to 5% of cases have distant metastases. In terms of prognosis, the tumour characteristics of interval cancers are clearly less favourable than those of screen-detected cancers.

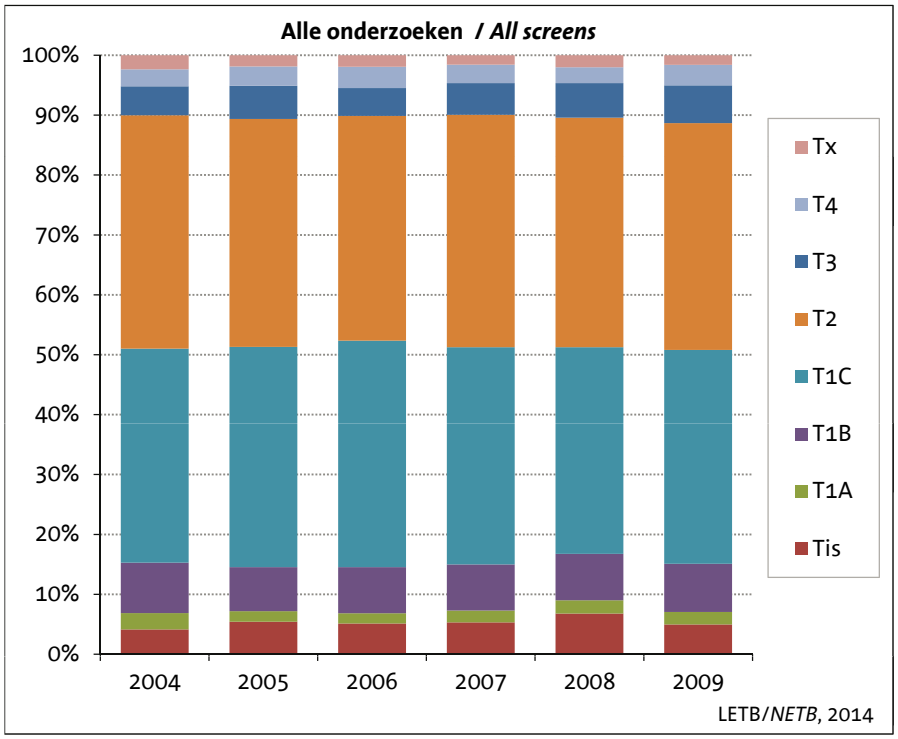

Figure 5.5
Tumour size distribution (%) of interval cancers (first two years after screening), all screens 2004-2009

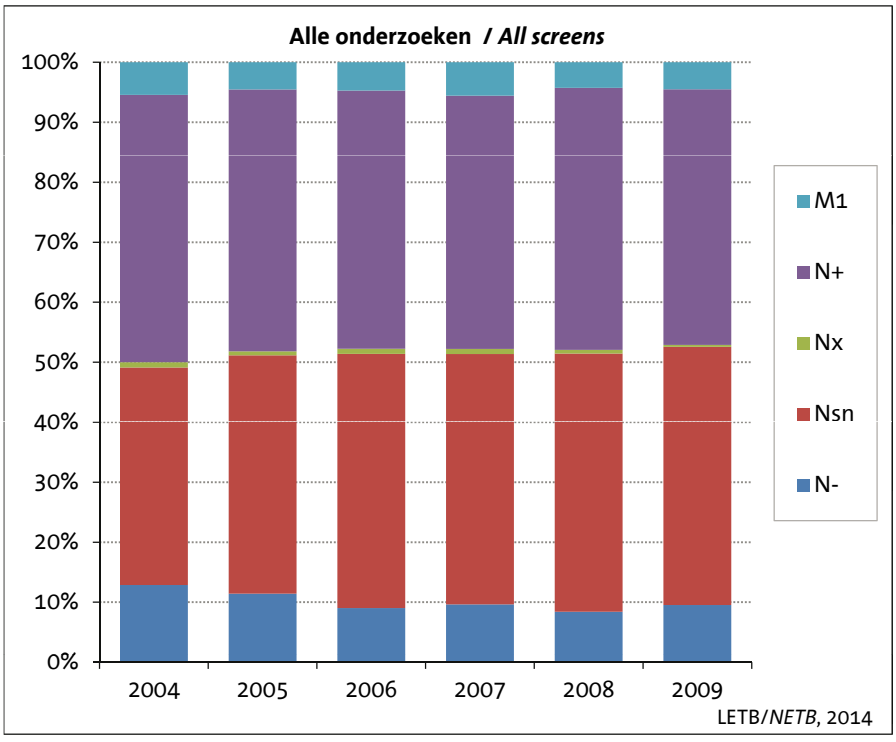

Figure 5.6
Lymph node status distribution (%) of invasive interval cancers (first two years after screening), all screens 2004-2009

Figure 5.7 shows the interval cancer rates per 1,000 for various tumour stages. While these are relatively stable, there has been an increase in lymph node negative carcinomas (T1 N- and T2+ N-). The in situ interval cancer rate is slightly higher after initial screening tests. In 2008, it even exceeded 0.2 per 1,000 (Figure 5.7, C). The higher figures can be accounted for by the fact that the subjects in question are young women around the age of 50, who generally have higher DCIS detection rates. However, there is some evidence of an increase in the number of in situ interval cancers. This points to a percentage of tumours that were found by chance during mammography, possibly partly in connection with opportunistic screening. After all, in situ cancers tend not to cause clinical symptoms.

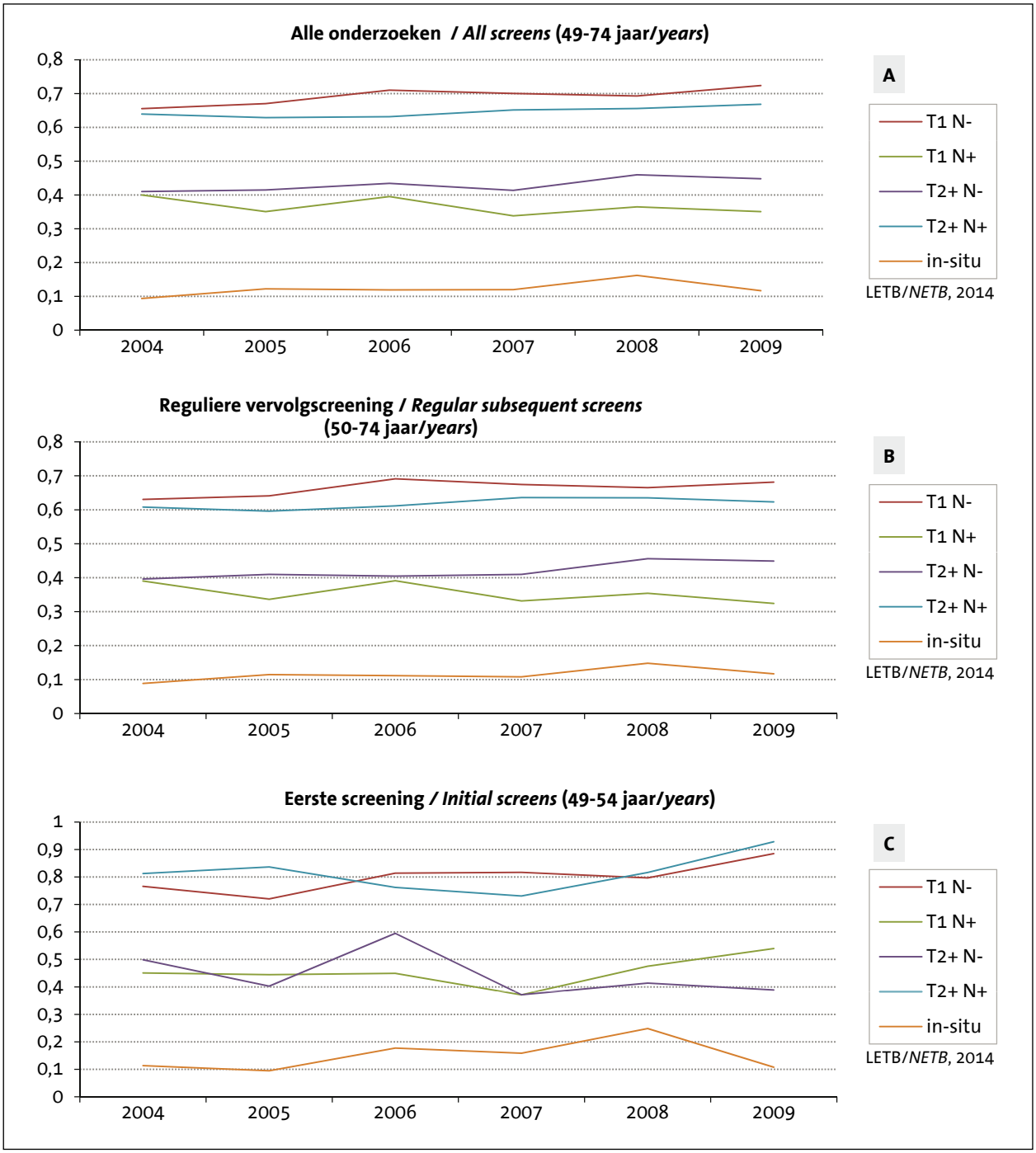

Figure 5.7 Age-adjusted interval cancer rates per 1000 by tumour stage for
A: all screens 2004-2009,
B: regular subsequent screens, and
C: initial screens

5.2 Interval cancers in screened individuals from 1990 to 2009

After 1993, the available national data on interval cancers was not complete, as at least one of the nine regions was unable to supply it. The assessment of the progression of interval cancer rates (Figure 5.8, A), and programme sensitivity (Figure 5.8, B) from 1990 onwards is limited to individuals in the 50-69 age group. It has been adjusted for possible differences in age distribution. As they are based on less complete national data, the results for the period from 2000 to 2003 are presented separately in the figures, by means of a dotted line (Appendix V).

For the first 10 years, Figures 5.8 A and B show an increase in the interval cancer rate and a decrease in programme sensitivity. However, this is partly due to a probable underreporting of interval cancers in the early 1990s, before link-ups had been established at regional level. There was almost certainly some under-reporting in 2003. In that year, various regions supplied data on interval cancers relatively soon after the end of the two-year interval, before full details on interval cancer were known.

Given the uncertainty about the reliability of interval cancer rates in the first decade of the screening programme, it would be premature to conclude that the pre-2004 increase resulted from the supposed increase in the background incidence of breast cancer. This hypothesis is more likely for the period from 2004 to 2009. At that time, despite a continuous rise in breast cancer detection rates, there was no decline in interval cancer rates. During this period, programme sensitivity (averaged for all screens) remained constant. That could also mean that there is a greater incidence of breast cancer. That in turn would mean that the screening programme's higher breast cancer detection rate cannot be solely attributed to improved performance, in terms of a modified referral pattern. Instead, it would also be partly due to a greater "supply" of breast cancers.

Workers in England (Dibden et al, 2013) reported a decline in the number of interval cancers following the standard use of four exposures (two-view). The veracity of this claim will be tested during the upcoming assessment period in particular, even though the proportion of complete tests in most regions also started to rise in this period, following the launch of digitisation.

References

Dibden A, Offman J, Parmar D, Jenkins J, Slater J, Binysh K et al. Reduction in interval cancer rates following the introduction of two-view mammography in the UK breast screening programme. Br J Cancer 2013; 1-5 | doi: 10.1038/bjc.2013.778.

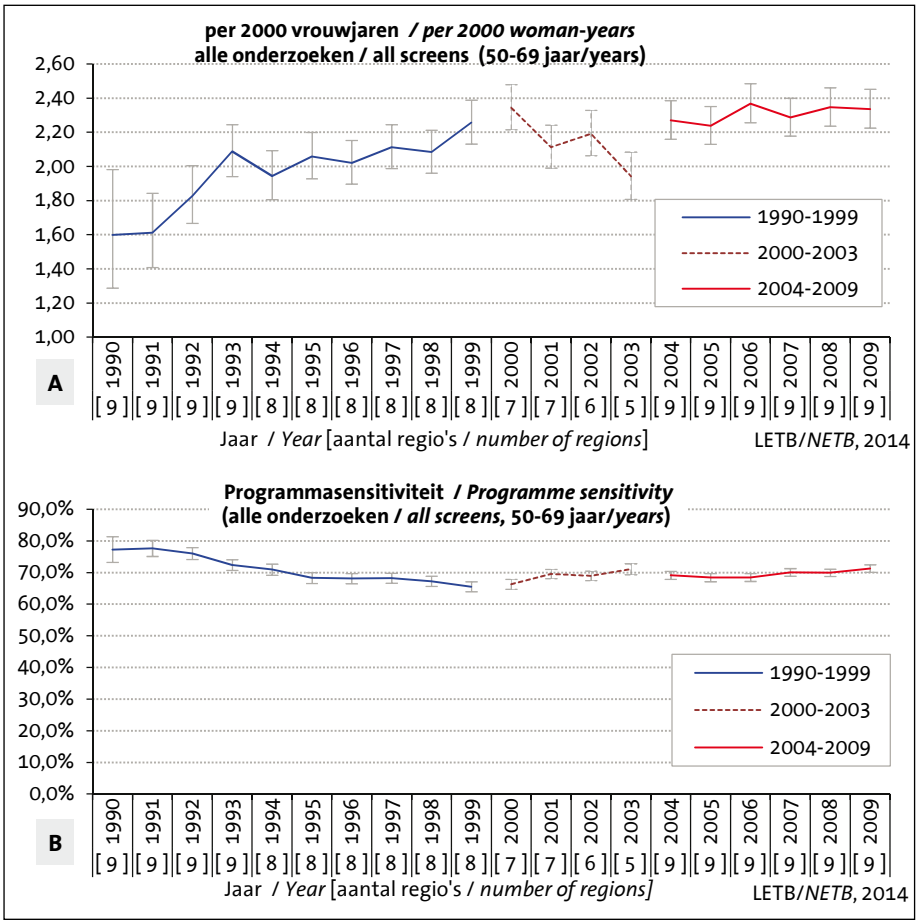

Figure 5.8
Age-adjusted
A: interval cancer rate (invasive + in-situ) per 2000 woman-years at risk, and
B: programme sensitivity, all screens 1990-2009, women aged 50-69 years

6

Breast cancer mortality

6.1 Trends in breast cancer mortality in the Netherlands

Figure 6.1 shows the trend in breast cancer mortality among various age groups in the Netherlands, from 1969 to 2012. To better understand the trends, the age-adjusted mortality rate per 100,000 women (ESR), derived on the basis of the European Standard Population, is plotted on a logarithmic scale. In the course of more than 40 years, breast cancer mortality in all age groups has declined, but the progression of this decline is not identical for all ages. For instance, in the first two decades (1970-1980) among women aged 50 and above, breast cancer mortality increased slightly or remained constant. The decline did not take effect until after 1990. In women below the age of 50, breast cancer mortality was already in decline from 1970 to 1990. It subsequently fell even more strongly.

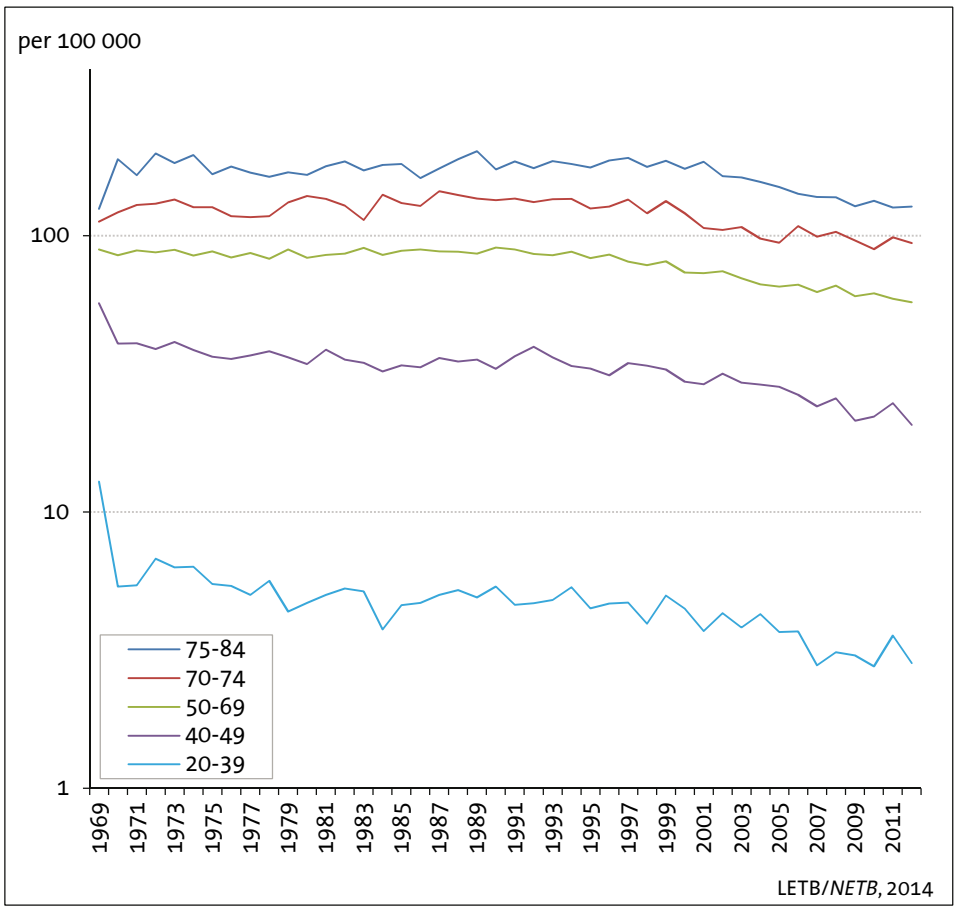

Figure 6.1
Age-adjusted breast cancer mortality rates per 100,000 (ESR) 1969-2012 (logarithmic scale) (source: Statistics Netherlands)

The difference between younger and older women, in terms of the progression of the decline in breast cancer mortality, suggests that there are a variety of causes. The introduction of adjuvant systemic treatment for breast cancer (in premenopausal women) in the 1970s, contributed to a reduction in breast cancer mortality. The same may be true of the hormone therapy that became widely used in the 1980s, in the treatment of postmenopausal women with breast cancer. Under-treatment of the oldest groups of women may account for the increase in breast cancer mortality among these individuals at that time. During the same period, mortality among women aged 50-69 remained virtually unchanged. Unfortunately, no national data on breast cancer incidence is available for the period prior to 1990. However, data from the former SOOZ (Cooperative Body of Hospitals for Oncology) cancer registry in Eindhoven indicate that breast cancer incidence has been rising since the early 1970s.

Figures 6.2, A and 6.2, B show the percentage change in breast cancer mortality in specific periods (four and two periods respectively) between 1970 and 2011, for the various age groups. Three-year averages of breast cancer mortality are used (1969-1971 for 1970, 1979 to 1981 for 1980, 1989 to 1991 for 1990, 1999 to 2001 for 2000, and 2010 to 2012 for 2011) to smooth out the effects of random fluctuations. The bars of solid colour indicate that the change in breast cancer mortality in the corresponding period is statistically significant. With the outline-only bars this is not the case.

In women aged 40-49, breast cancer mortality in all four periods fell between 1970 and 2011, albeit that there was no significant decline between 1980 and 1990 (Figure 6.2, A). In all other age groups, there was a non-significant increase in mortality for at least one ten-year period prior to 1990.

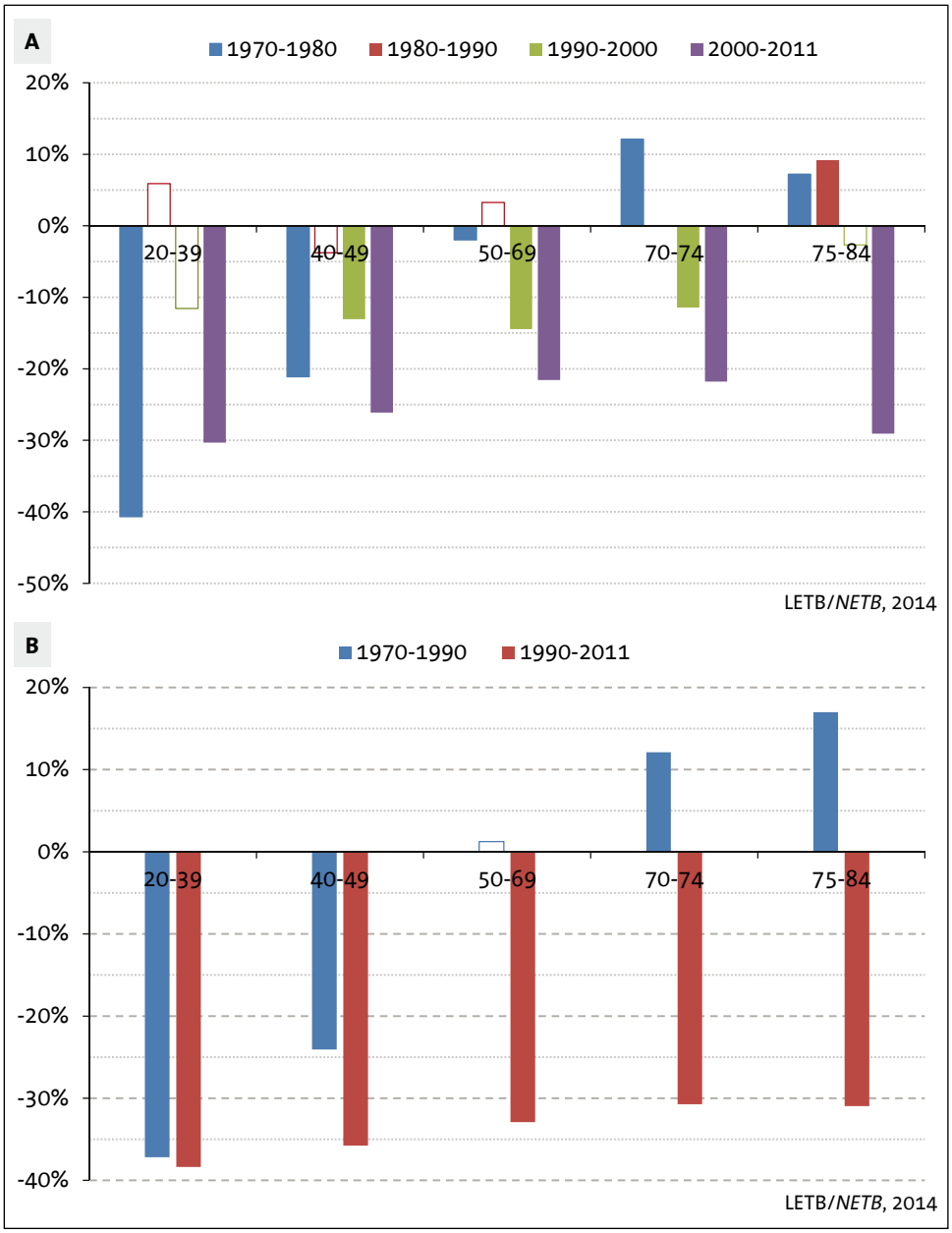

Figure 6.2
Per cent change of the age-specific breast cancer mortality rate (per 100,000, ESR) during **A:** four periods (1970-1980, 1980-1990, 1990-2000, 2000-2011), and **B:** two time periods (1970-1990, 1990-2011); blank bars: change non-significant

When comparing the situations before and after 1990, it is noticeable that, in women below the age of 50, there was already a substantial and significant reduction in breast cancer mortality prior to 1990. Yet in the same period, mortality was still increasing among women aged 50 and above (Figure 6.2, B). In the 21 years since 1990, breast cancer mortality among older women has also fallen, by about 30%. This is slightly lower than the recent 35-38% decline in younger women, but compared to the previous twenty year period this change in breast cancer mortality is much less pronounced than that seen in women aged 50-84. In the youngest group, the decline in breast cancer mortality has hardly changed since the period from 1970 to 1990. In the 40-49 age group, this has fallen by a further 13% since 1990.

However, it is difficult to say whether the decline in mortality that started back in 1970 can be solely attributed to the arrival of adjuvant chemotherapy. It may, in part, have been due to the increasing use of mammography and ultrasound in symptomatic patients during that period. At that time, this was combined with a steadily growing awareness that a real problem was developing with regard to breast cancer. This involved the pronouncements of oncologists and surgeons, who were inclined to refer patients with any kind of palpable abnormality (regardless of its nature) to a hospital, rather than awaiting developments. This led to trial mammography screening programmes in Utrecht and Nijmegen in 1975 and, ultimately, from 1990 onwards, to the national breast cancer screening programme.

Critics of this programme often focus solely on the period during which the screening programme has been in existence. They view the greater percentage reduction in breast cancer mortality in young women as "proof" that mammographic screening contributes nothing to the decline in breast cancer mortality. However, this does not explain the sudden change in the trend of breast cancer mortality in women aged 50 and above that coincided with the introduction of the screening programme. Previous studies that used sophisticated trend analyses, right down to local authority level, indicate that the change in the progression of breast cancer mortality in postmenopausal women is indeed associated with the introduction of the mammography screening programme (Otto et al, 2003; Otten et al, 2008). For instance, breast cancer mortality among women aged 55-74 switched from an annual increase of 0.3% to an annual decrease of 1.7%. The timing of this trend reversal's tipping point coincided exactly with the moment when the screening programme was introduced in the local authority in question (Otto et al, 2003).

6.2 Recent Dutch studies on breast cancer mortality

In association with the National Evaluation Team for Breast Cancer Screening in the Netherlands, a number of detailed studies have recently been carried out to further determine the contribution made by screening for breast cancer to the reduction in breast cancer mortality. This information is briefly recapitulated below.

6.2.1 Case control studies

Limburg

A case-control study is used to compare the participation rates of women who had died of breast cancer to those of women who had been invited to attend for screening. The difference in participation between these two groups indicates the extent to which screening cuts the mortality rate.

In 2010, a case-control study was conducted in the province of Limburg. This study used data on every woman who, from 1989 to 2006, had been invited to participate in screening in this province (Paap et al, 2010). A group of 118 women, who had died of breast cancer in 2004 or 2005, was selected from this population of invited individuals. Each of these cases was matched to a control subject (or referent) who had been born in the same year as the case in question, who lived in the same area, who was free of breast cancer at the time the case was diagnosed, and who was still alive at the time of the case's death. An analysis of the screening history of these case-control sets showed a reduction in mortality of 70% in screened versus unscreened women (OR = 0.30, 95% CI 0.14-0.63).

Case-control studies suffer from the potential drawback that estimates of the effect in question could be affected by self-selection bias. In terms of their risk of dying from breast cancer, the group of women who do take part in screening programmes may not be entirely comparable to those who decide not to participate. For instance, women participating in screening programmes may lead healthier lives. This alone could mean that they are at lower risk of dying from breast cancer. Using the incidence-based mortality method, we have calculated a correction factor to adjust for this. The correction factor was derived from a group of unscreened women and a group of uninvited women. We selected both groups from the Dutch screening programme's lengthy implementation period (1990-1995), during which time some of these women did not receive an invitation. The extent of any self-selection can be determined by comparing the breast cancer mortality in each of these groups (unscreened versus uninvited). If the number of deaths in the as yet uninvited group was much

Table 6.1 Odds ratio corrected for self-selection bias

Formule van Duffy ***Formula Duffy***	$p\,\Psi\,D_r\,/\,(1-(1-p)D_r)$
Met Ψ = ongecorrigeerde odds ratio (95% CI) *non-adjusted odds ratio (95% CI)*	0.30 (0.14-0.63)
p = deelnamepercentage in Limburg *participation rate in Limburg*	0.82
D_r = correctiefactor voor zelfselectie in Limburg (95% CI) *Factor for correcting self-selection (95% CI)*	0.84 (0.58-1.21)
Gecorrigeerde OR (95% CI)	0.82 x 0.30 x 0.84 / (1-0.18 x 0.84) 0.24 (0.10-0.58)

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lower than that in the group of non-participants, for example, this would suggest that the women who deliberately chose not to take part in the screening programme did indeed have a higher risk of breast cancer mortality than those who choose to participate.

The outcome of the case-control study can be adjusted for self-selection using the formula developed by Duffy (Table 6.1) (Duffy et al, 2002). After adjustment for self-selection bias, the decline in mortality in the province of Limburg was 76% (OR = 0.24, 95% CI 0.24 to 0.58).

Correction factors were calculated for a total of five screening regions in the Netherlands, which all differed from one another (Table 6.2) (Paap et al, 2011). This shows that it is necessary to determine separate correction factors for self-selection for each individual country or region. In three regions (including Limburg), correcting for self-selection did not change the outcome of the case-control study. The effect in the other two regions was to enhance the effect of screening, i.e., to yield a slightly greater reduction in mortality. However, in the light of all the regional correction factors, the influence of self-selection in the Netherlands is very limited.

The South-west Netherlands region

The main goal of breast cancer screening is to reduce breast cancer mortality. Since 1997, there has been a significant decrease in breast cancer mortality, but the effect of screening on breast cancer mortality cannot be determined using trend analysis. Accordingly, a case-control study was carried out that also took account of an individual's screening history, treatment and cause of death. This study compared the screening history of a group of women who died of breast cancer (cases) with that of a control group of women who did not succumb to this disease (control subjects).

This study used data on every woman (N=375,086) who had been invited to participate in a screening programme in the South-west Netherlands region from 1990 to 2003 (Otto et al, 2012). A total of 755 breast cancer deaths (cases) were included (women who died of breast cancer from 1995 to 2003). For each case, five individuals were selected from the pool of suitable control subjects, based on their vital status (still alive at the time of the case's death), who had been free of breast cancer prior to the date on which the case was diagnosed with breast cancer. In addition, at the time of the last invitation, the control subjects must have been the same age as the case. They must also have the same year of birth as the case, the same year of initial invitation, and the same number of invitations. This gave a total of 3,739 control subjects.

With regard to the cases, 29.8% had been diagnosed as a result of a screening test, while 34.3% had an interval cancer. The remaining 35.9% of the diagnoses involved women who had never participated in the screening programme. In the group of control subjects (i.e. who had not died of breast cancer, but who had had the same screening opportunities) 18.1% had never participated in the screening programme.

Table 6.2 Correction factors for self-selection bias for five screening regions in the Netherlands

Regio ***Region***	**Borstkankersterfgevallen / persoonsjaren** ***Breast cancer deaths / person years***		**Rate ratio (95% CI) ***
	Niet-gescreend / *Not-screened*	**Niet-uitgenodigd / *Not invited***	
BBNN	36 / 73 412	702 / 917 668	0.64 (0.46 - 0.90)
SKP IKA	117 / 179 463	798 / 937 692	0.77 (0.63 - 0.93)
SKsL	39 / 63 341	189 / 282 716	0.92 (0.65 - 1.30)
SBBZWN	54 / 68 867	726 / 1 003 423	1.08 (0.82 - 1.43)
SVOKON	99 / 103 358	216 / 244 204	1.08 (0.85 - 1.37)

* Getallen staan niet voor reductie in borstkankersterfterisico als in Tabellen 6.1 en 6.3
Does not mean reduction in breast cancer mortality risk as in Tables 6.1 and and 6.3

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Table 6.3 Odds-ratio for risk of breast cancer death, adjusted for age at first invitation

	Cases *Cases* N	Controles *Controls* N	OR (95% CI)	OR (95% CI) gecorrigeerd* *adjusted**
Niet deelgenomen *Non-participants*	278 (37%)	846 (23%)		
Wel deelgenomen *Participants*	477 (63%)	2,893 (77%)	0.45 (0.37-0.54)	0.51 (0.40-0.66)

* Gecorrigeerd voor zelf-selectie bias / **Adjusted fors self-selection bias* LETB/*NETB*, 2014

The relationship between participation in screening and risk of breast cancer mortality was estimated by calculating the odds ratio (OR) (Table 6.3). This shows that 477 (63.2%) of the cases had participated in screening in the period up to three invitations before the diagnosis of breast cancer. The corresponding figure for the control subjects was 2,893 (77.4%). The odds ratio was 0.45, which amounts to a 55% reduction in breast cancer mortality after participating in screening. It should be noted that women who participate in screening may differ from those who do not, in terms of their risk of developing breast cancer and of dying from this disease. Accordingly, in this study too, the OR was adjusted for possible self-selection bias, in accordance with the previously described method (Duffy et al, 2002). When adjusted for self-selection bias, the OR is 0.51, i.e. there is a 49% reduction in breast cancer mortality. This outcome is consistent with the results obtained for screened women in randomised screening trials and other case-control studies.

6.2.2 Breast cancer mortality by birth cohort

Changes in breast cancer mortality in the Netherlands are often viewed over extended periods of time (see Figure 6.1). However, changes in breast cancer mortality can also be viewed in birth cohorts. A birth cohort is a group of women who were all born in the same period, and who are monitored over time.
Figure 6.3 shows breast cancer mortality in birth cohorts that were never invited to participate in breast cancer screening (Figure 6.3, A) and for those that were (Figure 6.3, B). Figure 6.3, A clearly shows that breast cancer mortality increases with age, and that it is higher in women who were born more recently. In addition, Figure 6.3, B shows that breast cancer mortality fell after the introduction of the screening programme. This effect was already visible in the first five years after the introduction of the screening programme. It continues on beyond the age of 75, the point at which women cease to participate in the screening programme.

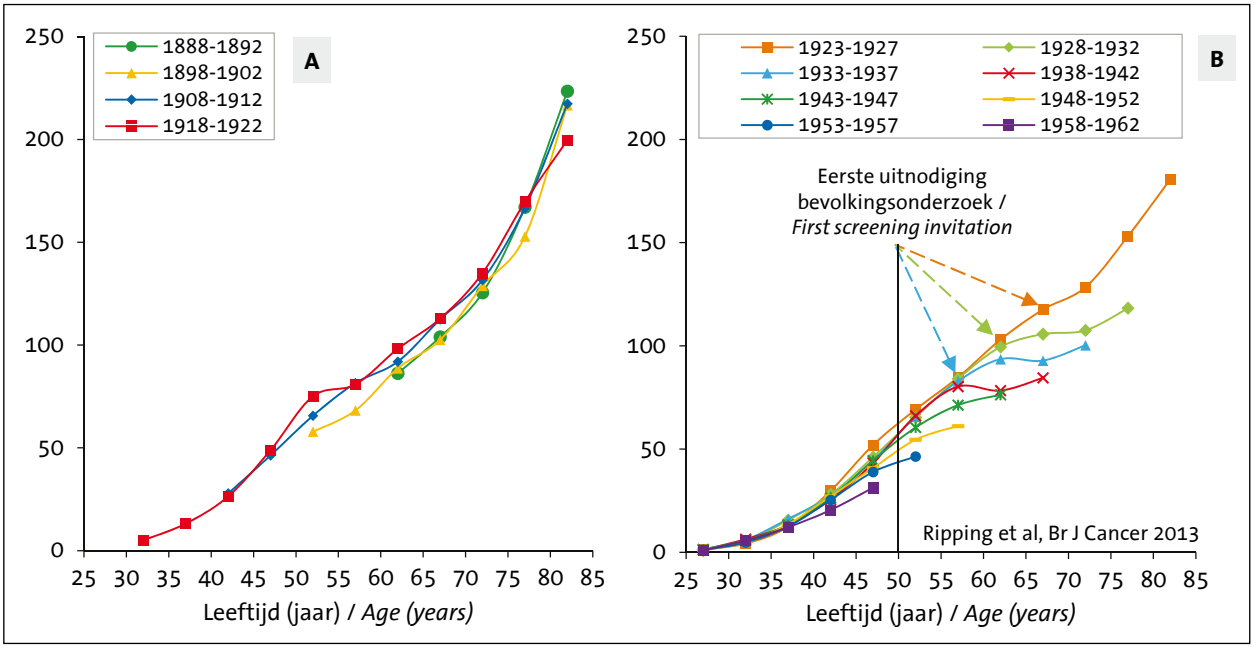

Figure 6.3 Breast cancer mortality rates per 100,000 person years for birth cohorts **(A)** uninvited and **(B)** invited to participate in the national mammographic screening programme (Ripping et al., 2013)

Breast cancer mortality among women over the age of 75 is thus lower than might be expected on the basis of Figure 6.3, A. This can be attributed to the fact that a screening programme does not have an immediate effect on breast cancer mortality. In other words, women who have already been diagnosed in the screening programme do not die immediately but several years later, if at all. Accordingly, the reduction in breast cancer mortality is small in the first few years following the introduction of the screening programme, but this continues if women are no longer invited for screening.

A major advantage of the birth cohort approach compared to the more conventional 'age over time' graphs is that it makes the indirect, delayed effect of screening for breast cancer more visible and more easily measured. In addition, these figures also show that the reduction in breast cancer mortality due to the screening programme cannot simply be estimated by examining breast cancer mortality in the age group that is invited for screening (50-75). It is also necessary to include the reduction in breast cancer mortality among women over the age of 75. Finally, Figure 6.3, B also shows that for women below the age of 50, the more recently they were born, the lower their breast cancer mortality. One possible explanation for this is the combination of improved therapy and early detection (due to greater awareness and to the use of mammography outside the context of screening programmes).

However, the use of trend studies to determine the effect of mammography screening on breast cancer mortality does present a number of difficulties. This is because other factors, such as therapy, change over time. The birth cohort approach does nothing to alleviate this problem. Therefore, attempts to determine the effect of screening on breast cancer mortality will continue to rely on other types of studies, such as case-control studies.

6.2.3 Effects of screening and adjuvant therapy on breast cancer mortality

Although breast cancer mortality has been in decline since the introduction of screening, this cannot be automatically attributed to the effects of the programme alone. During the same period there have also been significant improvements in the treatment of breast cancer, particularly in terms of adjuvant therapy. Accordingly, the effects of screening and adjuvant therapy are evaluated together. The Microsimulation Screening Analysis (MISCAN) model has been used to model both the introduction of screening and the use of endocrine therapy, chemotherapy and a combination of the two by age group and tumour stage (De Gelder, 2012). This model suggested that adjuvant therapy achieved a 13.9% reduction in breast cancer mortality (15.3% in the 50-74 age group) in 2007 (Figure 6.4). Screening reduced this by a further 15.7% (20.9% in the 50-74 age group).

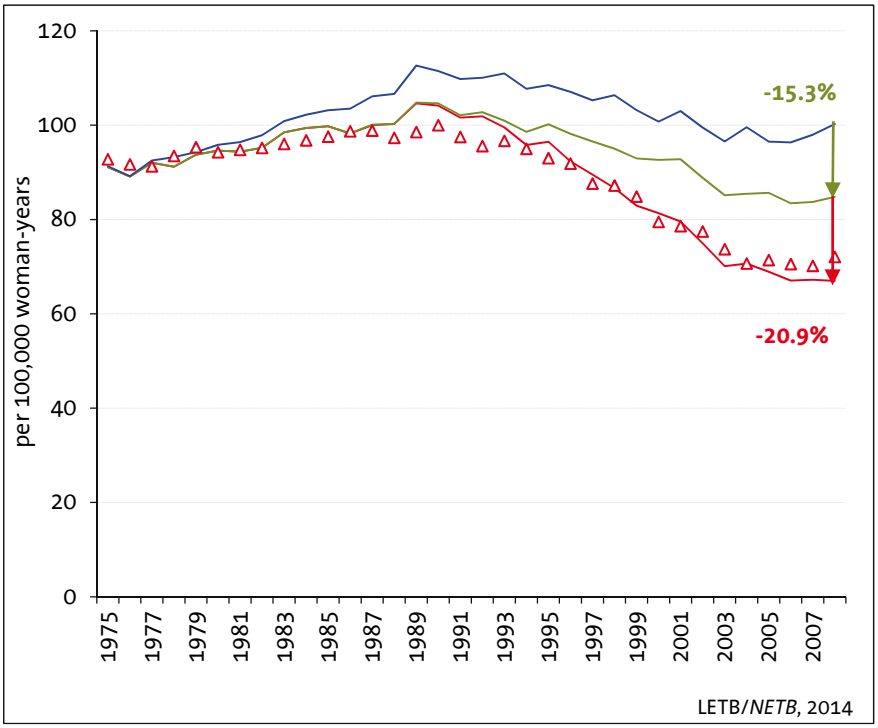

Figure 6.4
The predicted breast cancer mortality in the age group 50-74 years in the following scenarios:
- blue line: without screening and without adjuvant therapy
- green line: without screening and with adjuvant therapy
- red line: with screening and with adjuvant therapy
- triangles: observed breast cancer mortality

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7

Cost of breast cancer screening from 2008 onwards

From 2008 to 2012, as previously stated, a number of major changes took place in the breast cancer screening programme. The analogue screening was completely replaced by digital screening. The programme has also been fundamentally reorganised at regional level. One effect of this has been that boundaries have been re-drawn, reducing the number of regions from nine to five. These modifications were completed in 2012.

Regarding cost trends of the screening programme, a distinction can be drawn between regional costs (which are incurred by the screening organisations) and national costs. The national costs include coordination, quality assurance, monitoring and evaluation (including the National Expert and Training Centre for Breast Cancer Screening, the development of DigiBOB, and the National Evaluation Team for Breast Cancer Screening in the Netherlands). These costs have now fallen slightly, as financial support for DigiBOB terminated after the completion of digitisation.

The cost trend can be broken down into three component trends:

- Increased number of screening tests;
- Reorganisation from 9 to 5 regions, completed in 2012;
- Increasing percentage of digital screening (relatively more expensive), completed in 2012;

The number of screening tests being given is increasing, which pushes up the costs (at regional level) of the screening programme. From 2009 onwards, a reorganisation of the regions took place. The nine regions were reduced to five. The goal is improved efficiency, which should result in lower administrative costs. However, the introduction of digital screening was relatively expensive, compared to the analogue screening that had been carried out previously. Since both trends operate simultaneously, these effects cannot be readily isolated.

Table 7.1 Costs of the Dutch breast cancer screening programme 2008-2013

		2008	2009	2010	2011	2012	2013*
Regionaal *Regional*	€	47.269.503	48.254.227	51.549.186	54.352.534	61.511.150	61.949.746
Landelijk *National*	€	3.431.000	3.380.000	3.401.000	3.043.826	3.054.826	2.977.000
Totaal *Total*	€	50.700.503	51.634.227	54.905.186	57.396.360	64.565.976	64.926.746
Onderzoeken[1] *Screens*[1]	N	918.925	911.489	975.597	995.151	1.008.049	1.015.237

* Cijfers 2013 zijn verleende bedragen en ingeschat aantal onderzoeken.
Figures 2013 are estimates.

[1] Aantal vastgestelde onderzoeken waarop bekostiging is gebaseerd.
Number of approved screening examinations on which costs are based.

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Bron / *Source:* RIVM 2013

The reorganisation was completed in 2012, resulting in the stabilisation of operating costs. Also, the 2012 digitisation has full nationwide coverage, leading to a sharp increase in the number of digital screening tests used (and to a corresponding fall in the use of cheaper analogue screening tests). In 2012, in particular, this resulted in a one-off increase in costs.
This trend is also reflected in the cost per screening test. The regional cost per screening test increased from 2011 to 2012 from €54.62 to €61.02. The corresponding total cost (including the national component) rose from €57.68 to €64.05 per screening test, which amounts to an increase of 12%. In the previous year, the increase was 3.4%. In 2011, due to the uneven development of both the reorganisation and the rollout of digitisation, the costs per screening test among the various regional screening organisations ranged from €52.71 to €55.15.
The regions were compensated for this retrospectively (actual costing). From 2012 onwards, actual costing was based solely on realised volume but not anymore on regional price per screening test. From 2012 onwards, the regional cost per screening test remained constant. As a result, the total cost of the screening programme is affected only by the rising trend in the number of screening tests performed.

Conclusions

- The cost per screening test has increased in recent years, due to digitisation. However, the lower administrative costs resulting from the reorganisation have had a dampening effect on this increase in cost. Without further analysis, however, these concurrent effects cannot be separated from one another.
- In 2012, the total cost per screening test stabilised at €64.
- Since 2010, there has been a steady increase in total annual costs, mainly driven by the increasing number of screening tests.

Table 7.2 Mean regional and national costs per screening exam, 2008-2013

		2008	2009	2010	2011	2012	2013*
Regionaal *Regional*	€	51,44	52,94	52,84	54,62	61,02	61,02
Landelijk *National*	€	3,95	3,82	3,54	3,06	3,03	2,95
Totaal *Total*	€	55,39	56,76	56,38	57,68	64,05	63,97

* Cijfers 2013 zijn verleende bedragen en ingeschat aantal onderzoeken.
Figures 2013 are estimates.

LETB/*NETB,* 2014
Bron / *Source:* RIVM 2013

8

Overdiagnosis

Overdiagnosis means diagnosing a disorder in a situation where the person involved gains no benefit from this diagnosis. Asymptomatic individuals are diagnosed and treated for a disease, while in hindsight it is clear that they would never have been troubled by the disease in question. The debate about overdiagnosis involves many fields of medicine, such as asthma, thyroid problems and prostate cancer. In the case of population-based screening programmes, too, overdiagnosis can occur, resulting in overtreatment. This is considered to be one of the main harms of mammography screening.

Overdiagnosis of breast cancer occurs because screening detects tumours that would never have come to light if the women in question had not taken part in the screening programme. In such cases, while a preclinical stage of the tumour is certainly present, it would not have produced clinical symptoms during life and the woman in question would have died of other causes, without ever being aware that she had breast cancer. There is a particular risk of overdiagnosis in the case of non-invasive tumours (ductal carcinoma in situ, DCIS), slow-growing invasive tumours, and tumours that may even regress. Since almost all breast tumours are treated, overdiagnosis will result in unnecessary treatment (overtreatment).

It is not easy to estimate the extent of overdiagnosis involved in any given population screening programme. After all, there is no way of knowing whether the tumour would have been diagnosed later on if the woman in question had not participated in screening. Thus, for any given individual, it is not possible to determine in advance whether a tumour has been overdiagnosed. Nor are there any tumour markers that can be used to determine this matter.

Published estimates of overdiagnosis range from 0% to 54% of all diagnosed tumours (Biesheuvel et al, 2007; De Gelder et al, 2011; Jorgensen and Gotzsche, 2009; Morrell et al, 2010). These widely differing estimates are mainly caused by differences and inaccuracies in the methods used to estimate the scope of overdiagnosis, and by differences in the denominators by which overdiagnosis is expressed. In this chapter, we will show how the level of overdiagnosis can be determined. We will also indicate the estimated level of overdiagnosis in the Dutch screening programme.

The theory of overdiagnosis

Screening leads to a temporary increase in the incidence of breast cancer in the age group that has been invited to participate in screening. This is mainly because screening causes diagnoses to be made at an earlier stage than would otherwise have been the case. The initial screening test detects tumours that are part of the large group of asymptomatic, pre-clinical tumours present in the population at that point in time. This causes an immediate increase in incidence (Figure 8.1). Even during subsequent screening tests, the prior detection of tumours will still cause more tumours to be diagnosed than would have been the case if screening had not taken place. The extra tumours detected in the age group in which women are invited to participate in screening are referred to as the "excess" incidence. If the screening programme has already been running for several years, then the age group above the invited group will exhibit a lower incidence than if screening had not taken place. This is referred to as the "deficit" incidence. Previously diagnosed tumours cannot subsequently be detected clinically. If there was no overdiagnosis, the excess incidence would be of exactly the same mag-

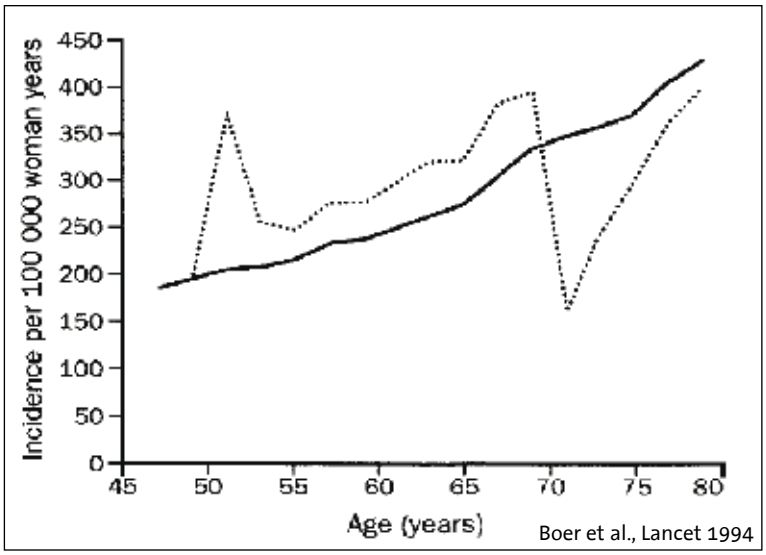

Figure 8.1 Schematic picture of excess and deficit incidence. The solid line is the incidence by age in the absence of screening and the dashed line the incidence by age in the presence of screening. When women are screened between age 50 and 69 years, the incidence will increase in that age group (excess), especially in women who are invited for the first time. After age 70 the incidence is lower (deficit). (Boer et al., 1994)

nitude as the deficit incidence. In practice, this is not the case. We see that the excess incidence is slightly larger than the deficit incidence. This difference corresponds to the level of overdiagnosis, or the extra breast cancers that would not have been diagnosed in the absence of screening. Diagnosis takes place earlier as a result of screening. The time difference involved is referred to as the lead time. The average lead time has been estimated at 2 to 4 years (Duffy et al, 2008; Puliti & Paci, 2009), but there are some major exceptions. Randomised controlled trials in which the control group is not screened would provide a suitable setting in which to determine overdiagnosis. However, this is now no longer feasible, due to the widespread use of mammography. For that reason, observational studies and simulation studies are needed to estimate the level of overdiagnosis.

A model for estimating overdiagnosis

The level of overdiagnosis can be determined by comparing the life courses of non-screened women with that of a comparable group of screened women. Overdiagnosis can then be quantified through the use of micro-simulation with the help of the MISCAN model. This model was created in the 1980s by the Department of Public Health at Erasmus MC. Since then, it has been further developed and continuously updated with the latest results of the Dutch breast cancer screening programme, together with international data on the effect of screening on breast cancer mortality (De Gelder et al, 2011; Groenewoud et al, 2007). The model simulates women's life course, the natural history of breast cancer, and the screening programme. The natural history of breast cancer is modelled as a progression from preclinical screen-detectable DCIS to preclinical T1A, T1B, T1C and T2+. At each of these pre-clinical stages, a tumour can produce symptoms that can lead to its diagnosis. Next the screening programme is simulated, and screening detects tumours in a number of women. The average duration of the tumour stages, the probabilities of transition between various preclinical stages, the sensitivity of the screening test, survival following diagnosis and treatment, and the improvement in survival due to detection by screening are estimated using data obtained by the Dutch screening programme between 1990 and 2006 and by Swedish breast cancer screening trials (Bjurstam et al, 2003; Nystrom et al, 2002; Tabar et al, 2000). To estimate overdiagnosis in the Netherlands, the female Dutch population (between the ages of 0 and 100) in 1989 (the year before the start of the breast cancer screening programme) is simulated. Participation rates by year and age corresponded to the gradual build-up of the programme in the Netherlands. The model incorporates a rising background incidence of 1.4% per year, corresponding to the increase in the number of women with risk factors and to increased alertness in terms of the symptoms and diagnosis of breast cancer. The model generates a reliable estimate of incidence in the period from 1990 to 2000. From the year 2000 onwards, the estimated incidence is slightly lower than the observed incidence.

Estimates of overdiagnosis

The Dutch breast cancer screening programme can be divided into three phases. The first of these was the 1990-1998 implementation phase, in which women between the ages of 50 and 69 were invited to participate. The second was the 1998 to 2002 expansion phase, in which invitations were also sent to women in the 70 to 74 age group. The third and final phase was the steady-state phase, from 2002 onwards, in which the number of screening tests remained more or less the same. Using the MISCAN model, incidence was predicted per 5-year age group for every year up to 2006, in situations with and without screening (Figure 8.2) (De Gelder et al, 2011). From the moment that the screening programme first started, in 1990, incidence among women of screening age has been rising.

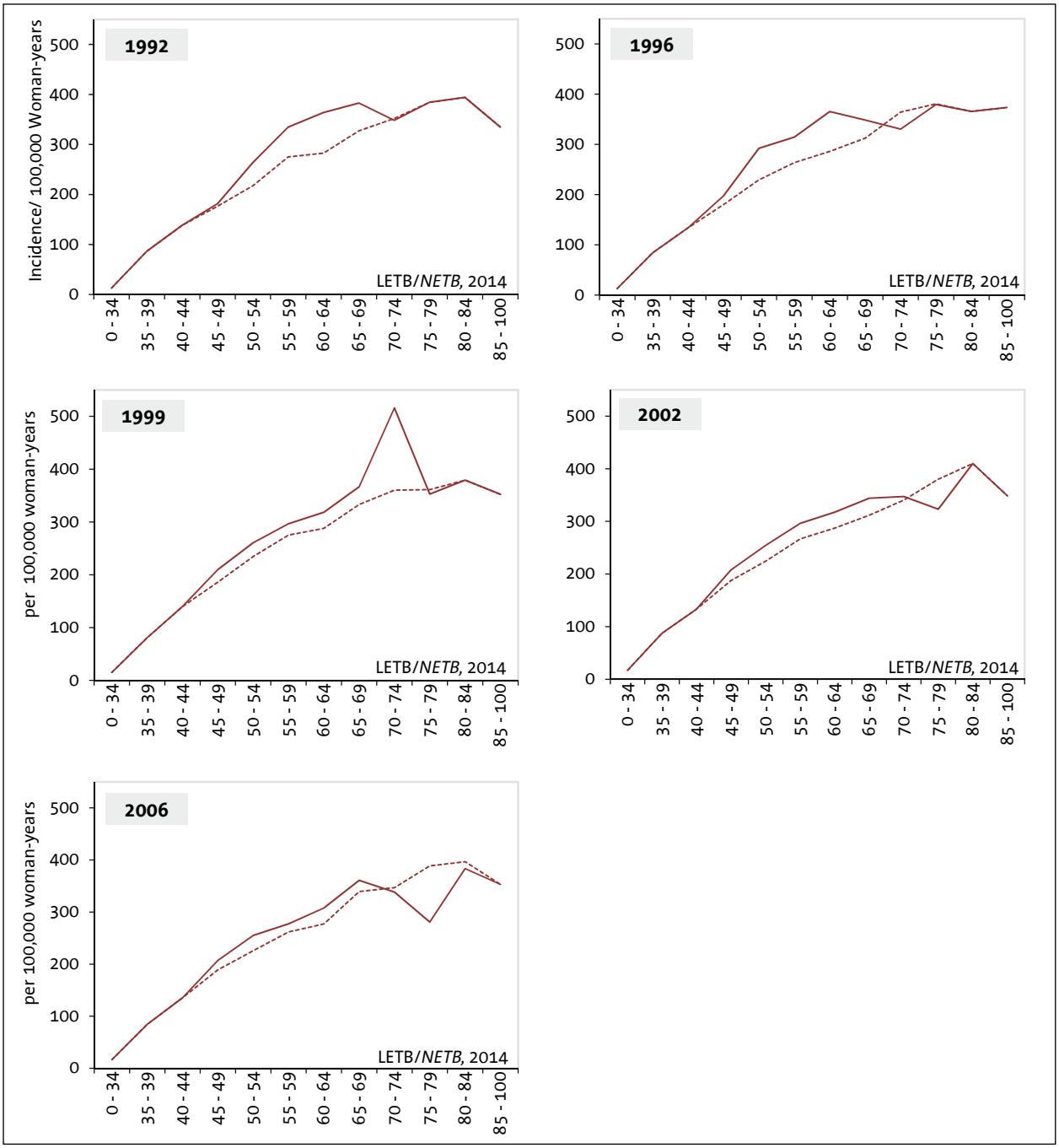

Figure 8.2 Predicted breast cancer incidence by 5-year age group. The dashed line is the predicted incidence in the absence of screening, the solid line in the presence of screening.

At the end of the implementation phase, there was a slight fall in this excess incidence (Figure 8.3), while the deficit incidence started to rise (Figure 8.4). The expansion of the screening programme to cover women of up to 74 years of age led to a large increase in incidence within the 70-74 age group. This caused excess incidence to rise again, and deficit incidence to fall. During the steady-state phase, excess incidence among women of screening age falls, while deficit incidence in the 74-79 and 80-84 age groups rises.

The number of overdiagnosed tumours is calculated based on the difference between excess incidence and deficit incidence. This is then expressed as a percentage of all detected tumours. In the implementation phase, the percentage of overdiagnosis increased from 1% of all detected tumours to 11% in 1993. Overdiagnosis subsequently fell to 5% before the screening programme was expanded to cover women of up to 74 years of age. This expansion raised the level of overdiagnosis to 10% in 1999. After that, the level of overdiagnosis fell to 2.8% in 2006 (Figure 8.5). A further reduction of overdiagnosis cannot be ruled out. Any estimate of overdiagnosis is, therefore, highly dependent on the implementation phase of the screening programme. For a proper analysis, it also depends on the period for which data is available. Re-

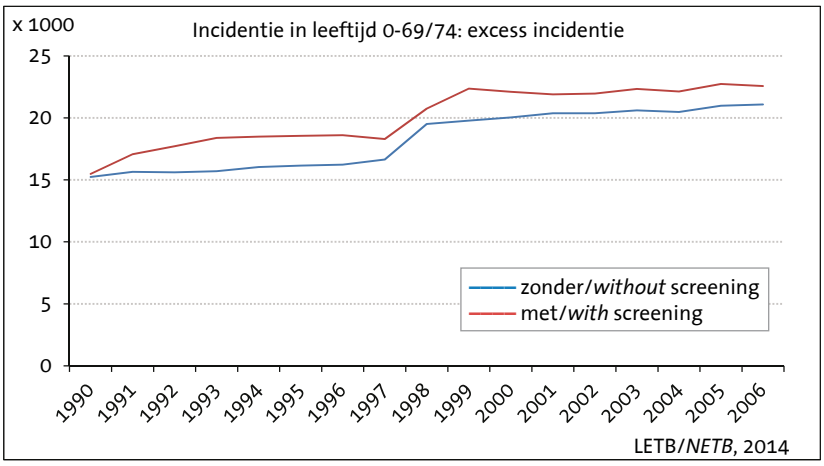

Figure 8.3
Predicted number of breast cancers in the presence and absence of screening in the age group until the age of last screen (0-69 years until 1998 and 0-74 years from 1998). The difference is the excess incidence.

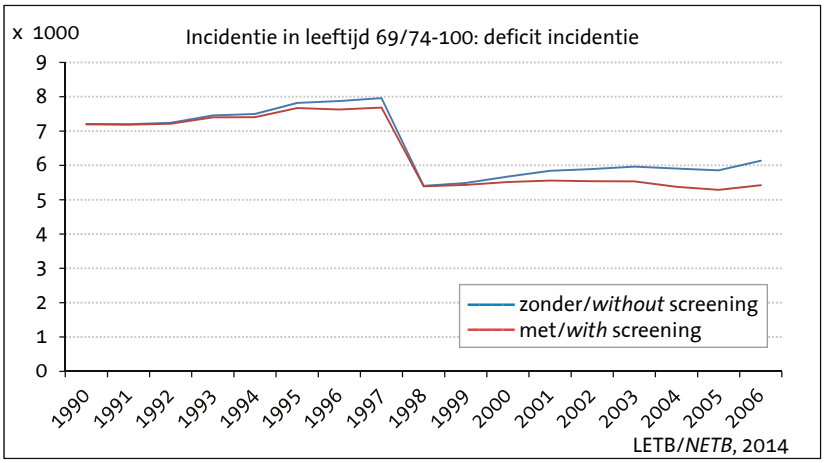

Figure 8.4
Predicted number of breast cancers in the presence and absence of screening in the age group above the age of last screen (69-100 years until 1998 and 74-100 from 1998). The difference is the deficit incidence.

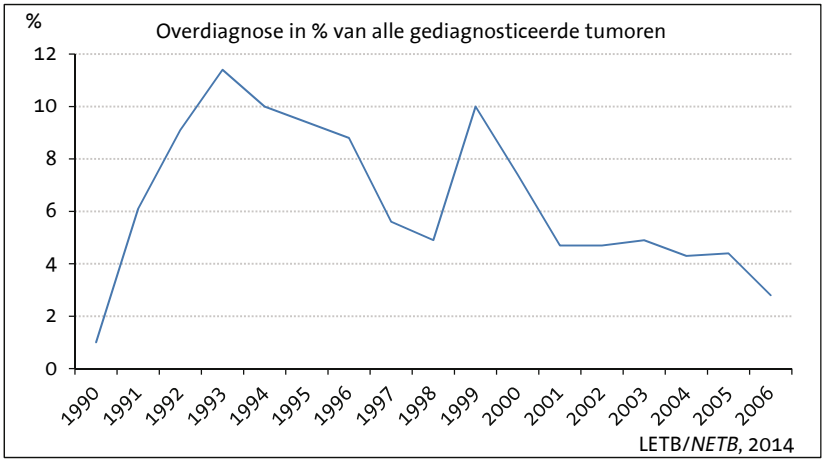

Figure 8.5
The estimated overdiagnosis as percentage of all tumors that would have been diagnosed in the absence of screening in the ages 0-100.

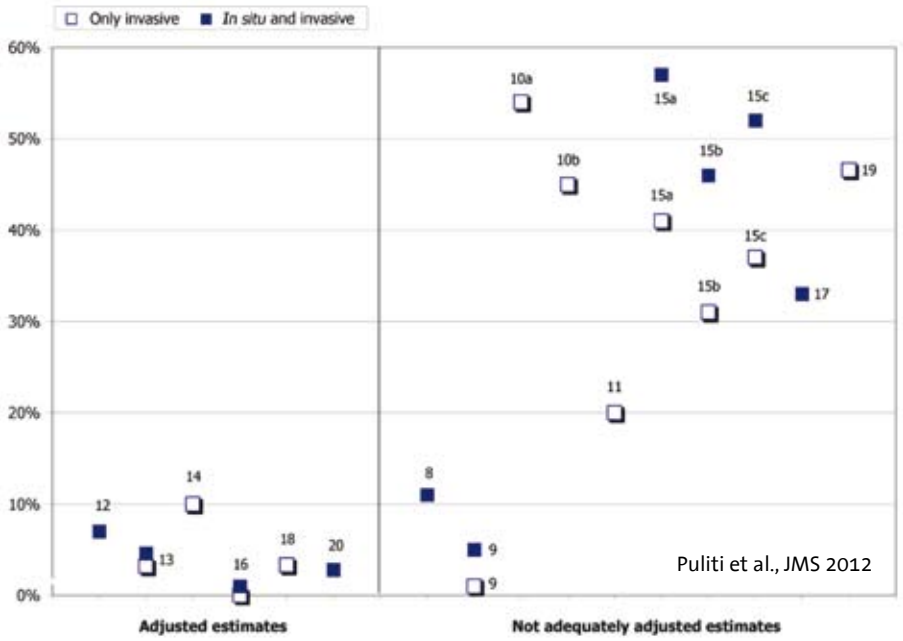

Figure 8.6
Estimates of overdiagnosis from studies in which the increasing background incidence and lead time divided in correctly adjusted estimates and not adequately adjusted estimates (Puliti et al., 2012).

liable estimates can only be made if the screening programme in question has been in a steady-state phase for a number of years.
Overdiagnosis is often also expressed as a percentage of the total number of tumours detected in women in the screening age-range. The model mentioned above gave an estimate of 9.7% for the Netherlands in 2006.

Overdiagnosis in observational studies

A recently published literature review examined all 13 observational studies of overdiagnosis in European breast cancer screening programmes (Puliti et al, 2012). In each study, overdiagnosis was expressed as a percentage of expected incidence in the absence of screening. Checks were also made to determine whether these studies made adjustments to allow for the two main forms of bias involved in estimations of overdiagnosis: an increase in the underlying incidence of breast cancer and lead time. Studies that effectively adjusted for these two forms of bias produced much lower estimates of overdiagnosis, ranging from 0% to 10% (Figure 8.6). Those studies that did not effectively adjust for bias, if at all, produced estimates of overdiagnosis ranging from 0% to 54%. An independent UK-based review panel was appointed in 2011 to evaluate the benefits and harms of breast cancer screening. It concluded that many observational studies use inappropriate methodology when making estimates of overdiagnosis (Independent UK Panel on Breast Cancer Screening, 2012).

Conclusion

Of all the breast cancers detected each year in the Netherlands, 2.8% are the result of overdiagnosis due to the screening programme. The higher estimates found in the literature are often based on inappropriate adjustments for the rise in the underlying incidence of breast cancer and for the lead time.

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9

Screening outcomes

Information for the population, subgroups and individual participants

The outcomes of mammographic screening tests can be determined separately for each round of screening. It is also possible to examine broad trends spanning several rounds. This is done at the level of the population being screened.
Evaluation can also be targeted at individual participants. Longitudinal data analyses are then used to show whether women complete the entire sequence of 13 screening tests between the ages of 50 and 75. One intermediate variant of evaluation shows the screening outcomes for subgroups in terms of breast cancer risk. These include for instance groups with dense mammographic patterns. This covers about 15% to 20% of all the women taking part in screening. In addition to making the assessment of mammograms more difficult – resulting in poorer accuracy (more false-positive and false-negative results) – mammographic density is also a risk factor for breast cancer.

In this section, the screening outcomes are analysed at three levels: total population screened, subgroup and individual participants. Longitudinal data from the Nijmegen screening programme (from the year 2000 onwards) was used for this purpose.

9.1 Performance of the screening test at population level

Table 9.1 lists the most important Dutch screening outcomes from 1990 to 2009, at population level (see Sections 2-5). In the period from 1998 to 2001, the post-screening referral rate was significantly lower than in 2009: 1.2% versus 1.9%. This increase was due to the switch to a less restrictive referral policy (in response to a national evaluation study), and to the gradual introduction of digital screening. (Verbeek et al., 2013)
The proportion of women in whom a mammary carcinoma is detected has also increased, from 0.5% to 0.6%. At the same time, the less restrictive referral policy has caused the positive predictive value of mammographic screening to fall from 42% to 30%.
The Screening Odds Ratio (SOR) is a unit of measurement that expresses a screening test's screening power as a single number. This shows the ratio of the chance (Odds) that someone with a positive test result will actually have the disease in question, compared to this probability (Odds) for someone with a negative test result. The higher the SOR, the greater the screening test's discriminating power. A SOR of

Table 9.1 Breast cancer screening outcomes in the Netherlands, period 1998-2001 and 2009

Uitkomst % / *Outcome %*	**Periode / *Period***	
	1998-2001	**2009**
Opkomst / *Participation*	78,7	81,5
Huisartsverwijzing / *Referral recommendation*	1,2	1,9
Invasief onderzoek / *Invasive assessment*	0,7	0,9
Detectie van mammacarcinoom / *Screen detected cancer*	0,5	0,6
Foutpositieve mammografie-uitslag / *False positive result*	0,7	1,3
Intervalkanker / *Interval cancer*	0,2	0,2

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Table 9.2 Referral recommendations and screen detected breast cancer in the Netherlands, period 1998-2001 and 2009 per 100 screened women

	Borstkanker < 2 jr na screening / *Breast cancer < 2 yrs after screening*					
	1998-2001			2009		
Verwijzing % / *Referral %*	**Ja / *Yes***	**Nee / *No***	**Totaal / *Total***	**Ja / *Yes***	**Nee / *No***	**Totaal / *Total***
Ja / *Yes*	0,5	0,7	1,2	0,6	1,3	1,9
Nee / *No*	0,2	98,6	98,8	0,2	97,9	98,1
Screening Odds Ratio (SOR)	(0,5/0,7) : (0,2/98,6)			(0,6/1,3) : (0,2/97,9)		
SOR	= 352			= 226		

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200, for example, means that the chance that an individual with a positive test result will actually have the disease in question is two hundred times greater than for an individual with a negative test result.
The SOR is a composite measure that incorporates the breast cancer detection rate and the incidence of interval cancers, as well as the frequency of false-positive and true-positive mammograms. Instead of the frequency of disease (see Table 9.1), however, the odds are used, i.e. the ratio of the frequency of disease to its complement. The screening outcomes of Table 9.1 are shown in Table 9.2 as breast cancer frequency rates, both for women who have been referred and for those who have not. This can be used to calculate the odds of breast cancer and the odds ratio.
For women who have been referred, the odds of developing breast cancer are equivalent to 0.5% / 0.7%. For those who have not been referred, the odds of developing breast cancer are equivalent to 0.2% / 98.6%. Both odds can then be divided by one another: this is the Odds Ratio. Here, this Screening Odds Ratio (SOR) is 352. This means that referred women are 352 times more likely to have breast cancer than non-referred women.

In the case of diagnostic tests that are routinely used in contemporary clinical practice, a SOR of between 2 and 20 would be quite normal. A SOR > 200 is the objective in screening situations. Anything less and adverse situations will arise involving excessive numbers of referrals, and a screening test with a poor predictive value.
In the period from 1998 to 2001, based on this criterion, mammographic screening in the Netherlands had a perfectly acceptable SOR. By 2009, the SOR value had fallen to 226. This was because the figure for false-positive referrals had almost doubled in the space of 10 years, from 0.7% to 1.3%.

9.2 Subgroup analysis: Influence of mammographic density on the Screening Odds Ratio (SOR)

In terms of mammographic density, mammograms can be classified into one of two types. The first type has a dense pattern, containing many mammographically dense structures corresponding to substantial quantities of glandular and connective tissue in the breast. The second type has a translucent pattern, that 'lights up' due to the relative abundance of fat compared to the limited quantity of glandular and connective tissue. Based on 2001-2002 data from the former SVOKON region, a SOR of 339 was calculated for dense patterns. The SOR value for lucent patterns was 915. During that period, the overall SOR was 518. Figures 9.1 to 9.3 below provide an update to the SVOKON study, using more recent data from the four rounds of screening in Nijmegen from 1999-2000 to 2005-2006.
The effect of mammographic density is explored in terms of referral rate, detection rate and the incidence of interval cancers.
As mentioned earlier, we can summarise the detection rate, the incidence of interval cancer, and false-positive results (referral rates, respectively) in the SOR. The values for lucent and dense breast patterns are summarised in Table 9.3. The trend is clear. Where overall sensitivity is around 70%, specificity in excess of 99%, and the SOR is 'around' 200, the numbers for for the subgroup of women with dense patterns on screening mammograms are less favourable than for women with lucent breast patterns, where the screening performance is more than satisfactory.

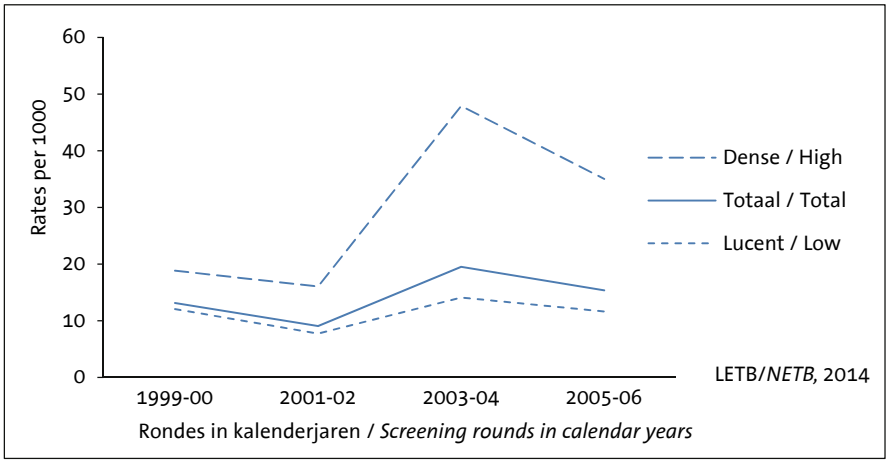

Figure 9.1
Referral recommendations for women by mammographic density, 1999-2006.

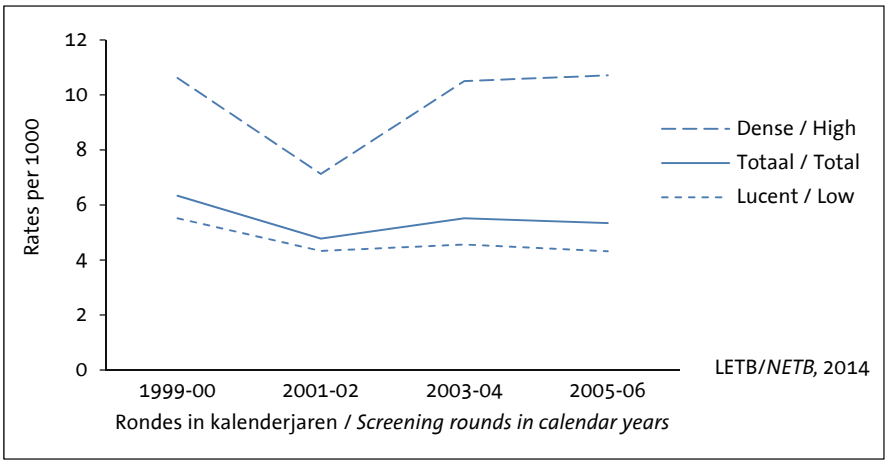

Figure 9.2
Detection rates for women by mammographic density, 1999-2006.

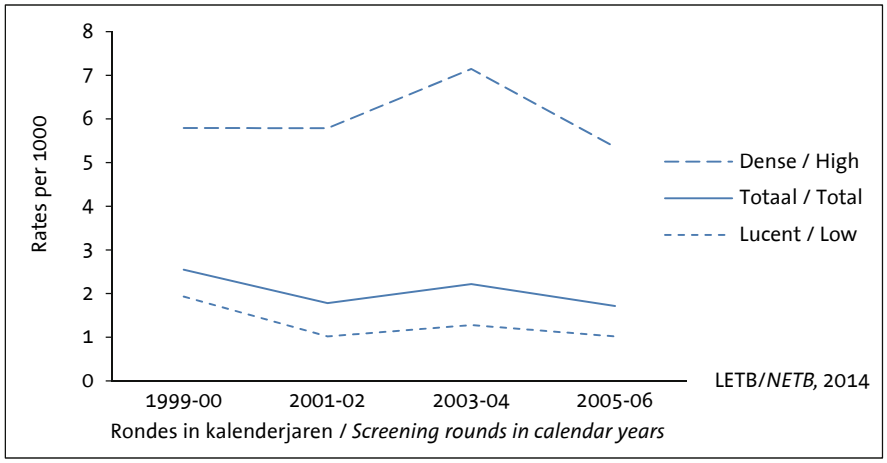

Figure 9.3
Incidence of interval breast cancer for women by mammographic density, 1999-2006.

Table 9.3 Influence of mammographic density on mammographic sensitivity, specificity and the ScreeningOddsRatio, averages 1999-2006.

Sensitiviteit / *Sensitivity*	Totaal / *Total*	70%
	lucent	80%
	dense	60%
Specificiteit / *Specificity*	Totaal / *Total*	99,3%
	lucent	99,7%
	dense	98,5%
SOR	Totaal / *Total*	400
	lucent	600
	dense	200

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9.3 Interval cancers in the population and subgroups

The more sensitive the screening test used, the greater the number of smaller tumours that will be detected. As a result, the number of interval cancers would be expected to fall. Data from the 1999-2006 screening rounds in Nijmegen is summarised in Figure 9.4 below. This shows the cumulative incidence of interval cancers (per 1,000 women screened) in the 24-month period following a negative screening test.
The number of interval cancers gradually increases until, within a period of two years, it reaches an incidence of 2 per 1,000. This means that screened women with a negative screening mammogram have a 0.2% risk of developing an interval cancer.
In this scenario, it is not possible to determine whether the cancer resulted from a tumour that was 'missed at screening' or whether it is a 'de novo' tumour. The only way to find out is to conduct a revision study, as the National Expert and Training Centre for Breast Cancer Screening does in its periodic independent quality inspection rounds of the central reading units. At the time of screening, these 'de novo' tumours would not yet have reached the preclinically detectable phase. Clearly, however, they subsequently underwent a rapid process of development, causing them to manifest as interval cancers.

In Figure 9.5, interval cancer occurrence for each breast pattern (dense and lucent) is presented separately. The cumulative incidence is 1.3 per 1,000 in women with lucent breast tissue compared to 6.0 per 1,000 in women with dense breast tissue.
Incidence density is calculated by dividing the numbers of interval cancers by the number of years for

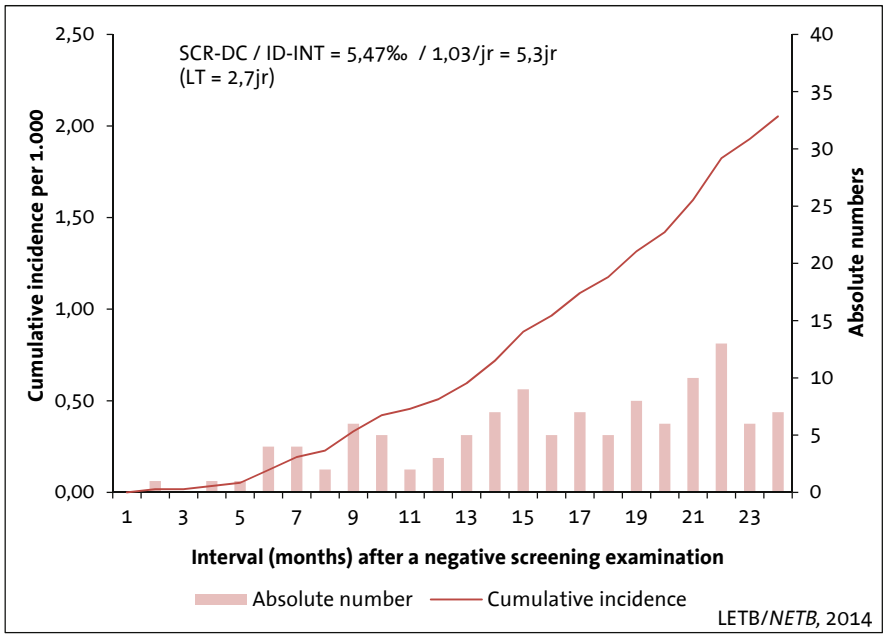

Figure 9.4
Cumulative incidence of interval breast cancer per 1.000 screened women (line) and absolute numbers (bars) in 0-24 months after a negative screening examination. SCR-DC = screen detected breast cancer rate, ID-INT = incidence density interval breast cancer, LT = lead time.

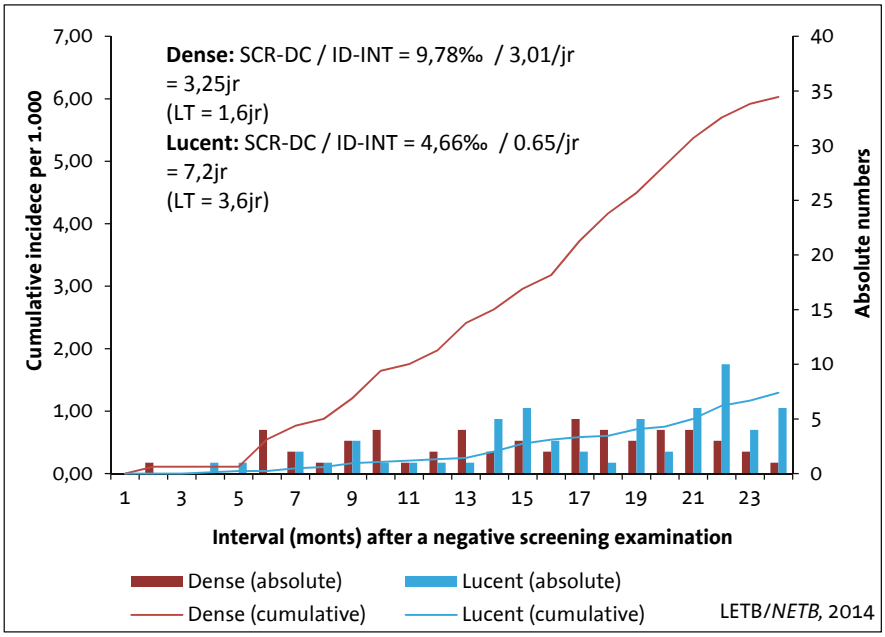

Figure 9.5
Cumulative incidence of interval breast cancer per 1.000 screened women (line) and absolute numbers (bars) by mammographic density in 0-24 months after a negative screening examination. SCR-DC = screen detected breast cancer rate, ID-INT = incidence density interval breast cancer, LT = lead time.

which the screened women have been under observation. The detection rate divided by this incidence density provides a unit of measurement for the duration of the detectable pre-clinical phase. This is 3.25 years for women with a dense breast pattern, compared to more than 7 years in the case of a translucent pattern. Accordingly, the screening test evidently performs better for the latter group. More than three quarters of participants have lucent mammographic breast patterns. These numbers also mean that the lead time (the number of years that diagnosis is brought forward due to screening) is greater in lucent patterns than in the case of cancers that develop in a mammographically dense matrix.

Lead time as an alternative performance measure

The goal of screening is to prevent women dying from breast cancer by detecting as many cases as possible, as early on as possible. In more technical terms, it is to detect cases of breast cancer at the earliest possible point in time relative to the moment of symptomatic diagnosis. Since symptoms usually appear when tumours reach a diameter of 20 mm, just how sensitive is screening in the case of preclinical screen-detectable carcinomas with a circumference of 15 mm or a diameter of 5-10 mm, for example?

Another legitimate question is how much earlier can tumours of this size (with diameters of 5, 10, 15 mm etc.) actually be detected? Also, what is the theoretical maximum limit of early detection (in years) in a scenario where participants are screened every day? The theoretical value in question is expressed in terms of the length of a carcinoma's preclinical screen-detectable phase (PCDP). Reference is made to this in Figures 9.4 and 9.5 above.

The concept of 'lead time' (LT) is used to describe the distribution of the actual length of time involved in 'earlier detection'. A simple rule of thumb is that lead time (e.g. 2-3 years) is half the length of the PCDP (e.g. 4-6 years). In reality, lead times (growth rates) have an exponential distribution. The screening tests that perform best will have longer LTs and PCDPs. This will also correspond to a greater reduction in the anticipated breast cancer mortality rate.

To substantiate the latter statement, as a measure of a screening test's performance, its lead time must also be externally validated against the corresponding reduction in breast cancer mortality. Given sufficient longitudinal epidemiological data on women with a screen-detected cancer or an interval cancer, it is a relatively straightforward matter to derive accurate estimates of the lead time involved. Incidentally, this goal is now within reach at both regional and national level. That, in turn, will enable the lead time and Screening Odds Ratio (SOR) to be effectively calculated at regional and subregional level.

9.4 Individual risk of breast cancer

It is legitimate to screen for breast cancer because this disease represents a major public health problem. Another argument in favour of screening is that breast cancer has a huge impact on the individuals concerned. At the start of the screening programme in 1990, 8,451 women in the Netherlands were diagnosed with invasive breast cancer and 258 with ductal carcinoma in situ. Twenty years later, in 2010, the numbers involved were 13,257 and 1,760 respectively. Incidence rates can be calculated by breaking these incidence levels down by age and by linking them to population levels. Based on these age-specific incidence rates, the method described by Ellen Paap (Paap et al, 2008) can be used to determine individual risks of breast cancer. Our updated figures for the Netherlands are shown in Table 9.4.

The lifetime risk of breast cancer rose from 11% in 1991 to almost 16% in 2011. For 50-year-old women, the risk is now 13.5%. At 7%, 70-year-olds, too, are still at moderate risk of developing breast cancer. Over the same period, the risk of dying of breast cancer (determined using the same method) fell from 4.7%

Table 9.4 Life-time risk for breast cancer diagnosis (invasive and in situ)

Jaar *Year*	**Startleeftijd** *Starting age*	**Risico op borstkanker (95%-BI)** *Life-time risk of breast cancer (95%-CI)*
1991	0 jaar / *year*	11,2% (10,9-11,4)
	50 jaar/ *year*	9,5% (9,3-9,7)
	70 jaar/ *year*	5,1% (4,9-5,3)
2001	0 jaar/ *year*	13,8% (13,6-14,1)
	50 jaar/ *year*	11,9% (11,6-12,1)
	70 jaar/ *year*	6,3% (6,1-6,6)
2011	0 jaar/ *year*	15,7% (15,5-16,0)
	50 jaar/ *year*	13,5% (13,3-13,8)
	70 jaar/ *year*	7,0% (6,8-7,2)

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to 3.7%. However, these figures cannot be used to calculate the extent to which the introduction of screening has reduced the risk of mortality.

The changes in risk are undeniably related to the breast cancer screening programme for women aged 50 to 75. The outcomes of screening in terms of individual risks accumulated over 13 rounds of screening are discussed in the following paragraph. In addition to the chance that a cancer will be detected during screening, this also covers the likelihood of a referral, the chance of a false-positive screening test throughout the entire process, and the risk of interval cancer.

9.5 Information for the women invited to participate: cumulative risks

This paragraph is based on the paper entitled *Likelihood of early detection of breast cancer in relation to false-positive risk in life-time mammographic screening: population-based cohort study* (Otten JDM, Fracheboud J, den Heeten GJ, Otto SJ, Holland R, de Koning HJ, Broeders MJM, Verbeek ALM. Annals of Oncology, 2013, with editorial by Njor SH and von Euler-Chelpin M).

Cumulative risk of carcinoma (or screen-detected cancer) and false-positive referrals in "regular" participants

Once every two years, every woman in the Netherlands between the ages of 50 and 75 receives an invitation to participate in the screening programme. This equates to a maximum of 13 such invitations in their total 'screening life'. In 2011, 21 women out of every 1,000 screened were referred for further tests. Six of these individuals were subsequently found to have breast cancer (true-positive referral), while the remaining 15 did not (a false-positive referral). What, then, are an individual's cumulative risks of various screening outcomes if they participate in 13 consecutive screening tests? It is important for individuals to weigh up such information when taking decisions about whether or not to participate in the screening programme. The same applies to policy decisions concerning the structure, organisation, and funding of regional or national screening programmes. To calculate these risks, we used data from the Nijmegen screening programme for the period from 1975 to the present.

The probabilities of different screening outcomes over a total of 13 screening rounds are estimated for a historical cohort, a recent cohort screened using analogue mammography (based on 5 full rounds), and a cohort that was screened using digital mammography (based on a pilot study).

Cumulative screening outcomes over 13 rounds: historical cohort

In 1975, 3,539 women around the age of 50 participated in the Nijmegen screening programme. During the subsequent 24 years (13 rounds of screening), 157 women were referred once and 4 were referred twice, resulting in the detection of 74 cases of breast cancer. Forty-eight women were diagnosed with breast cancer in the interval between two screening tests (interval cancer).

The cumulative risks of a screen-detected cancer, an interval cancer, or a false-positive referral throughout the 13 consecutive rounds are shown in Figure 9.6.

At the initial screening test, there was a greater likelihood of a false-positive referral than of being found to have breast cancer (1.1% versus 0.6%), while the long-term risk of breast cancer was actually higher (4.2% versus 5.3%). The risk of an interval cancer was

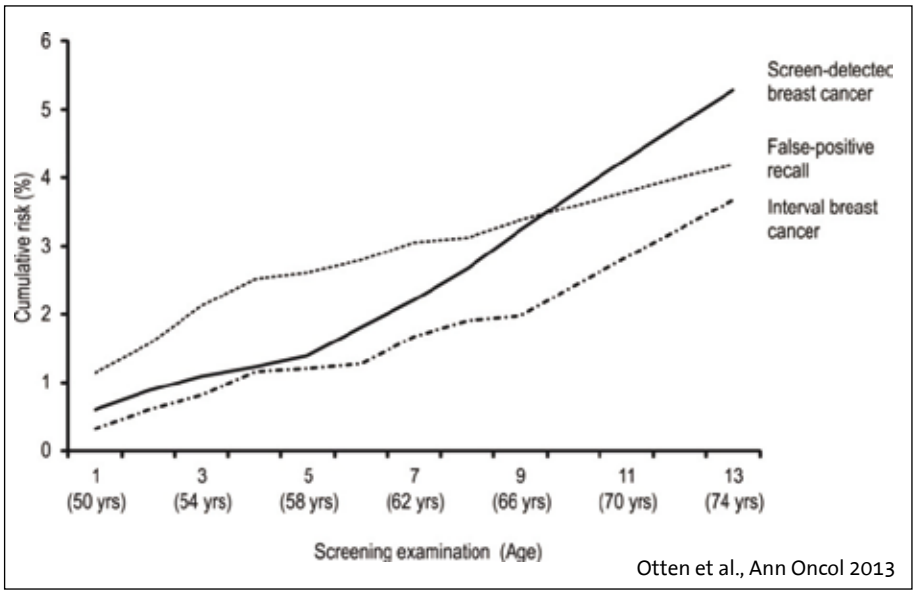

Figure 9.6
Age related cumulative risks of false-positive referral in relation to screen-detected and interval cancers (historical cohort).

fairly stable from round to round, amounting to 3.7% after 13 rounds.

Cumulative risks (after 13 screening tests): historical cohort versus current participants

Table 9.5 shows the cumulative risks for different endpoints. The historical cohort (13 rounds starting in 1975) is in column 2, the more recent period of analogue screening (1997-2006) is in column 3, while column 4 gives estimates for the digital screening situation.

When compared to historical data from the trial mammography screening programme (the first few decades of the Nijmegen programme), the cumulative risk across 13 screening tests of being referred at least once rose from 9.3% to 14.5%. This also boosted the cumulative risk of at least one false-positive result, from 4.2% to 7.3%. At 7.3%, this risk is still much lower than in neighbouring countries, where analogue mammography is associated with a false-positive rate in excess of 20% (Hofvind et al, 2012); See Figure 9.7 for the cumulative risks of a false-positive referral in a number of international studies (circles) and in various scenarios (lines). The differences between countries can be largely accounted for by differences in referral rates (Njor et al, 2007 and Fletcher et al, 2005).

The expectation is that, with the advent of digital screening, the cumulative risk of a false-positive referral will rise to about 16% (NL-u in Figure 9.7). However, this is still below the level seen in other countries, where false-positive rates of 30% or more are seen (Del Turco et al, 2007, and Sala et al, 2009).

At 6.9%, the cumulative risk of a true-positive result (breast cancer detected by screening) is currently about the same as the risk of a false-positive referral (7.3%). At the initial screening test, the ratio of true-positive results to false-positive ones is 1 to 2. Thus, the more frequently a woman undergoes screening tests, the more favourable the ratio. In addition, the long-term risk of an invasive screen-detected cancer where the tumour is <15 mm in size, increases from 2.3% to 3.7%. Women with such small tumours have a normal life expectancy (Otten et al, 2010). This means that (with proper treatment) approximately 67% (3.7%/5.5%, Table 9.5 present cohort) of women with an invasive screen-detected cancer have the same life expectancy as women without breast cancer.

Today, the estimated cumulative risk of an interval cancer has dropped to 2.9%. Yet in the first decades of the trial programme in Nijmegen it was still 3.7%. This gives a more favourable ratio of screen-detected cancer to interval cancer (it was 3:2, and is now 5:2).

All in all, the policy of more frequent referrals has delivered a higher cumulative chance of detecting early breast cancer and a reduced risk of an interval cancer. This is at the expense of a slight increase in the risk of at least one false-positive result, a risk that will increase still further in the digital situation and with further increases in referral rates.

Table 9.5 Cumulative risks for recall and breast cancer diagnosis for a 50 year old woman based on 13 screening examinations

	Long-term risks early period* (95% CI)	Extrapolation of the rates in current cohort† (95% CI)	Expected figures in digital mammography§
Recall	9.3% (7.8 to 10.7)	14.5% (11.5 to 17.5)	22.2%
Screen-detected breast cancer	5.3% (4.1 to 6.5)	6.9% (4.2 to 9.6)	7.1%
invasive	4.4% (3.2 to 5.7)	5.5% (3.1 to 7.9)	5.6%
invasive cancer <15 mm	2.3% (1.5 to 3.2)	3.7% (0.9to 6.4)	data not available
Interval cancer	3.7% (1.5 to 5.8)	2.9% (1.5 to 4.2)	data not available
False-positive recall	4.2% (3.3 to 5.1)	7.3% (5.5 to 9.0)	16.1%
invasive assessment‡ 1st exam	0.8% (0.5 to 1.1)	0.9% (0.7 to 1.1)	data not available
invasive assessment 13 exams	2.4% (1.7 to 3.1)	2.6% (1.7 to 3.4)	data not available

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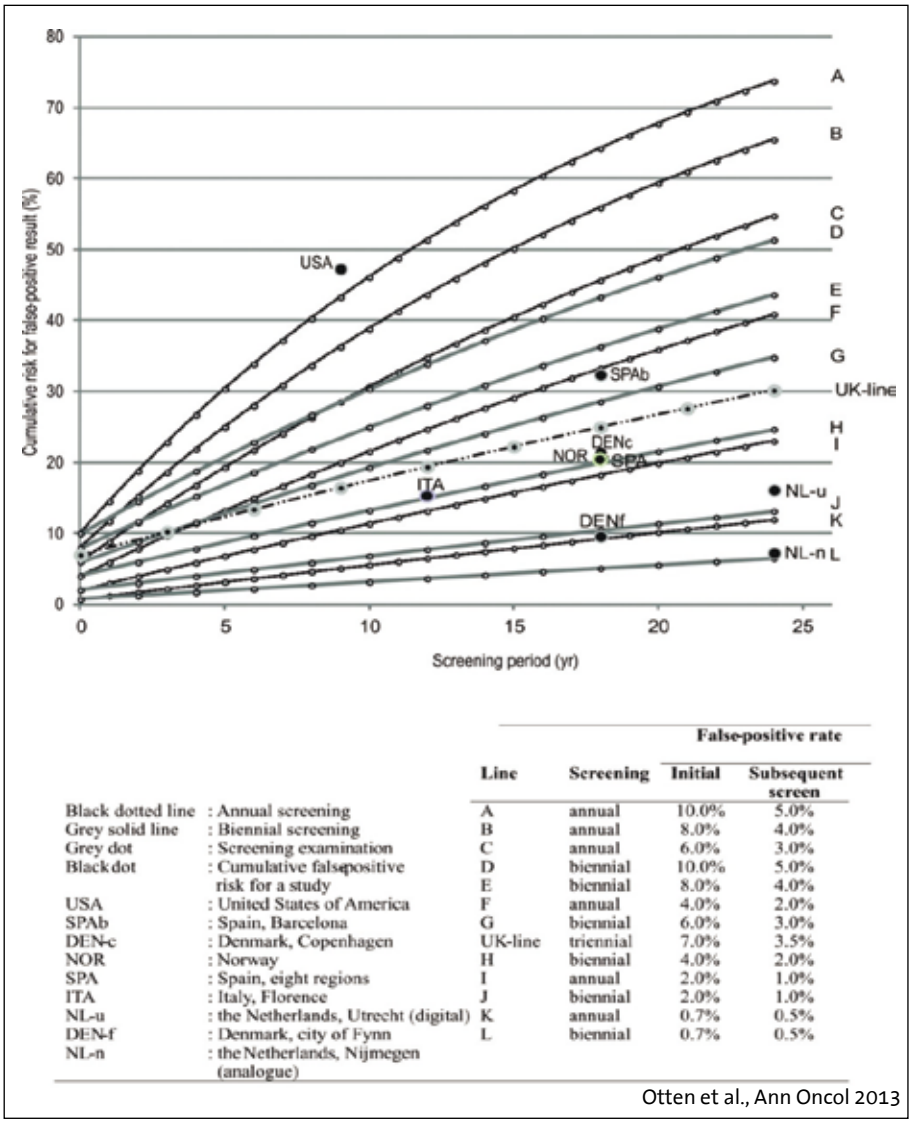
* Early period (historical cohort): first screening in 1975, extrapolation for 13 examinations are based on 10 examinations.
† Current cohort: first screening examination in the period 1997–2006, extrapolation for 13 examinations are based on observations of 5 examinations from the early and current screening period.
‡ Invasive work-up: invasive clinical examination like fine needle aspiration cytology, core needle biopsy or surgical biopsy.
§ Calculation based on figures from a digital pilot study from Netherlands, Utrecht. See original article (Otten et al.,2013).



Line	Screening	False-positive rate: Initial	False-positive rate: Subsequent screen
A	annual	10.0%	5.0%
B	annual	8.0%	4.0%
C	annual	6.0%	3.0%
D	biennial	10.0%	5.0%
E	biennial	8.0%	4.0%
F	annual	4.0%	2.0%
G	biennial	6.0%	3.0%
UK-line	triennial	7.0%	3.5%
H	biennial	4.0%	2.0%
I	annual	2.0%	1.0%
J	biennial	2.0%	1.0%
K	annual	0.7%	0.5%
L	biennial	0.7%	0.5%

Black dotted line : Annual screening
Grey solid line : Biennial screening
Grey dot : Screening examination
Black dot : Cumulative false-positive risk for a study
USA : United States of America
SPAb : Spain, Barcelona
DEN-c : Denmark, Copenhagen
NOR : Norway
SPA : Spain, eight regions
ITA : Italy, Florence
NL-u : the Netherlands, Utrecht (digital)
DEN-f : Denmark, city of Fynn
NL-n : the Netherlands, Nijmegen (analogue)

Otten et al., Ann Oncol 2013

Figure 9.7
Cumulative risk of false-positive recall for various scenarios (lines, rates originating from IARC Handbooks of Cancer Prevention. Studies (black dots), cf. supplementary Table 2, available at Annals of Oncology online)

9.6 Summary

- While trend studies into the incidence of disease tackle the situation at population level, there is also a demand for individual risk estimates. "Everything depends on participating and referred women being given the correct information by the healthcare professionals involved" see a submitted comment in response to Verbeek et al, 2013. The answer is as follows: A 50-year-old woman who is about to commence the series of 13 mammographic screening tests that will end when she turns 75, will face the following: a 6.9% chance of one carcinoma being detected during screening; a 7.3% chance of a false-positive referral, and 2.9% chance of an interval cancer.

- An evaluation of national and regional screening data has yielded information on the extent of intended and unintended effects of screening. It would be useful to express 'performance' in terms of a single unit of measurement or as a number, to allow comparisons to be made over time, between regions, or within subgroups. The SOR (or Screenings Odds Ratio) was introduced in the XIth NETB report (2005), to meet this very need. The SOR for the 15% to 20% of participants with dense mammographic patterns is markedly lower than it is for women with lucent breast patterns. Following the completion of the transition to full digital screening, it is recommended that similar SOR studies take place in the Netherlands.

- Next, we focused on another performance measure that places greater emphasis on anticipated mortality reduction. Epidemiological information on detection rates and interval cancer rates can be used to estimate the length of the preclinically detectable phase and the lead time. As improving screening tests enable us to discover and treat carcinomas at ever earlier points in their development, relative to the moment at which they would give rise to symptoms, the more likely it is that death from mammary carcinoma will ultimately be en-

tirely preventable. A clear relationship has been found between lead time and mammographic density.

- A cross-sectional data analysis at aggregated population level and individual longitudinal data analysis can generate information of relevance to policymakers, as well as background information for all those who are considering whether or not to participate in screening. Details of the significance of mammographically dense breast patterns are shown above. A similar type of evaluation is important with regard to issues such as co-morbidity, breast cancer in the family, socioeconomic status (SES), and urban/rural or other regional characteristics. This has placed the topic of risk stratification firmly on the agenda.

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10

Discursive summary

Cancer is the number one cause of death in the Netherlands. The most common form of cancer in women is breast cancer. Twenty-nine percent of all cancers in women are forms of breast cancer. In the late 1980s, women in the Netherlands had a "lifetime" risk of almost 5% of dying from breast cancer.
Over the past twenty-five years there has been a steady improvement in the effectiveness of breast cancer treatment. The introduction of breast cancer screening meant that increasing numbers of women could be diagnosed at ever earlier stages. Randomised trials and observational studies have conclusively proven that early treatment is more effective than late treatment. The risk of metastasis, which cannot be cured, is considerably smaller in the case of small tumours than it is with large tumours. If the tumour is surgically removed while it is still small, this reduces risk of metastasis. Improvements in treatment are helping to increase the cure rate for patients with metastases (and micrometastases). Depending on the age of the patient, these have about the same effect on survival as early detection.

There is an ongoing debate about the pros and cons of breast cancer screening. And rightly so. The Dutch programme costs nearly 65 million euros per year, i.e. 64 euros per screening test. Nearly 1.3 million women receive an invitation, which means that 31% of the female population belongs to the target population. If these women are asked to consider an invitation to a free screening test, they are entitled to understand the full implications of their decision. Hence the need for a more comprehensive NETB report giving details of the main pros and cons involved. In 2014, this 13th evaluation report presents the results of the 15 million screening tests that have been carried out in the Netherlands since the start of the screening programme in 1990.

While just as many screens have, by now, been carried out in other countries, the level at which we are capable of evaluating the Dutch programme is quite exceptional. The parameters involved include participation rate, referrals, detection rates and stages of diagnosis. The infrastructure associated with individual invitations in the Netherlands, which enables data (with the individual's consent) to be linked to data from the screening files, the Cancer Registry and Statistics Netherlands (more than 95% complete follow-up), makes it possible to evaluate the most important measures of outcome. In this way, a number of crucial questions can be asked and answered. How much of the decline in breast cancer mortality in the Netherlands is due to early detection and treatment? How many breast cancers are missed during screening? How many of the women diagnosed with (and treated for) breast cancer would have remained undiagnosed (and untreated) if they had not participated in the screening programme?
A nationwide link-up made it possible, for the first time, to measure the effects in those women who were screened in 2004-2009, for a period of up to two years after their last invitation. The screening programme also underwent some major changes. These involved a reorganisation into five screening regions, changes in the radiologists' groups who evaluate screening mammograms, and the complete transition to digital screening.

In the period from 1990 to 2011, 80% of the women invited accepted the invitation. Initially, only 0.8% were referred for further testing. This currently stands at 2.1%, which is still a very modest referral rate by in-

ternational standards. Three obvious reasons can be given for this change over time: the introduction of screening for women aged 69-74, a deliberate policy of referring more women with subtle mammographic abnormalities (prompted by a study into how to optimise the programme [NETB, 2002]), and the introduction of digital screening.
Since 2007, there has been a slight decrease in participation rate, from 82.4% to 79.6% in 2012. We have not been able to identify a clear cause for this. The participation rate stabilised for the first time in 2012, among the newly invited group of women (aged 49-51). An issue that is more important than the participation rate itself is whether or not Dutch women are in a position to make a properly informed choice about whether or not to participate. A random sample survey has shown that this was indeed the case: Eighty-eight percent made a well-informed choice (Van Agt et al, 2012).

Throughout the evaluation period, a total of more than 78,000 cases of breast cancer were detected by screening. Nearly 80% of these cancers are invasive, only 2 cm or less in diameter, or involve a non-invasive form of breast cancer. Forty percent are actually invasive tumours 1 cm or less in diameter, or non-invasive tumours, which cannot be detected by palpation. Moreover, 75% of invasive tumours show no metastasis to the lymph nodes. We also see that, since 2001, the rising trend in the incidence of lymph node positive (N+) tumours (age 49-69) has flattened out, while the incidence of lymph node-negative (N-) tumours continues to increase. In general, the incidence of breast cancer in the Netherlands (independent of the screening programme) is increasing by about 1.4% per year, due to changes in risk factors.
After the implementation stage of the screening programme, 88% of all screens involve subsequent screening tests (in women who have already been screened). In this summary, we want to focus primarily on these subsequent screening tests (conducted within the standard period of 2.5 years after a previous screening). In the most recent period (2007-2011), nearly 4 million regular subsequent screening tests have been conducted. The referral rate increased slightly from 1.5% to 1.7%, while breast cancer detection per 1,000 screened individuals rose from 5 to 6. The increase mostly involves small invasive tumours (T1a,b; 1 cm or less) and non-invasive tumours (DCIS).
There is a 33% chance that breast cancer will be detected in women who are referred (and who participated in previous screens). In the recent past, this has remained fairly stable. The introduction of digital screening initially led to a sharp increase in the number of referrals. In two-thirds of those women who have been referred and found not to have breast cancer, this disease can now be excluded with a high degree of certainty, using only non-invasive (imaging) diagnostics.

The goal of screening is to draw a sharp distinction between individuals who are at high risk of the disease (who need to be referred for (legitimate) further diagnosis), and individuals who are at relatively low risk, who should not be referred at this point in time. Referring more women can lead to more early detection and treatment of breast cancer. However, referring too many women leads to anxiety and unnecessary diagnostic assessment in women who are at low risk. The latter situation can be prevented by referring relatively few women. However, this also prevents the possible early detection of breast cancer in women who are at risk, and who stand to benefit from early treatment. In the Netherlands, there is a relatively high threshold for referral. This is due to the centralised training courses associated with accreditation for the Dutch screening programme, to the radiologists themselves, and to feedback about women who have been referred and about those who have not. How well is the Dutch breast cancer screening programme currently performing in this regard?

In *subsequent screening tests* carried out from 2004 to 2009, 984 of every 1,000 women screened were correctly given good news ("In your case, no evidence of breast cancer has been found"). In another five women, further diagnosis revealed the presence of breast cancer. Another three subjects are referred for suspected cancer which, following a needle biopsy, is found to be benign ("false-positive biopsy") and six others found to be benign after additional imaging only. In a further two women, breast cancer is detected in the two years following the mammogram.
Following negative screening results, not all of the breast cancers discovered in the subsequent screening interval are cases that were 'missed at screening'. Some will be breast cancers that, during the last screening test, were not yet detectable using existing techniques. In the intervening period, these cancers will have grown to the point at which they can be detected. In the Dutch screening programme, test sensitivity (a test's ability to actually detect the presence of breast cancer) is currently 88% or above. This has increased slightly with the advent of digital screening. Test specificity (the performance of the Dutch screening programme in terms of not referring women who do not have breast cancer for further testing) is 99%, which is a very high level. This means that referred women are 200 times more likely to have breast cancer than non-referred women.

These calculations and conclusions were made possible by the large-scale link-up of individual screening

files to data from the Netherlands Cancer Registry of the Comprehensive Cancer Centre of the Netherlands (IKNL), which was a very time-consuming and labour-intensive exercise. However, this work made it possible to analyse data on nearly 12,000 women who were diagnosed with breast cancer in the period between two screening tests (interval cancer). Over time, the interval cancer rate per 2,000 woman-years "at risk" has increased slightly, from 2.0 to 2.3. However, given that the risk of breast cancer has gradually risen, a slight increase in the number of cases of breast cancer – even in a screening interval – is to be expected. It appears that programme sensitivity ("how well is the two-year programme performing?") has stabilised, and that – in recent years – it has even improved slightly.

What are the ultimate benefits of this policy, in terms of breast cancer mortality? And is there any way to measure this? Fortunately, breast cancer mortality in women has fallen in recent years, both in younger individuals and in middle-aged and elderly women. From 1969 until the start of the breast cancer screening programme in the Netherlands, however, there was a visible increase in mortality in the age group that today is invited to participate in population screening. Yet trend analyses like this cannot be used to identify the underlying causes of this phenomenon. In more sophisticated analyses at local authority level, we have concluded that the limited (0.3%) annual increase in breast cancer mortality among women aged 55 to 74 has now changed into a significant (1.7%) annual decline, and that the tipping point for every local authority in the Netherlands occurred immediately after the start of local screening (Otto et al, 2003).
If we narrow down the focus even further, i.e. to the level of the individual, we find that women in the Netherlands who have been screened are only half as likely to die of breast cancer (due to earlier diagnosis and treatment) as those who do not participate in the screening programme. This figure has already been adjusted to allow for the possibility of a higher breast cancer mortality risk among non-participating women. Indeed, clinical studies conducted in the Netherlands have shown that "participation in screening" is an independent (positive) prognostic factor (Mook et al, 2011). That is to say, women whose breast cancer is detected during screening have more favourable survival rates than those with tumours of the same stage that are detected in clinical settings.

Surely, over this period, there have also been improvements in the treatment of breast cancer? The above-mentioned analyses clearly reveal the specific effect of screening, which leads to the earlier treatment of smaller breast tumours. Another method of analysis involves the simultaneous modelling of screening and treatment in the Dutch population. This is based on randomised controlled trials (both for screening and treatment) and on treatments and screens that were actually administered. In the 50-74 age group, it has been shown that improved treatments have cut mortality by at least 15%, while earlier detection accounts for 21%. For the entire female population between the ages of 0 and 100, it is estimated that improved treatment currently prevents 700 deaths per year (including relatively young individuals). The corresponding figure for participation in the national screening programme (in women aged 50-74), is 775 prevented deaths per year. Despite the increased incidence of breast cancer, a Dutch woman's risk of dying of this disease has now fallen to less than 3%.

What are the most important harms of mammography screening? The detection of breast cancer in cases where, in retrospect, this was not necessary, is one major harm. An effective screening is one that brings forward the time of diagnosis. However, this also means that very slow-growing breast cancers may be detected that would not otherwise have come to light (for example, because the woman in question would previously have died of another disease). In statistical terms, this means that there is always a significant rise in the number of breast cancers detected at the start of screening. When the target group in question is no longer invited for screening, this will be offset by a fall in the number of clinically diagnosed breast cancers. For this purpose, the programme must be in a "steady state" period. Accordingly, for the Netherlands, it was not until 2006 that the true extent of what, in retrospect, proved to be unnecessarily detected cases of cancer could be calculated. This amounted to 3% of all breast cancers diagnosed that year in the Netherlands, or up to 10% of the cases of breast cancer that were detected by screening.
Most of these diagnoses involve non-invasive carcinoma (DCIS), of which a large part might be overdiagnosed. This is because, on average, such cancers take a long time to become invasive. Moreover, the majority of the least malignant variants never go on to develop into invasive (and therefore dangerous) tumours. Digitisation resulted in a sharp increase in DCIS, which now accounts for 20-25% of all the breast cancers detected. Some of these lesions, especially those that occur at a relatively young age, can progress to a fatal invasive form. Here, there is a clear case for intervention. However, in most cases of DCIS, the merits of intervention remain unclear. Ideally, therefore, a randomised trial should be started in which not all forms of DCIS detected by screening need to be treated immediately, and are instead actively monitored.

In 2012, an independent committee in the United Kingdom reported on the strength of the evidence in favour of screening for breast cancer (in the UK). The conclusion was clear: significant health gains can be achieved. There are also a number of harms (Marmot et al, 2012). For many women, the pros outweigh the cons. The committee found that a number of important published studies were not sufficiently robust, as these had either used very high estimates of overdiagnosis, or very low estimates of effect. These studies presented relationships between pros and cons that were mainly based on past randomised trials, that were calculated prior to the start of the programme in the United Kingdom (with more referrals and less frequent screens), and that largely excluded current results obtained in ongoing breast cancer screening programmes from the analyses.

The results of 15 million screens in the Netherlands that are presented here, together with an independent evaluation of key indicators and key outcomes, indicate a favourable balance between the pros and cons of breast cancer screening in the Netherlands. The Health Council of the Netherlands endorses this finding in its recently published evaluation, which addresses the Dutch results obtained by the National Evaluation Team for Breast Cancer Screening in the Netherlands. We advise women to make their own judgements on this matter. Screening will have no repercussions for most of the women who participate. A rather small proportion will be affected by harms, but a slightly larger proportion will gain some very important benefits. At the time that the invitations are issued, it is not possible to predict who belongs to which group.

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Appendices

As of 1 January 2010, 21 screening organisations providing cervical and breast cancer screening were merged into five new foundations for cancer screening, each focused on a specific region: North, East, South, South-West and Mid-West.

Cancer screening foundation	Reading units from 2012* onwards
Northern Regional Population Screening Organisation Queridolaan 5 Postbus 425 9700 AK Groningen	Groningen Meppel
Eastern Regional Population Screening Organisation Zutphenseweg 51 7418 AH Deventer Postbus 2107 7420 AC Deventer	Apeldoorn Doetinchem Nijmegen
SouthernRegional Population Screening Organisation • Eindhoven site Postbus 690 5600 AR Eindhoven Larixplein 5 5616 VB Eindhoven • Maastricht site Australiëlaan 12 6199 AA Maastricht-Airport	Maastricht Breda Eindhoven Venlo
South-Western Regional Population Screening Organisation Postbus 91163 3007 MD Rotterdam Maasstadweg 124 3079 DZ Rotterdam	Den Haag (tot 2013: Leiden) Dordrecht Goes Rotterdam
Mid-West Regional Population Screening Organisation Hoogoorddreef 54-e 1101 BE Amsterdam	Amsterdam Amsterdam Utrecht

* once totalled 28 reading units

	1990-1997[1]	1998-2006	2007	2008	2009	2010	2011	1990-2011
Doelgroep per jaar (x 1000)[2] *Targeted per year (x 1000)* [2]	733 - 813	1.021-1.164	1.183	1.204	1.227	1.250	1.275	–
Uitnodigingen *Invitations*	4.071.120	9.210.600	1.108.163	1.120.828	1.121.185	1.193.347	1.230.577	19.055.820
Totale deelname *Overall participation*	78,2%	80,7%	82,4%	82,0%	81,5%	80,8%	80,1%	80,0%
Heruitnodiging binnen 24 ± 2 maanden *Re-invitation within 24 ± 2 months*	–	–	78,3%	73,9%	75,2%	72,7%	71,8%	73,8%
Deelnametrouw[3] *Re-attendance* [3]	91,8%	92,6%	93,8%	93,5%	93,1%	92,6%	92,5%	92,7%
Screeningsonderzoeken[4] *Screen examinations* [4]	3.128.241	7.371.443	911.547	918.578	911.441	961.765	986.885	15.189.900
- eerste / *initial*	47%	14%	12%	12%	12%	12%	11%	20%
- vervolg / *subsequent* < 2,5 jaar	51%	80%	84%	84%	84%	84%	84%	75%
- vervolg / *subsequent* >= 2,5 jaar	1,6%	5,9%	4,0%	4,1%	4,0%	4,4%	4,7%	4,5%
- digitaal / *digital* (% van totaal / *of total*)	–	1,2%	7%	10%	42%	94%	100%	17%
Gemiddeld screeningsinterval (maanden) *Mean individual screen interval (months)*	24,1	24,3	24,6	24,7	24,7	24,7	23,9	24,3
Einduitslag screening bekend *Final screen result known*	97,7%	98,3%	97,8%	99,0%	98,9%	98,2%	98,9%	98,9%
Verwijsadviezen *Recalls (referral recommendations)*	30.901	97.010	16.414	16.752	17.413	19.406	21.129	219.025
Verwijscijfer per 1000 gescreende vrouwen *Recall (referral) rate per 1000 women screened*	9,9	13,2	18,0	18,2	19,1	20,2	21,4	14,4
Verwijsadviezen opgevolgd (v.a. 2002) *Response to recall (referral) (as of 2002)*	–	99,5%	99,7%	99,7%	99,7%	99,8%	99,7%	99,7%
Fout-positieve uitslagen per 1000 gescreende vrouwen *False positive results per 1000 women screened*	5,1	8,3	12,5	12,7	13,4	14,3	15,2	9,3
- na niet-invasieve diagnostiek per 1000 gescreende vrouwen *after non-invasive assessment per 1000 women screened*	2,4	4,8	8,0	8,3	6,8	9,0	9,9	5,2
- na invasieve diagnostiek per 1000 gescreende vrouwen *after invasive assessment per 1000 women screened*	2,5	3,2	4,2	4,2	3,9	5,0	5,1	3,3
Screeningscarcinomen *Screen-detected cancers*	14.966	36.289	4.999	5.110	5.190	5.667	6.108	78.329
Borstkankerdetectie per 1000 gescreende vrouwen *Breast cancer detection per 1000 women screened*	4,8	4,9	5,5	5,6	5,7	5,9	6,2	5,2
PVW[5] verwijsadvies *PPV*[5] *recall (referral recommendation)*	48%	37%	30%	31%	30%	29%	29%	36%
In-situ carcinoom (DCIS) *Ductal carcinoma in situ*	14,3%	14,3%	15,1%	14,8%	17,3%	20,4%	19,5%	15,4%
Invasieve carcinomen *Invasive breast cancers*	83,7%	84,1%	83,2%	84,3%	81,2%	78,7%	77,9%	82,9%
Tumormorfologie onbekend *Tumour morfology unknown*	2,1%	1,6%	1,7%	0,9%	1,6%	0,9%	2,5%	1,7%
(Gemiddelde) Totale kosten per jaar (mln €) *(Average) Annual total cost (million €)*	18,5	39,0	49,1	50,9	51,7	55,0	57,7	34,7
Kosten per onderzoek (€) *Cost per screen examination (€)*	47,43	45,03	53,77	55,39	56,76	56,38	57,97	48,41
Invasieve borstkankerincidentie /100 000 (ESR)[6] *Invasive breast cancer incidence /100 000 (ESR)* [6]	279,6	306,7	329,5	330,4	325,3	330,1	339,0	302,3
In-situ borstkankerincidentie /100 000 (ESR)[6] *In situ breast cancer incidence /100 000 (ESR)* [6]	26,5	40,2	47,6	49,1	56,3	64,3	63,7	38,8
Borstkankersterfte /100 000 (ESR)[6] *Breast cancer mortality /100 000 (ESR)* [6]	91,6	76,7	67,0	70,4	64,7	65,2	64,6	79,7
Borstkankersterfte t.o.v. 1986/88 (50-74 jaar) *Breast cancer mortality comp. with 1986/88 (50-74 years)*	-	-	-28,8%	-25,2%	-31,3%	-30,7%	-31,3%	
Borstkankersterfte t.o.v. 1986/88 (55-79 jaar)[7] *Breast cancer mortality comp. with 1986/88 (55-79 years)* [7]	-	-	-28,1%	-24,4%	-31,0%	-29,9%	-31,3%	

LETB/*NETB*, 2014

[1] Leeftijd 49-68 jaar; vanaf 1998 49-75 - *Ages 49-68 years; as of 1998 49-75 years*
[2] Bron: CBS - *Source: Statistics Netherlands*
[3] Berekend over laatste twee screeningsronden - *Calculated over last two screening rounds*
[4] Uitgevoerde onderzoeken in verslagperiode (ongeacht de uitnodigingsdatum) - *Performed screening examination in reported time period (irrespective of invitation date)*
[5] PVW: positief voorspellende waarde - *PPV: positive predictive value*
[6] Voor leeftijdscategorie 50-74 jaar (Bron: www.ikcnet.nl; ESR = Europees Standaardcijfer) - *For age category 50-74 years (source: www.ikcnet.nl; ESR = European Standardised Rate)*
[7] Rekening houdend met later optredend effect (*lag time*) - *Taking delayed effect (lag time) into account*

Jaar *Year*	Leeftijd Age	Uitnodigingen *Invitations* Uitgenodigd *Invited* N	Onderzocht *Screened* N	Opkomst *Participation* %	Herinneringen *Reminders* Uitgenodigd *Invited* N	Onderzocht *Screened* N	van alle uitnod. *of all invitations* %	van *of reminders* %	Totaal *Total* Onderzocht *Screened* N	Deelname *Participation* %
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%
2008	49-75	1.120.828	902.179	80,5%	102.813	16.706	1,5%	16,2%	918.885	82,0%
2009	49-75	1.121.185	897.308	80,0%	95.152	16.175	1,4%	17,0%	913.483	81,5%
2010	49-75	1.193.347	944.870	79,2%	109.519	18.870	1,6%	17,2%	963.740	80,8%
2011	49-75	1.230.577	964.490	78,4%	119.462	21.581	1,8%	18,1%	986.071	80,1%
2012	49-75	1.266.559	986.084	77,9%	123.110	22.560	1,8%	18,3%	1.008.644	79,6%
2012	49	72.376	52.284	72,2%	13.783	3.076	4,3%	22,3%	55.360	76,5%
2012	50-54	299.758	227.847	76,0%	37.320	6.443	2,1%	17,3%	234.290	78,2%
2012	55-59	267.947	211.509	78,9%	22.852	4.613	1,7%	20,2%	216.122	80,7%
2012	60-64	255.557	204.040	79,8%	19.594	3.762	1,5%	19,2%	207.802	81,3%
2012	65-69	211.236	169.375	80,2%	15.364	2.809	1,3%	18,3%	172.184	81,5%
2012	70-74	158.440	120.213	75,9%	14.006	1.839	1,2%	13,1%	122.052	77,0%
2012	> 74	1.245	816	65,5%	191	18	1,4%	9,4%	834	67,0%
1990-2012	49	1.172.068	888.188	75,8%	167.645	33.586	2,9%	20,0%	921.774	78,6%
1990-2012	50-54	5.187.875	4.051.800	78,1%	623.552	101.603	2,0%	16,3%	4.153.403	80,1%
1990-2012	55-59	4.545.830	3.635.193	80,0%	467.222	75.512	1,7%	16,2%	3.710.705	81,6%
1990-2012	60-64	3.980.003	3.188.267	80,1%	404.670	60.511	1,5%	15,0%	3.248.778	81,6%
1990-2012	65-69	3.215.230	2.518.920	78,3%	354.318	45.639	1,4%	12,9%	2.564.559	79,8%
1990-2012	70-74	2.098.973	1.540.795	73,4%	261.085	24.910	1,2%	9,5%	1.565.705	74,6%
1990-2012	> 74	24.093	14.520	60,3%	4.453	308	1,3%	6,9%	14.828	61,5%
1990-2012	49-75	20.224.072	15.837.683	78,3%	2.282.945	342.069	1,7%	15,0%	16.179.752	80,0%
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%
1990-2012	49-75	20.322.379	15.909.576	78,3%	2.290.488	343.081	1,7%	15,0%	16.252.657	80,0%

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IV.1 – Number of screening examinations by year

Jaar *Year*	Leeftijd *Age*	1e onderzoeken *Initial screens*		Vervolgonderzoeken *Subsequent screens*						Alle onderzoeken *All screens*	Groei *Change*
				< 2,5 jaar/*years*		³ 2,5 jaar/*years*		Totaal / *total*			
		N	%	N	%	N	%	N	%	N	%
1990-1997	49-69	1.478.573	47,3%	1.598.075	51,1%	51.593	1,6%	1.649.668	52,7%	3.128.241	
1998	49-75	125.881	19,0%	503.079	75,9%	33.865	5,1%	662.825	7,3%	536.944	
1999	49-75	130.495	17,5%	540.600	72,7%	72.808	9,8%	743.903	12,2%	613.408	+14,2%
2000	49-75	125.432	15,8%	588.392	74,2%	79.346	10,0%	793.170	6,6%	667.738	+8,9%
2001	49-75	109.693	13,6%	647.030	80,5%	47.002	5,8%	803.725	1,3%	694.032	+3,9%
2002	49-75	113.749	13,6%	674.538	80,8%	46.691	5,6%	834.978	3,9%	721.229	+3,9%
2003	49-75	111.912	12,9%	713.984	82,5%	39.793	4,6%	865.689	3,7%	753.777	+4,5%
2004	49-75	115.101	12,9%	733.396	82,5%	40.333	4,5%	888.830	2,7%	773.729	+2,6%
2005	49-75	111.187	12,5%	744.855	83,5%	36.257	4,1%	892.299	0,4%	781.112	+1,0%
2006	49-75	112.079	12,6%	738.464	83,3%	35.482	4,0%	886.025	-0,7%	773.946	-+0,9%
2007	49-75	109.486	12,0%	765.455	84,0%	36.606	4,0%	911.547	2,9%	802.061	+3,6%
2008	49-75	107.651	11,7%	773.541	84,2%	37.386	4,1%	918.578	0,8%	810.927	+1,1%
2009	49-75	105.313	11,6%	769.379	84,4%	36.749	4,0%	911.441	-0,8%	806.128	-+0,6%
2010	49-75	111.617	11,6%	808.200	84,0%	41.948	4,4%	961.765	5,5%	850.148	+5,5%
2011	49-75	110.522	11,2%	830.272	84,1%	46.090	4,7%	986.884	2,6%	876.362	+3,1%

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IV.2a – Screening results 1990-2011 all screening examinations

Jaar *Year*	Leeftijd *Age*	Onderzoeken *Screens*	Verwijsadviezen *Referrals*		Aanvullende diagnostiek *Diagnostic assessment*				Fout-positief *False-positive*		Pos.voorsp.waarde *Pos.predict.value*	Borstkanker *Breast cancer* a.g.v. screening *screen-detected*		DCIS		invasief *invasive*		onbekend *unknown*	
					Follow-up onbekend *Follow-up unknown*	Beeld-vormend *Additional imaging*	Cytologie *Cytology*	Histologie *Histology*	o.b.v. non-invasief *non-invasive*	o.b.v. invasief *invasive*									
		N	N	per 1000	%	%	%	%	per 1000	per 1000	%	N	per 1000	N	per 1000	N	per 1000	N	per 1000
1990-1997	49-69	3.128.241	30.901	9,9	2,3%	24,6%	4,3%	68,8%	2,4	2,5	48,4%	14.966	4,8	2.132	0,7	12.510	4,0	324	0,1
1998	49-75	662.824	6.530	9,9	1,7%	32,1%	5,0%	61,4%	3,1	2,2	44,0%	2.870	4,3	449	0,7	2.390	3,6	31	0,0
1999	49-75	743.903	8.200	11,0	2,4%	31,6%	5,0%	61,2%	3,5	2,4	44,3%	3.634	4,9	480	0,6	3.099	4,2	55	0,1
2000	49-75	793.170	9.289	11,7	1,9%	28,9%	4,4%	63,7%	3,4	3,0	42,4%	3.937	5,0	538	0,7	3.412	4,3	-13	0,0
2001	49-75	803.725	11.058	13,8	1,8%	38,0%	7,5%	52,6%	5,2	3,2	37,5%	4.151	5,2	598	0,7	3.501	4,4	52	0,1
2002	49-75	834.978	10.885	13,0	1,8%	37,0%	7,2%	54,0%	4,7	3,1	38,0%	4.131	4,9	533	0,6	3.508	4,2	90	0,1
2003	49-75	865.689	11.326	13,1	1,9%	35,9%	6,1%	56,0%	4,7	3,3	37,4%	4.232	4,9	579	0,7	3.499	4,0	154	0,2
2004	49-75	888.830	12.523	14,1	1,4%	31,0%	6,7%	49,5%	4,2	3,1	35,1%	4.399	4,9	660	0,7	3.655	4,1	84	0,1
2005	49-75	892.299	12.910	14,5	2,0%	32,9%	7,2%	45,7%	4,7	2,9	33,7%	4.353	4,9	630	0,7	3.665	4,1	58	0,1
2006	49-75	886.025	14.289	16,1	1,0%	35,6%	6,8%	45,1%	5,6	3,3	32,1%	4.582	5,2	723	0,8	3.792	4,3	67	0,1
2007	49-75	911.547	16.414	18,0	2,2%	44,9%	7,4%	45,7%	8,0	4,2	30,5%	4.999	5,5	754	0,8	4.160	4,6	85	0,1
2008	49-75	918.578	16.752	18,2	1,0%	46,3%	7,3%	45,6%	8,3	4,2	30,5%	5.110	5,6	756	0,8	4.306	4,7	48	0,1
2009	49-75	911.441	17.413	19,1	1,1%	36,0%	5,1%	44,6%	6,8	3,9	29,8%	5.190	5,7	896	1,0	4.212	4,6	82	0,1
2010	49-75	961.765	19.406	20,2	1,7%	44,8%	6,1%	47,4%	9,0	5,0	29,2%	5.667	5,9	1.154	1,2	4.460	4,6	53	0,1
2011	49-75	986.885	21.129	21,4	1,1%	46,8%	6,7%	45,4%	9,9	5,1	28,9%	6.108	6,2	1.194	1,2	4.761	4,8	153	0,2
2011	49	51.980	2.515	48,4	1,2%	53,3%	7,2%	38,3%	25,6	15,4	14,1%	354	6,8	96	1,8	244	4,7	14	0,3
2011	50-54	231.148	5.700	24,7	1,2%	51,6%	7,1%	40,1%	12,6	6,9	19,9%	1.134	4,9	277	1,2	820	3,5	37	0,2
2011	55-59	214.215	3.631	17,0	1,0%	46,4%	5,7%	46,9%	7,8	3,9	30,4%	1.103	5,1	226	1,1	844	3,9	33	0,2
2011	60-64	213.711	3.878	18,1	1,0%	43,0%	6,7%	49,4%	7,7	3,6	36,5%	1.417	6,6	250	1,2	1.142	5,3	25	0,1
2011	65-69	153.534	2.956	19,3	1,0%	41,0%	7,0%	51,0%	7,8	3,7	39,1%	1.157	7,5	199	1,3	935	6,1	23	0,1
2011	70-74	121.006	2.426	20,0	1,4%	42,7%	6,6%	49,3%	8,4	3,6	38,5%	934	7,7	145	1,2	768	6,3	21	0,2
2011	> 74	1.291	23	17,8	0,0%	47,8%	0,0%	52,2%	8,5	2,3	39,1%	9	7,0	1	0,8	8	6,2	0	0,0
1990-2011	49	853.875	21.001	24,6	1,6%	44,3%	6,7%	43,6%	10,8	7,5	19,9%	4.183	4,9	863	1,0	3.182	3,7	138	0,2
1990-2011	50-54	3.929.188	59.280	15,1	1,7%	41,9%	6,9%	46,0%	6,3	4,1	25,9%	15.337	3,9	2.934	0,7	12.080	3,1	323	0,1
1990-2011	55-59	3.497.617	40.371	11,5	1,7%	35,8%	6,0%	53,4%	4,1	2,6	37,7%	15.232	4,4	2.454	0,7	12.578	3,6	200	0,1
1990-2011	60-64	3.045.965	38.837	12,8	1,7%	33,0%	5,5%	57,2%	4,2	2,5	43,2%	16.789	5,5	2.504	0,8	14.042	4,6	243	0,1
1990-2011	65-69	2.395.618	34.043	14,2	1,7%	31,5%	5,5%	58,7%	4,4	2,7	45,5%	15.491	6,5	1.959	0,8	13.314	5,6	218	0,1
1990-2011	70-74	1.446.306	25.140	17,4	1,6%	32,7%	6,1%	56,3%	5,6	3,3	44,2%	11.122	7,7	1.342	0,9	9.599	6,6	181	0,1
1990-2011	> 74	17.073	332	19,4	0,6%	29,8%	6,6%	58,4%	5,6	3,3	48,8%	162	9,5	20	1,2	135	7,9	7	0,4
1990-2011	49-75	15.189.900	219.025	14,4	1,7%	36,7%	6,1%	52,3%	5,2	3,3	35,8%	78.329	5,2	12.076	0,8	64.930	4,3	1.323	0,1

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Erratum: on 18-5-2014 correction of numbers in the third column ('Onderzoeken/*Screens'*), top section.

IV.2b – Screening results 1990-2011 initial screening examinations

Jaar *Year*	Leeftijd *Age*	Onderzoeken *Screens*	Verwijsadviezen *Referrals*		Aanvullende diagnostiek *Diagnostic assessment*				Fout-positief *False-positive*			Borstkanker *Breast cancer*							
					Follow-up onbekend *Follow-up unknown*	Beeld-vormend *Additional imaging*	Cytologie *Cytology*	Histologie *Histology*	o.b.v. non-invasief *non-invasive*	o.b.v. invasief *invasive*	Pos.voorsp.waarde *Pos.predict.value*	a.g.v. screening *screen-detected*		DCIS		invasief *invasive*		onbekend *unknown*	
		N	N	per 1000	%	%	%	%	per 1000	per 1000	%	N	per 1000	N	per 1000	N	per 1000	N	per 1000
1990-1997	49-69	1.478.573	19.360	13,1	2,3%	22,8%	4,3%	70,9%	3,0	3,8	46,6%	9.030	6,1	1.286	0,9	7.593	5,1	151	0,1
1998	49-75	125.881	1.961	15,6	1,9%	33,7%	5,3%	59,3%	5,3	4,8	33,8%	663	5,3	119	0,9	544	4,3	0	0,0
1999	49-75	130.495	2.237	17,1	2,5%	35,9%	5,0%	57,0%	6,1	4,7	34,6%	775	5,9	116	0,9	646	5,0	13	0,1
2000	49-75	125.432	2.324	18,5	2,5%	31,8%	5,1%	59,7%	5,8	6,2	31,8%	740	5,9	129	1,0	614	4,9	-3	0,0
2001	49-75	109.693	2.607	23,8	2,1%	42,8%	9,1%	46,0%	10,1	7,1	25,5%	665	6,1	122	1,1	527	4,8	16	0,1
2002	49-75	113.749	2.479	21,8	2,0%	42,5%	7,9%	47,6%	9,2	6,7	25,2%	624	5,5	89	0,8	506	4,4	29	0,3
2003	49-75	111.912	2.537	22,7	2,4%	39,6%	6,7%	51,3%	8,9	7,8	23,6%	600	5,4	102	0,9	482	4,3	16	0,1
2004	49-75	115.101	2.961	25,7	1,4%	32,6%	6,7%	44,7%	8,2	7,8	21,7%	642	5,6	115	1,0	508	4,4	19	0,2
2005	49-75	111.187	2.933	26,4	1,9%	37,3%	8,1%	37,6%	9,7	7,0	19,7%	579	5,2	106	1,0	457	4,1	16	0,1
2006	49-75	112.079	3.318	29,6	1,1%	41,0%	6,3%	38,6%	12,0	7,9	18,7%	620	5,5	124	1,1	483	4,3	13	0,1
2007	49-75	109.486	3.766	34,4	2,4%	51,7%	6,7%	39,1%	17,5	10,2	17,0%	641	5,9	111	1,0	514	4,7	16	0,1
2008	49-75	107.651	4.145	38,5	1,2%	53,1%	8,1%	37,7%	20,2	11,8	15,8%	656	6,1	127	1,2	511	4,7	18	0,2
2009	49-75	105.313	4.402	41,8	1,4%	43,0%	5,2%	35,5%	17,9	10,9	14,9%	656	6,2	130	1,2	500	4,7	26	0,2
2010	49-75	111.617	5.180	46,4	1,8%	51,8%	7,0%	39,4%	23,9	14,7	14,9%	774	6,9	199	1,8	552	4,9	23	0,2
2011	49-75	110.519	5.398	48,8	1,3%	52,9%	7,4%	38,3%	25,6	15,4	14,8%	798	7,2	203	1,8	556	5,0	39	0,4
2011	49	51.972	2.515	48,4	1,2%	53,3%	7,2%	38,3%	25,6	15,4	14,1%	354	6,8	96	1,8	244	4,7	14	0,3
2011	50-54	54.388	2.645	48,6	1,4%	53,0%	7,8%	37,8%	25,5	15,4	14,4%	382	7,0	97	1,8	263	4,8	22	0,4
2011	55-59	2.216	125	56,4	3,2%	53,6%	4,8%	38,4%	29,8	14,4	18,4%	23	10,4	3	1,4	19	8,6	1	0,5
2011	60-64	1.177	70	59,5	2,9%	42,9%	7,1%	47,1%	25,5	15,3	28,6%	20	17,0	2	1,7	19	16,1	-1	-0,8
2011	65-69	500	27	54,0	0,0%	37,0%	7,4%	55,6%	18,0	14,0	40,7%	11	22,0	3	6,0	6	12,0	2	4,0
2011	70-74	264	16	60,6	6,3%	31,3%	6,3%	56,3%	15,2	11,4	50,0%	8	30,3	2	7,6	5	18,9	1	3,8
2011	> 74	2	0	-	-	-	-	-	-	-	-	0	-	0	-	0	-	0	-
1990-2011	49	844.261	20.946	24,8	1,6%	44,3%	6,7%	43,5%	10,9	7,6	19,9%	4.162	4,9	860	1,0	3.164	3,7	138	0,2
1990-2011	50-54	1.258.223	28.443	22,6	1,9%	41,3%	6,8%	46,7%	9,2	7,1	22,5%	6.405	5,1	1.247	1,0	4.977	4,0	181	0,1
1990-2011	55-59	361.748	5.350	14,8	2,7%	27,1%	4,9%	63,9%	4,0	4,1	41,5%	2.222	6,1	326	0,9	1.891	5,2	5	0,0
1990-2011	60-64	321.042	5.017	15,6	2,3%	21,9%	3,8%	71,3%	3,4	4,0	49,5%	2.483	7,7	332	1,0	2.106	6,6	45	0,1
1990-2011	65-69	242.368	4.449	18,4	2,2%	19,4%	3,2%	74,6%	3,5	4,1	55,7%	2.480	10,2	250	1,0	2.204	9,1	26	0,1
1990-2011	70-74	49.387	1.363	27,6	2,5%	25,5%	4,7%	66,4%	6,9	5,8	50,6%	689	14,0	62	1,3	632	12,8	-5	-0,1
1990-2011	> 74	1.659	40	24,1	0,0%	20,0%	10,0%	72,5%	4,8	6,6	55,0%	22	13,3	1	0,6	19	11,5	2	1,2
1990-2011	49-75	3.078.688	65.608	21,3	1,9%	37,8%	6,1%	51,3%	8,0	6,3	28,1%	18.463	6,0	3.078	1,0	14.993	4,9	392	0,1

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IV.2c – Screening results 1990-2011 regular subsequent screening examinations

Jaar *Year*	Leeftijd *Age*	Onderzoeken *Screens*	Verwijsadviezen *Referrals*		Aanvullende diagnostiek *Diagnostic assessment*				Fout-positief *False-positive*		Pos.voorsp.waarde *Pos.predict.value*	Borstkanker *Breast cancer* a.g.v. screening *screen-detected*		DCIS		invasief *invasive*		onbekend *unknown*	
					Follow-up onbekend *Follow-up unknown*	Beeld-vormend *Additional imaging*	Cytologie *Cytology*	Histologie *Histology*	o.b.v. non-invasief *non-invasive*	o.b.v. invasief *invasive*									
		N	N	per 1000	%	%	%	%	per 1000	per 1000	%	N	per 1000	N	per 1000	N	per 1000	N	per 1000
1990-1997	49-69	1.593.817	10.993	6,9	2,4%	27,8%	4,4%	65,6%	1,9	1,3	51,3%	5.642	3,5	815	0,5	4.672	2,9	155	0,1
1998	49-75	503.079	4.046	8,0	1,8%	32,3%	4,7%	61,4%	2,6	1,5	47,4%	1.918	3,8	295	0,6	1.599	3,2	24	0,0
1999	49-75	540.600	4.690	8,7	2,6%	31,2%	5,2%	61,3%	2,7	1,8	46,2%	2.166	4,0	291	0,5	1.845	3,4	30	0,1
2000	49-75	588.392	5.550	9,4	1,7%	29,1%	4,1%	64,1%	2,7	2,2	44,6%	2.478	4,2	321	0,5	2.162	3,7	-5	0,0
2001	49-75	647.030	7.475	11,6	1,7%	37,1%	6,9%	54,3%	4,2	2,4	41,0%	3.066	4,7	425	0,7	2.607	4,0	34	0,1
2002	49-75	674.538	7.556	11,2	1,5%	36,0%	7,0%	55,5%	4,0	2,4	41,3%	3.123	4,6	404	0,6	2.669	4,0	50	0,1
2003	49-75	713.984	8.091	11,3	1,8%	35,4%	5,9%	57,0%	4,0	2,5	41,4%	3.352	4,7	445	0,6	2.786	3,9	121	0,2
2004	49-75	733.396	8.736	11,9	1,4%	30,9%	6,7%	50,8%	3,5	2,3	39,3%	3.429	4,7	502	0,7	2.877	3,9	50	0,1
2005	49-75	744.855	9.177	12,3	2,0%	31,9%	6,8%	48,1%	3,8	2,2	37,8%	3.469	4,7	489	0,7	2.947	4,0	33	0,0
2006	49-75	738.464	10.093	13,7	0,9%	34,3%	6,5%	47,2%	4,6	2,5	36,2%	3.657	5,0	553	0,7	3.057	4,1	47	0,1
2007	49-75	765.455	11.646	15,2	2,1%	43,0%	7,5%	47,6%	6,4	3,2	34,5%	4.013	5,2	597	0,8	3.355	4,4	61	0,1
2008	49-75	773.541	11.634	15,0	0,9%	44,3%	6,9%	48,1%	6,6	3,0	35,4%	4.117	5,3	597	0,8	3.494	4,5	26	0,0
2009	49-75	769.379	12.070	15,7	0,9%	33,4%	5,1%	47,8%	5,2	2,8	35,1%	4.235	5,5	716	0,9	3.469	4,5	50	0,1
2010	49-75	808.200	13.076	16,2	1,6%	42,0%	5,7%	50,7%	6,7	3,5	34,9%	4.562	5,6	900	1,1	3.630	4,5	32	0,0
2011	49-75	830.276	14.427	17,4	1,0%	44,7%	6,3%	47,9%	7,7	3,6	34,0%	4.905	5,9	924	1,1	3.883	4,7	98	0,1
2011	49	8	0	-	-	-	-	-	-	-	-	0	-	0	-	0	-	0	-
2011	50-54	169.952	2.888	17,0	1,0%	50,3%	6,4%	42,2%	8,5	4,1	24,7%	712	4,2	171	1,0	531	3,1	10	0,1
2011	55-59	199.441	3.180	15,9	0,9%	45,9%	5,6%	47,5%	7,2	3,6	31,4%	997	5,0	207	1,0	760	3,8	30	0,2
2011	60-64	200.468	3.482	17,4	0,9%	43,3%	6,3%	49,6%	7,4	3,4	36,9%	1.285	6,4	235	1,2	1.029	5,1	21	0,1
2011	65-69	144.796	2.652	18,3	1,1%	40,6%	6,9%	51,4%	7,3	3,5	39,6%	1.051	7,3	178	1,2	852	5,9	21	0,1
2011	70-74	114.470	2.202	19,2	1,3%	42,8%	6,7%	49,2%	8,1	3,4	38,6%	851	7,4	132	1,2	703	6,1	16	0,1
2011	> 74	1.141	23	20,2	0,0%	47,8%	0,0%	52,2%	9,6	2,6	39,1%	9	7,9	1	0,9	8	7,0	0	0,0
1990-2011	49	9.478	55	5,8	1,8%	29,1%	10,9%	60,0%	1,7	1,9	38,2%	21	2,2	3	0,3	18	1,9	0	0,0
1990-2011	50-54	2.585.702	29.437	11,4	1,5%	42,5%	7,0%	45,3%	4,8	2,7	29,0%	8.535	3,3	1.624	0,6	6.782	2,6	129	0,0
1990-2011	55-59	2.965.252	31.974	10,8	1,5%	37,3%	6,0%	51,8%	4,0	2,3	37,3%	11.935	4,0	1.965	0,7	9.797	3,3	173	0,1
1990-2011	60-64	2.585.843	30.925	12,0	1,5%	34,7%	5,6%	55,4%	4,1	2,3	42,7%	13.201	5,1	2.024	0,8	11.001	4,3	176	0,1
1990-2011	65-69	2.048.556	27.125	13,2	1,6%	33,3%	5,7%	56,5%	4,3	2,4	44,3%	12.021	5,9	1.591	0,8	10.253	5,0	177	0,1
1990-2011	70-74	1.217.545	19.534	16,0	1,6%	34,4%	6,3%	54,1%	5,4	2,9	42,6%	8.328	6,8	1.055	0,9	7.126	5,9	147	0,1
1990-2011	> 74	12.630	210	16,6	1,0%	33,8%	7,1%	51,9%	5,5	2,7	43,3%	91	7,2	12	1,0	75	5,9	4	0,3
1990-2011	49-75	11.425.006	139.260	12,2	1,5%	36,6%	6,1%	52,5%	4,4	2,5	38,9%	54.132	4,7	8.274	0,7	45.052	3,9	806	0,1

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IV.2d – Screening results 1990-2011 subsequent screening examinations >=2.5 years

Jaar *Year*	Leeftijd *Age*	Onderzoeken *Screens*	Verwijsadviezen *Referrals*		Aanvullende diagnostiek *Diagnostic assessment*				Fout-positief *False-positive*		Pos.voorsp.waarde *Pos.predict.value*	Borstkanker *Breast cancer* a.g.v. screening *screen-detected*		DCIS		invasief *invasive*		onbekend *unknown*	
					Follow-up onbekend *Follow-up unknown*	Beeld-vormend *Additional imaging*	Cytologie *Cytology*	Histologie *Histology*	o.b.v. non-invasief *non-invasive*	o.b.v. invasief *invasive*									
		N	N	per 1000	%	%	%	%	per 1000	per 1000	%	N	per 1000	N	per 1000	N	per 1000	N	per 1000
1990-1997	49-69	51.593	527	10,2	2,3%	25,4%	4,4%	67,7%	2,6	1,9	53,3%	281	5,4	31	0,6	245	4,7	5	0,1
1998	49-75	33.865	523	15,4	0,8%	24,1%	5,9%	69,0%	3,7	3,1	55,3%	289	8,5	35	1,0	247	7,3	7	0,2
1999	49-75	72.808	1.273	17,5	1,8%	25,8%	3,9%	67,9%	4,5	3,1	54,4%	693	9,5	73	1,0	608	8,3	12	0,2
2000	49-75	79.346	1.415	17,8	1,6%	23,3%	4,5%	69,1%	4,1	4,1	50,8%	719	9,1	88	1,1	636	8,0	-5	-0,1
2001	49-75	47.002	976	20,8	1,8%	32,3%	8,0%	57,9%	6,6	4,8	43,0%	420	8,9	51	1,1	367	7,8	2	0,0
2002	49-75	46.691	850	18,2	3,9%	30,0%	6,4%	59,8%	5,3	4,0	45,2%	384	8,2	40	0,9	333	7,1	11	0,2
2003	49-75	39.793	698	17,5	2,1%	29,1%	6,3%	62,5%	5,1	5,1	40,1%	280	7,0	32	0,8	231	5,8	17	0,4
2004	49-75	40.333	826	20,5	1,3%	27,4%	7,5%	53,4%	5,3	4,6	39,7%	328	8,1	43	1,1	270	6,7	15	0,4
2005	49-75	36.257	800	22,1	2,8%	29,1%	8,4%	48,8%	6,2	4,5	38,1%	305	8,4	35	1,0	261	7,2	9	0,2
2006	49-75	35.482	878	24,7	1,8%	30,3%	12,3%	44,8%	7,2	5,8	34,7%	305	8,6	46	1,3	252	7,1	7	0,2
2007	49-75	36.606	1.002	27,4	2,5%	41,5%	8,4%	48,2%	11,1	6,3	34,4%	345	9,4	46	1,3	291	7,9	8	0,2
2008	49-75	37.386	973	26,0	1,2%	41,6%	8,3%	48,9%	10,6	6,1	34,6%	337	9,0	32	0,9	301	8,1	4	0,1
2009	49-75	36.749	941	25,6	1,2%	35,9%	5,6%	45,6%	9,1	5,1	31,8%	299	8,1	50	1,4	243	6,6	6	0,2
2010	49-75	41.948	1.150	27,4	1,9%	45,2%	7,4%	45,5%	12,3	6,7	28,8%	331	7,9	55	1,3	278	6,6	-2	0,0
2011	49-75	46.090	1.304	28,3	1,0%	44,6%	8,5%	45,9%	12,5	6,7	31,1%	405	8,8	67	1,5	322	7,0	16	0,3
2011	49	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2011	50-54	6.808	167	24,5	1,2%	49,7%	8,4%	40,7%	12,0	6,3	24,0%	40	5,9	9	1,3	26	3,8	5	0,7
2011	55-59	12.558	326	26,0	0,3%	48,2%	7,1%	44,5%	12,4	6,8	25,5%	83	6,6	16	1,3	65	5,2	2	0,2
2011	60-64	12.066	326	27,0	1,5%	39,6%	11,3%	47,5%	10,7	6,6	34,4%	112	9,3	13	1,1	94	7,8	5	0,4
2011	65-69	8.238	277	33,6	0,4%	44,4%	8,7%	46,6%	14,8	7,2	34,3%	95	11,5	18	2,2	77	9,3	0	0,0
2011	70-74	6.272	208	33,2	1,9%	42,8%	6,3%	49,0%	13,9	6,7	36,1%	75	12,0	11	1,8	60	9,6	4	0,6
2011	> 74	148	0	-	-	-	-	-	-	-	-	0	-	0	-	0	-	0	-
1990-2011	49	137	0	-	-	-	-	-	-	-	-	0	-	0	-	0	-	0	-
1990-2011	50-54	85.263	1.400	16,4	1,7%	41,5%	8,0%	45,9%	6,7	4,3	28,4%	397	4,7	63	0,7	321	3,8	13	0,2
1990-2011	55-59	170.617	3.047	17,9	2,1%	35,0%	7,9%	51,9%	6,1	4,5	35,3%	1.075	6,3	163	1,0	890	5,2	22	0,1
1990-2011	60-64	139.080	2.895	20,8	1,8%	34,5%	7,6%	52,4%	7,1	4,6	38,2%	1.105	7,9	148	1,1	935	6,7	22	0,2
1990-2011	65-69	104.694	2.469	23,6	1,9%	33,9%	7,0%	54,4%	7,8	5,2	40,1%	990	9,5	118	1,1	857	8,2	15	0,1
1990-2011	70-74	179.374	4.243	23,7	1,7%	27,6%	5,8%	62,9%	6,4	4,6	49,6%	2.105	11,7	225	1,3	1.841	10,3	39	0,2
1990-2011	> 74	2.784	82	29,5	0,0%	24,4%	3,7%	68,3%	6,5	4,3	59,8%	49	17,6	7	2,5	41	14,7	1	0,4
1990-2011	49-75	681.949	14.136	20,7	1,8%	33,1%	7,0%	55,2%	6,7	4,6	40,5%	5.721	8,4	724	1,1	4.885	7,2	112	0,2

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IV.3a – Screen-detected breast cancers all screening examinations

Jaar *Year*	Leeftijd *Age*	Onderzoeken *Screens*	Screeningscarcinomen *Screen-detected breast cancers*										Invasieve screeningscarcinomen *Invasive breast cancers*				
			Totaal *Total*	Tis (DCIS)	T1a 1-5 mm	T1b 6-10 mm	T1c 11-20 mm	T2 21-50 mm	T3 >50 mm	T4	Tx	not classified	N0	N1	Nsn*	Nx	M1
		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
1990-1997	49-69	3.128.241	14.966	2.132	624	3.023	5.640	2.545	154	108	416	324	8.675	3.211	0	563	61
1998	49-75	662.824	2.870	449	130	573	1.112	483	28	8	56	31	1.654	591	0	138	7
1999	49-75	743.903	3.634	480	166	773	1.416	653	26	19	45	55	2.062	770	0	258	8
2000	49-75	793.170	3.937	538	167	810	1.659	677	39	22	38	-13	2.199	955	0	236	22
2001	49-75	803.725	4.151	598	203	814	1.692	694	30	28	40	52	2.262	1.005	89	130	15
2002	49-75	834.978	4.131	533	183	746	1.749	731	40	17	42	90	1.553	1.000	856	85	14
2003	49-75	865.689	4.232	579	159	746	1.762	739	39	12	42	154	1.327	958	1.130	62	22
2004	49-75	888.830	4.399	660	191	782	1.866	720	39	12	45	84	1.251	1.068	1.231	78	27
2005	49-75	892.299	4.353	630	184	796	1.885	733	30	5	32	58	1.038	963	1.579	68	17
2006	49-75	886.025	4.582	723	202	838	1.964	706	36	4	42	67	779	953	1.955	72	33
2007	49-75	911.547	4.999	754	201	929	2.158	788	39	5	40	85	840	1.056	2.189	58	17
2008	49-75	918.578	5.110	756	233	986	2.204	790	44	10	39	48	835	1.063	2.304	75	29
2009	49-75	911.441	5.190	896	238	954	2.169	731	46	13	61	82	767	1.051	2.294	75	25
2010	49-75	961.765	5.667	1.154	318	1.038	2.242	768	59	4	31	53	621	1.090	2.679	48	22
2011	49-75	986.885	6.108	1.194	360	1.142	2.310	845	62	13	29	153	803	1.156	2.728	47	27
2011	49	51.980	354	96	17	63	99	53	6	1	5	14	30	76	131	5	2
2011	50-54	231.148	1.134	277	63	173	409	156	12	2	5	37	125	224	456	9	6
2011	55-59	214.215	1.103	226	67	205	401	150	12	3	6	33	135	230	471	6	2
2011	60-64	213.711	1.417	250	80	281	557	204	14	1	5	25	202	271	643	15	11
2011	65-69	153.534	1.157	199	82	241	444	151	10	4	3	23	161	210	556	4	4
2011	70-74	121.006	934	145	50	179	396	129	8	2	4	21	149	145	464	8	2
2011	> 74	1.291	9	1	1	0	4	2	0	0	1	0	1	0	7	0	0
1990-2011	49	853.875	4.183	863	180	618	1.535	744	42	14	49	138	1.182	1.003	882	102	13
1990-2011	50-54	3.929.188	15.337	2.934	732	2.500	5.843	2.564	161	52	228	323	4.807	3.735	3.136	340	62
1990-2011	55-59	3.497.617	15.232	2.454	757	2.794	6.153	2.463	146	57	208	200	5.126	3.494	3.513	376	69
1990-2011	60-64	3.045.965	16.789	2.504	725	3.286	6.948	2.685	142	58	198	243	5.877	3.564	4.104	419	78
1990-2011	65-69	2.395.618	15.491	1.959	667	3.321	6.498	2.421	137	60	210	218	5.911	3.019	3.888	426	70
1990-2011	70-74	1.446.306	11.122	1.342	494	2.406	4.777	1.699	81	39	102	181	3.707	2.047	3.472	322	50
1990-2011	> 74	17.073	162	20	4	25	74	27	2	0	3	7	56	28	39	8	4
1990-2011	49-75	15.189.900	78.329	12.076	3.559	14.950	31.828	12.603	711	280	998	1.323	26.666	16.890	19.034	1.993	346

* Nsn= sentinel node negative

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IV.3b – Screen-detected breast cancers initial screening examinations

Jaar *Year*	Leeftijd *Age*	Onderzoeken *Screens*	Screeningscarcinomen *Screen-detected breast cancers*										Invasieve screeningscarcinomen *Invasive breast cancers*				
			Totaal *Total*	Tis (DCIS)	T1a 1-5 mm	T1b 6-10 mm	T1c 11-20 mm	T2 21-50 mm	T3 >50 mm	T4	Tx	not classified	N0	N1	Nsn*	Nx	M1
		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
1990-1997	49-69	1.478.573	9.030	1.286	384	1.687	3.457	1.601	99	83	282	151	5.147	2.090	0	322	34
1998	49-75	125.881	663	119	36	118	245	117	8	3	17	0	372	147	0	24	1
1999	49-75	130.495	775	116	37	156	267	159	6	6	15	13	394	190	0	62	0
2000	49-75	125.432	740	129	29	119	299	150	7	4	6	-3	362	208	0	40	4
2001	49-75	109.693	665	122	33	98	262	121	4	2	7	16	290	193	19	21	4
2002	49-75	113.749	624	89	28	68	266	134	8	1	1	29	213	184	99	9	1
2003	49-75	111.912	600	102	23	88	223	132	9	2	5	16	175	149	149	8	1
2004	49-75	115.101	642	115	27	83	239	143	5	1	10	19	152	199	141	12	4
2005	49-75	111.187	579	106	29	81	233	107	5	0	2	16	122	145	174	14	2
2006	49-75	112.079	620	124	26	86	251	108	9	2	1	13	93	139	241	4	6
2007	49-75	109.486	641	111	19	105	244	134	8	2	2	16	102	171	234	6	1
2008	49-75	107.651	656	127	34	88	263	111	11	1	3	18	106	157	236	7	5
2009	49-75	105.313	656	130	27	85	266	105	9	3	5	26	92	157	237	12	2
2010	49-75	111.617	774	199	44	95	276	121	11	0	5	23	72	176	299	4	1
2011	49-75	110.519	798	203	39	130	256	113	10	2	6	39	78	170	293	10	5
2011	49	51.972	354	96	17	63	99	53	6	1	5	14	30	76	131	5	2
2011	50-54	54.388	382	97	18	50	139	52	2	1	1	22	41	81	136	3	2
2011	55-59	2.216	23	3	2	5	10	1	1	0	0	1	2	7	9	1	0
2011	60-64	1.177	20	2	1	8	6	4	0	0	0	-1	4	3	11	1	0
2011	65-69	500	11	3	1	0	1	3	1	0	0	2	0	3	2	0	1
2011	70-74	264	8	2	0	4	1	0	0	0	0	1	1	0	4	0	0
2011	> 74	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1990-2011	49	844.261	4.162	860	180	616	1.527	737	42	14	48	138	1.171	997	882	101	13
1990-2011	50-54	1.258.223	6.405	1.247	288	981	2.362	1.123	75	25	123	181	2.165	1.634	1.009	140	29
1990-2011	55-59	361.748	2.222	326	123	393	844	425	24	21	61	5	1.144	572	91	74	10
1990-2011	60-64	321.042	2.483	332	94	459	979	473	27	23	51	45	1.376	563	61	98	8
1990-2011	65-69	242.368	2.480	250	100	483	1.036	452	33	26	74	26	1.497	554	42	101	10
1990-2011	70-74	49.387	689	62	30	150	289	143	7	3	10	-5	407	149	36	39	1
1990-2011	> 74	1.659	22	1	0	5	10	3	1	0	0	2	10	6	1	2	0
1990-2011	49-75	3.078.688	18.463	3.078	815	3.087	7.047	3.356	209	112	367	392	7.770	4.475	2.122	555	71

* Nsn= sentinel node negative

LETB/*NETB*, 2014

IV.3c – Screen-detected breast cancers regular subsequent screens

Jaar *Year*	Leeftijd *Age*	Onderzoeken *Screens*	Screeningscarcinomen *Screen-detected breast cancers*										Invasieve screeningscarcinomen *Invasive breast cancers*				
			Totaal *Total*	Tis (DCIS)	T1a 1-5 mm	T1b 6-10 mm	T1c 11-20 mm	T2 21-50 mm	T3 >50 mm	T4	Tx	not classified	N0	N1	Nsn*	Nx	M1
		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
1990-1997	49-69	1.593.817	5.642	815	229	1.278	2.078	886	49	24	128	155	3.356	1.061	0	232	23
1998	49-75	503.079	1.918	295	81	393	744	324	17	4	36	24	1.104	391	0	98	6
1999	49-75	540.600	2.166	291	102	443	878	378	15	8	21	30	1.243	456	0	141	5
2000	49-75	588.392	2.478	321	110	543	1.051	399	25	10	24	-5	1.415	587	0	150	10
2001	49-75	647.030	3.066	425	154	625	1.239	516	23	20	30	34	1.718	725	62	95	7
2002	49-75	674.538	3.123	404	139	611	1.313	526	30	14	36	50	1.192	719	679	66	13
2003	49-75	713.984	3.352	445	125	612	1.435	546	26	8	34	121	1.069	750	903	47	17
2004	49-75	733.396	3.429	502	157	656	1.480	512	32	10	30	50	1.010	794	990	62	21
2005	49-75	744.855	3.469	489	142	670	1.527	555	23	4	26	33	836	747	1.302	47	15
2006	49-75	738.464	3.657	553	163	694	1.585	551	26	2	36	47	635	754	1.581	60	27
2007	49-75	765.455	4.013	597	170	755	1.777	587	31	3	32	61	674	801	1.816	48	16
2008	49-75	773.541	4.117	597	177	837	1.786	624	31	8	31	26	676	838	1.897	59	24
2009	49-75	769.379	4.235	716	197	816	1.780	582	34	7	53	50	622	837	1.935	55	20
2010	49-75	808.200	4.562	900	259	886	1.813	599	44	4	25	32	517	849	2.204	39	21
2011	49-75	830.276	4.905	924	287	930	1.915	673	48	10	20	98	676	896	2.258	32	21
2011	49	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2011	50-54	169.952	712	171	43	115	262	97	9	1	4	10	80	133	308	6	4
2011	55-59	199.441	997	207	57	186	360	140	10	3	4	30	122	205	427	5	1
2011	60-64	200.468	1.285	235	68	245	513	184	13	1	5	21	180	247	580	11	11
2011	65-69	144.796	1.051	178	75	225	404	134	8	4	2	21	152	183	510	4	3
2011	70-74	114.470	851	132	43	159	372	116	8	1	4	16	141	128	426	6	2
2011	> 74	1.141	9	1	1	0	4	2	0	0	1	0	1	0	7	0	0
1990-2011	49	9.478	21	3	0	2	8	7	0	0	1	0	11	6	0	1	0
1990-2011	50-54	2.585.702	8.535	1.624	419	1.443	3.339	1.377	82	23	99	129	2.522	2.007	2.028	192	33
1990-2011	55-59	2.965.252	11.935	1.965	588	2.217	4.869	1.846	113	33	131	173	3.654	2.675	3.137	276	55
1990-2011	60-64	2.585.843	13.201	2.024	581	2.623	5.501	2.023	107	30	136	176	4.149	2.767	3.727	293	65
1990-2011	65-69	2.048.556	12.021	1.591	526	2.641	5.037	1.797	94	33	125	177	4.095	2.262	3.540	302	54
1990-2011	70-74	1.217.545	8.328	1.055	374	1.805	3.613	1.191	57	17	69	147	2.285	1.474	3.165	163	39
1990-2011	> 74	12.630	91	12	4	18	34	17	1	0	1	4	27	14	30	4	0
1990-2011	49-75	11.425.006	54.132	8.274	2.492	10.749	22.401	8.258	454	136	562	806	16.743	11.205	15.627	1.231	246

* Nsn= sentinel node negative

LETB/*NETB*, 2014

IV.3d – Screen-detected breast cancers subsequent screens >=2.5 years

Jaar *Year*	Leeftijd *Age*	Onderzoeken *Screens*	Screeningscarcinomen *Screen-detected breast cancers*										Invasieve screeningscarcinomen *Invasive breast cancers*				
			Totaal *Total*	Tis (DCIS)	T1a 1-5 mm	T1b 6-10 mm	T1c 11-20 mm	T2 21-50 mm	T3 >50 mm	T4	Tx	not classified	N0	N1	Nsn*	Nx	M1
		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
1990-1997	49-69	51.593	281	31	11	58	105	58	6	1	6	5	172	60	0	9	4
1998	49-75	33.865	289	35	13	62	123	42	3	1	3	7	178	53	0	16	0
1999	49-75	72.808	693	73	27	174	271	116	5	5	9	12	425	124	0	55	3
2000	49-75	79.346	719	88	28	148	309	128	7	8	8	-5	422	160	0	46	8
2001	49-75	47.002	420	51	16	91	191	57	3	6	3	2	254	87	8	14	4
2002	49-75	46.691	384	40	16	67	170	71	2	2	5	11	148	97	78	10	0
2003	49-75	39.793	280	32	11	46	104	61	4	2	3	17	83	59	78	7	4
2004	49-75	40.333	328	43	7	43	147	65	2	1	5	15	89	75	100	4	2
2005	49-75	36.257	305	35	13	45	125	71	2	1	4	9	80	71	103	7	0
2006	49-75	35.482	305	46	13	58	128	47	1	0	5	7	51	60	133	8	0
2007	49-75	36.606	345	46	12	69	137	67	0	0	6	8	64	84	139	4	0
2008	49-75	37.386	337	32	22	61	155	55	2	1	5	4	53	68	171	9	0
2009	49-75	36.749	299	50	14	53	123	44	3	3	3	6	53	57	122	8	3
2010	49-75	41.948	331	55	15	57	153	48	4	0	1	-2	32	65	176	5	0
2011	49-75	46.090	405	67	34	82	139	59	4	1	3	16	49	90	177	5	1
2011	49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2011	50-54	6.808	40	9	2	8	8	7	1	0	0	5	4	10	12	0	0
2011	55-59	12.558	83	16	8	14	31	9	1	0	2	2	11	18	35	0	1
2011	60-64	12.066	112	13	11	28	38	16	1	0	0	5	18	21	52	3	0
2011	65-69	8.238	95	18	6	16	39	14	1	0	1	0	9	24	44	0	0
2011	70-74	6.272	75	11	7	16	23	13	0	1	0	4	7	17	34	2	0
2011	> 74	148	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1990-2011	49	137	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1990-2011	50-54	85.263	397	63	25	76	142	64	4	4	6	13	120	94	99	8	0
1990-2011	55-59	170.617	1.075	163	46	184	440	192	9	3	16	22	328	247	285	26	4
1990-2011	60-64	139.080	1.105	148	50	204	468	189	8	5	11	22	352	234	316	28	5
1990-2011	65-69	104.694	990	118	41	197	425	172	10	1	11	15	319	203	306	23	6
1990-2011	70-74	179.374	2.105	225	90	451	875	365	17	19	23	39	1.015	424	271	120	10
1990-2011	> 74	2.784	49	7	0	2	30	7	0	0	2	1	19	8	8	2	4
1990-2011	49-75	681.949	5.721	724	252	1.114	2.380	989	48	32	69	112	2.153	1.210	1.285	207	29

* Nsn= sentinel node negative

LETB/*NETB* , 2014

V.a – Interval cancers (invasive and in-situ) 1990-2009

Alle screeningsonderzoeken / *All screening examinations*

Jaar / *Year*	Regio's / *Regions*	Leeftijd / *Age*	Onderzoeken / Screens	Verwijsadviezen / *Referrals*		Screen'carcrcinomen / Screen-detectec		Intervalkankers / *Interval cancers*																
								<12 maanden / *<12 months*					12,0-23,9 maanden / *12.0-23.9 months*					<24,0 maanden / *<24.0 months*						
	N	Jr/*Yrs*	N	N	/ 1000	N	/ 1000	N	FU PJ / *PY*	/1000 PJ	Sensit-tiviteit	Specifi-citeit	N	FU PJ / *PY*	/1000 PJ	*Sensit-tivity*	*Speci-ficity*	N	FU PJ / *PY*	A / 1000	B / 1000	C /1000 PJ	sd/ivca	Sensit-tiviteit	Specifi-citeit
1990	9	49-70	58.003	843	14,5	341	5,9	35	48.800	0,72	90,7%	99,1%	57	51.838	1,10	85,7%	99,1%	92	100.638	1,59	1,61	0,91	3,7	78,8%	99,1%
1991	9	49-70	147.126	1.802	12,2	858	5,8	77	145.933	0,53	91,8%	99,4%	119	136.115	0,87	87,8%	99,4%	227	282.048	1,54	1,56	0,80	3,8	79,1%	99,4%
1992	9	49-70	283.186	3.367	11,9	1.660	5,9	160	280.957	0,57	91,2%	99,4%	329	253.018	1,30	83,5%	99,4%	489	533.974	1,73	1,75	0,92	3,4	77,2%	99,4%
1993	9	49-70	390.376	4.391	11,2	2.111	5,4	274	387.458	0,71	88,5%	99,4%	503	361.634	1,39	80,8%	99,4%	777	749.092	1,99	2,01	1,04	2,7	73,1%	99,4%
1994	8	49-70	403.047	4.352	10,8	1.920	4,8	267	400.595	0,67	87,8%	99,4%	501	377.530	1,33	79,3%	99,4%	768	778.125	1,91	1,93	0,99	2,5	71,4%	99,4%
1995	8	49-70	471.634	4.548	9,6	2.113	4,5	302	468.654	0,64	87,5%	99,5%	640	447.339	1,43	76,8%	99,5%	942	915.993	2,00	2,02	1,03	2,2	69,2%	99,5%
1996	8	49-70	537.851	4.752	8,8	2.288	4,3	394	533.060	0,74	85,3%	99,5%	687	508.575	1,35	76,9%	99,5%	1.081	1.041.634	2,01	2,03	1,04	2,1	67,9%	99,5%
1997	8	49-75	548.533	5.325	9,7	2.447	4,5	422	544.317	0,78	85,3%	99,5%	724	515.996	1,40	77,2%	99,5%	1.146	1.060.312	2,09	2,11	1,08	2,1	68,1%	99,5%
1998	8	49-75	587.156	6.077	10,3	2.573	4,4	420	582.867	0,72	86,0%	99,4%	781	543.301	1,44	76,7%	99,4%	1.201	1.126.168	2,05	2,07	1,07	2,1	68,2%	99,4%
1999	8	49-75	662.770	7.655	11,6	3.339	5,0	473	657.257	0,72	87,6%	99,3%	925	617.253	1,50	78,3%	99,3%	1.398	1.274.510	2,11	2,13	1,10	2,4	70,5%	99,3%
2000	7	49-75	657.411	8.090	12,3	3.344	5,1	490	650.725	0,75	87,2%	99,3%	965	603.012	1,60	77,6%	99,3%	1.455	1.253.736	2,21	2,24	1,16	2,3	69,7%	99,3%
2001	7	49-75	658.133	9.638	14,6	3.401	5,2	487	650.272	0,75	87,5%	99,0%	817	602.532	1,36	80,6%	99,0%	1.304	1.252.803	1,98	2,01	1,04	2,6	72,3%	99,0%
2002	6	49-75	611.886	8.377	13,7	3.118	5,1	448	604.756	0,74	87,4%	99,1%	816	562.364	1,45	79,3%	99,1%	1.264	1.167.120	2,07	2,09	1,08	2,5	71,2%	99,1%
2003	5	49-75	497.607	6.781	13,6	2.466	5,0	376	490.899	0,77	86,8%	99,1%	558	458.268	1,22	81,5%	99,1%	934	949.166	1,88	1,90	0,98	2,6	72,5%	99,1%
2004	9	49-75	888.830	12.523	14,1	4.544	5,1	661	875.777	0,75	87,3%	99,1%	1.244	814.572	1,53	78,5%	99,1%	1.905	1.690.349	**2,14**	2,17	**1,13**	2,4	**70,5%**	**99,1%**
2005	9	49-75	892.313	12.910	14,5	4.527	5,1	655	879.073	0,75	87,4%	99,1%	1.260	832.291	1,51	78,2%	99,1%	1.915	1.711.364	**2,15**	2,18	**1,12**	2,4	**70,3%**	**99,1%**
2006	9	49-75	886.023	14.290	16,1	4.716	5,3	686	871.659	0,79	87,3%	98,9%	1.300	826.565	1,57	78,4%	98,9%	1.986	1.698.223	**2,24**	2,28	**1,17**	2,4	**70,4%**	**98,9%**
2007	9	49-75	911.551	16.414	18,0	5.167	5,7	695	895.665	0,78	88,1%	98,8%	1.279	852.429	1,50	80,2%	98,8%	1.974	1.748.093	**2,17**	2,21	**1,13**	2,6	**72,4%**	**98,8%**
2008	9	49-75	918.580	16.752	18,2	5.236	5,7	698	901.444	0,77	88,2%	98,7%	1.389	853.080	1,63	79,0%	98,7%	2.087	1.754.524	**2,27**	2,31	**1,19**	2,5	**71,5%**	**98,7%**
2009	9	49-75	911.442	17.413	19,1	5.340	5,9	689	892.154	0,77	88,6%	98,7%	1.299	806.721	1,61	80,4%	98,7%	1.988	1.698.874	**2,18**	2,22	**1,17**	2,7	**72,9%**	**98,7%**
1990-2003	5-9	49-75	6.514.719	75.998	11,7	31.979	4,9	4.625	6.446.548	0,72	87,4%	99,3%	8.422	6.038.774	1,39	79,2%	99,3%	13.078	12.485.322	2,01	2,03	1,05	2,4	71,0%	99,3%
2004-2009	9	49-75	5.408.739	90.302	16,7	29.530	5,5	4.084	5.315.771	0,77	87,9%	98,9%	7.771	4.985.656	1,56	79,2%	98,9%	11.855	10.301.427	2,19	2,23	1,15	2,5	71,4%	98,9%
1990-2009		49-75	11.923.458	166.300	13,9	61.509	5,2	8.709	11.770.859	0,74	87,6%	99,1%	16.224	11.024.430	1,47	79,1%	99,1%	24.933	22.795.289	2,09	2,12	1,09	2,5	71,2%	99,1%

PJ: Persoonsjaren (vrouwjaren) / *PJ: Person-years*

LETB/*NETB* , 2014

A: per 1000 gescreende vrouwen / *per 1000 women screened*

B: per 1000 negatief gescreende vrouwen (na eventueel aanvullende diagnostiek) */per 1000 women screened negatively (after possible assessment)*

C: per 1000 vrouwjaren (PJ) at-risk / *per 1000 woman-years (PY) at risk*

V.b – Interval cancers (invasive and in-situ) 1990-2009

Eerste onderzoeken / *Initial screens*

Jaar *Year*	Regio's *Regions*	Leeftijd *Age*	Onderzoeken *Screens*	Verwijsadviesadviezen *Referrals*			Screen'carcrcinomen *Screen-detectec*		Intervalkankers / *Interval cancers*																
									<12 maanden / *<12 months*					**12,0-23,9 maanden / *12.0-23.9 months***					**<24,0 maanden / *<24.0 months***						
	N	Jr/*Yrs*	N	N	/ 1000	N	/ 1000	N	FU PJ / *PY*	/1000 PJ	Sensit-tiviteit	Specifi-citeit	N	FU PJ / *PY*	/1000 PJ	*Sensit-tivity*	*Speci-ficity*	N	FU PJ / *PY*	A / 1000	B / 1000	C /1000 PJ	sd/ivca	Sensit-tiviteit	Specifi-citeit
1990	9	49-75	42.385	681	16,1	284	6,7	24	41.911	0,57	92,2%	99,1%	32	38.407	0,83	89,9%	99,1%	56	80.319	1,32	1,34	0,70	5,1	83,5%	99,1%
1991	9	49-75	119.896	1.517	12,7	775	6,5	64	118.938	0,54	92,4%	99,4%	119	111.803	1,06	86,7%	99,4%	183	230.741	1,53	1,55	0,79	4,2	80,9%	99,4%
1992	9	49-75	220.224	2.886	13,1	1.433	6,5	128	218.532	0,59	91,8%	99,3%	263	199.072	1,32	84,5%	99,3%	391	417.604	1,78	1,80	0,94	3,7	78,6%	99,3%
1993	9	49-75	266.240	3.575	13,4	1.673	6,3	202	264.199	0,76	89,2%	99,3%	341	247.458	1,38	83,1%	99,3%	543	511.658	2,04	2,07	1,06	3,1	75,5%	99,3%
1994	8	49-75	201.072	3.038	15,1	1.246	6,2	140	199.572	0,70	89,9%	99,1%	275	189.584	1,45	81,9%	99,1%	415	389.156	2,06	2,10	1,07	3,0	75,0%	99,1%
1995	8	49-75	196.518	2.639	13,4	1.189	6,1	139	195.028	0,71	89,5%	99,3%	257	186.250	1,38	82,2%	99,3%	396	381.278	2,02	2,04	1,04	3,0	75,0%	99,3%
1996	8	49-75	218.223	2.501	11,5	1.209	5,5	156	215.432	0,72	88,6%	99,4%	280	203.869	1,37	81,2%	99,4%	436	419.301	2,00	2,02	1,04	2,8	73,5%	99,4%
1997	8	49-75	151.415	2.084	13,8	831	5,5	120	149.942	0,80	87,4%	99,2%	230	139.076	1,65	78,3%	99,2%	350	289.018	2,31	2,34	1,21	2,4	70,4%	99,2%
1998	8	49-75	112.270	1.833	16,3	610	5,4	98	111.213	0,88	86,2%	98,9%	164	103.506	1,58	78,8%	98,9%	262	214.719	2,33	2,37	1,22	2,3	70,0%	98,9%
1999	8	49-75	115.775	2.131	18,4	718	6,2	97	114.573	0,85	88,1%	98,8%	161	107.843	1,49	81,7%	98,8%	258	222.416	2,23	2,27	1,16	2,8	73,6%	98,8%
2000	7	49-75	104.458	2.022	19,4	622	6,0	90	103.073	0,87	87,4%	98,7%	183	95.721	1,91	77,3%	98,6%	273	198.794	2,61	2,67	1,37	2,3	69,5%	98,6%
2001	7	49-75	89.941	2.293	25,5	536	6,0	64	88.465	0,72	89,3%	98,0%	129	81.753	1,58	80,6%	98,0%	193	170.218	2,15	2,20	1,13	2,8	73,5%	98,0%
2002	6	49-75	81.796	1.963	24,0	464	5,7	72	80.461	0,89	86,6%	98,2%	123	74.348	1,65	79,0%	98,2%	195	154.809	2,38	2,44	1,26	2,4	70,4%	98,2%
2003	5	49-75	63.843	1.478	23,2	349	5,5	58	62.579	0,93	85,7%	98,2%	72	57.923	1,24	82,9%	98,2%	130	120.502	2,04	2,08	1,08	2,7	72,9%	98,2%
2004	9	49-75	110.803	2.866	25,9	637	5,7	106	108.052	0,98	85,7%	98,0%	176	99.797	1,76	78,4%	98,0%	282	207.849	**2,55**	2,61	**1,36**	2,3	**69,3%**	**98,0%**
2005	9	49-75	105.403	2.835	26,9	564	5,4	107	102.697	1,04	84,1%	97,8%	152	96.818	1,57	78,8%	97,8%	259	199.514	**2,46**	2,53	**1,30**	2,2	**68,5%**	**97,8%**
2006	9	49-75	107.021	3.212	30,0	603	5,6	108	103.981	1,04	84,8%	97,5%	177	98.061	1,80	77,3%	97,5%	285	202.042	**2,66**	2,75	**1,41**	2,1	**67,9%**	**97,5%**
2007	9	49-75	105.068	3.656	34,8	646	6,1	103	102.478	1,01	86,2%	97,1%	148	96.877	1,53	81,4%	97,1%	251	199.356	**2,39**	2,48	**1,26**	2,6	**72,0%**	**97,1%**
2008	9	49-75	107.650	4.144	38,5	666	6,2	104	103.693	1,00	86,5%	96,7%	179	97.868	1,83	78,8%	96,7%	283	201.561	**2,63**	2,73	**1,40**	2,4	**70,2%**	**96,7%**
2009	9	49-75	105.312	4.402	41,8	668	6,3	110	100.953	1,09	85,9%	96,4%	166	91.018	1,82	80,1%	96,4%	276	191.972	**2,62**	2,74	**1,44**	2,4	**70,8%**	**96,4%**
1990-2003	5-9	49-75	1.984.056	30.641	15,4	11.939	6,0	1.452	1.963.918	0,74	89,2%	99,1%	2.629	1.836.614	1,43	82,0%	99,1%	4.081	3.800.533	2,06	2,09	1,07	2,9	74,5%	99,0%
2004-2009	9	49-75	641.257	21.115	32,9	3.784	5,9	638	621.855	1,03	85,6%	97,3%	998	580.439	1,72	79,1%	97,3%	1.636	1.202.294	2,55	2,64	1,36	2,3	69,8%	97,3%
1990-2009		49-75	2.625.313	51.756	19,7	15.723	6,0	2.090	2.585.773	0,81	88,3%	98,6%	3.627	2.417.054	1,50	81,3%	98,6%	5.717	5.002.827	2,18	2,22	1,14	2,8	73,3%	98,6%

PJ: Persoonsjaren (vrouwjaren) / *PJ: Person-years*

A: per 1000 gescreende vrouwen / *per 1000 women screened*

B: per 1000 negatief gescreende vrouwen (na eventueel aanvullende diagnostiek) */per 1000 women screened negatively (after possible assessment)*

C: per 1000 vrouwjaren (PJ) at-risk / *per 1000 woman-years (PY) at risk*

LETB/*NETB* , 2014

V.c – Interval cancers (invasive and in-situ) 1990-2009

Reguliere vervolgonderzoeken (<2,5 jaar) / *Regular subsequent screens (<2.5 years)*

Jaar *Year*	Regio's *Regions*	Leeftijd *Age*	Onderzoeken Screens	Verwijsadvies *Referrals*		Screen'carcr Screen-detectec		Intervalkankers / *Interval cancers*																
								<12 maanden / *<12 months*					**12,0-23,9 maanden / *12.0-23.9 months***					**<24,0 maanden / *<24.0 months***						
	N	Jr/*Yrs*	N	N	/ 1000	N	/ 1000	N	FU PJ / *PY*	/1000 PJ	Sensit-tiviteit	Specifi-citeit	N	FU PJ / *PY*	/1000 PJ	*Sensit-tivity*	*Speci-ficity*	N	FU PJ / *PY*	A / 1000	B / 1000	C /1000 PJ	sd/ivca	Sensit-tiviteit	Specifi-citeit
1990	9	49-70	14.651	162	11,1	56	3,8	11	14.502	0,76	83,6%	99,3%	24	12.859	1,87	70,0%	99,3%	35	27.360	2,39	2,42	1,28	1,6	61,5%	99,3%
1991	9	49-70	24.731	270	10,9	73	3,0	12	24.511	0,49	85,9%	99,2%	119	22.345	5,33	38,0%	99,2%	42	46.856	1,70	1,72	0,90	1,7	63,5%	99,2%
1992	9	49-70	61.076	466	7,6	218	3,6	29	60.554	0,48	88,3%	99,6%	64	52.373	1,22	77,3%	99,6%	93	112.926	1,52	1,53	0,82	2,3	70,1%	99,6%
1993	9	49-70	120.843	796	6,6	428	3,5	72	119.981	0,60	85,6%	99,7%	159	111.174	1,43	72,9%	99,7%	231	231.155	1,91	1,92	1,00	1,9	64,9%	99,7%
1994	8	49-70	198.933	1.280	6,4	659	3,3	125	198.009	0,63	84,1%	99,7%	221	185.305	1,19	74,9%	99,7%	346	383.315	1,74	1,75	0,90	1,9	65,6%	99,7%
1995	8	49-70	269.288	1.841	6,8	887	3,3	163	267.855	0,61	84,5%	99,6%	374	255.651	1,46	70,3%	99,6%	537	523.506	1,99	2,01	1,03	1,7	62,3%	99,6%
1996	8	49-70	306.279	2.121	6,9	1.011	3,3	223	304.402	0,73	81,9%	99,6%	396	292.172	1,36	71,9%	99,6%	619	596.574	2,02	2,04	1,04	1,6	62,0%	99,6%
1997	8	49-75	380.371	3.041	8,0	1.519	4,0	291	377.790	0,77	83,9%	99,6%	462	361.331	1,28	76,7%	99,6%	753	739.121	1,98	2,00	1,02	2,0	66,9%	99,6%
1998	8	49-75	447.932	3.796	8,5	1.728	3,9	310	445.040	0,70	84,8%	99,5%	571	415.001	1,38	75,2%	99,5%	881	860.041	1,97	1,98	1,02	2,0	66,2%	99,5%
1999	8	49-75	481.451	4.335	9,0	1.979	4,1	338	478.100	0,71	85,4%	99,5%	676	448.711	1,51	74,5%	99,5%	1.014	926.811	2,11	2,13	1,09	2,0	66,1%	99,5%
2000	7	49-75	481.892	4.729	9,8	2.060	4,3	352	477.739	0,74	85,4%	99,4%	706	443.428	1,59	74,5%	99,4%	1.058	921.167	2,20	2,22	1,15	1,9	66,1%	99,4%
2001	7	49-75	529.166	6.507	12,3	2.529	4,8	393	523.446	0,75	86,6%	99,2%	639	486.128	1,31	79,8%	99,2%	1.032	1.009.574	1,95	1,97	1,02	2,5	71,0%	99,2%
2002	6	49-75	499.670	5.823	11,7	2.393	4,8	349	494.455	0,71	87,3%	99,3%	650	461.013	1,41	78,6%	99,3%	999	955.468	2,00	2,02	1,05	2,4	70,5%	99,3%
2003	5	49-75	411.850	4.891	11,9	1.954	4,7	305	406.859	0,75	86,5%	99,3%	461	380.532	1,21	80,9%	99,3%	766	787.391	1,86	1,88	0,97	2,6	71,8%	99,3%
2004	9	49-75	735.968	8.785	11,9	3.554	4,8	516	726.647	0,71	87,3%	99,3%	1.006	677.532	1,48	77,9%	99,3%	1.522	1.404.179	**2,07**	2,09	**1,08**	2,3	**70,0%**	**99,3%**
2005	9	49-75	748.843	9.231	12,3	3.646	4,9	514	739.262	0,70	87,6%	99,3%	1.037	700.989	1,48	77,9%	99,2%	1.551	1.440.250	**2,07**	2,10	**1,08**	2,4	**70,2%**	**99,2%**
2006	9	49-75	741.678	10.155	13,7	3.791	5,1	554	731.387	0,76	87,2%	99,1%	1.057	694.777	1,52	78,2%	99,1%	1.611	1.426.164	**2,17**	2,20	**1,13**	2,4	**70,2%**	**99,1%**
2007	9	49-75	768.340	11.716	15,2	4.157	5,4	558	756.176	0,74	88,2%	99,0%	1.064	720.792	1,48	79,6%	99,0%	1.622	1.476.969	**2,11**	2,14	**1,10**	2,6	**71,9%**	**99,0%**
2008	9	49-75	774.123	11.629	15,0	4.229	5,5	564	762.025	0,74	88,2%	99,0%	1.145	721.886	1,59	78,7%	99,0%	1.709	1.483.912	**2,21**	2,24	**1,15**	2,5	**71,2%**	**99,0%**
2009	9	49-75	770.022	12.059	15,7	4.360	5,7	549	756.182	0,73	88,8%	99,0%	1.056	684.560	1,54	80,5%	99,0%	1.605	1.440.742	**2,08**	2,12	**1,11**	2,7	**73,1%**	**99,0%**
1990-2003	5-9	49-75	4.228.133	40.058	9,5	17.494	4,1	2.973	4.193.241	0,71	85,5%	99,5%	5.522	3.928.023	1,41	76,0%	99,5%	8.406	8.121.263	1,99	2,01	1,04	2,1	67,5%	99,5%
2004-2009	9	49-75	4.538.974	63.575	14,0	23.737	5,2	3.255	4.471.679	0,73	87,9%	99,1%	6.365	4.200.536	1,52	78,9%	99,1%	9.620	8.672.215	2,12	2,15	1,11	2,5	71,2%	99,1%
1990-2009		49-75	8.767.107	103.633	11,8	41.231	4,7	6.228	8.664.919	0,72	86,9%	99,3%	11.798	8.128.559	1,45	77,8%	99,3%	18.026	16.793.478	2,06	2,08	1,07	2,3	69,6%	99,3%

PJ: Persoonsjaren (vrouwjaren) / *PJ: Person-years*

A: per 1000 gescreende vrouwen / *per 1000 women screened*

B: per 1000 negatief gescreende vrouwen (na eventueel aanvullende diagnostiek) */per 1000 women screened negatively (after possible assessment)*

C: per 1000 vrouwjaren (PJ) at-risk / *per 1000 woman-years (PY) at risk*

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V.d – Interval cancers (invasive and in-situ) 1990-2009

Vervolgonderzoeken >=2,5 jaar / *Subsequent screens >=2.5 years*

Jaar *Year*	Regio's *Regions*	Leeftijd *Age*	Onderzoeken Screens	Verwijsadvie;isadviezen *Referrals*		Screen'carcrcinomen Screen-detectec		Intervalkankers / *Interval cancers*																
								<12 maanden / *<12 months*					**12,0-23,9 maanden / *12.0-23.9 months***					**<24,0 maanden / *<24.0 months***						
	N	Jr/*Yrs*	N	N	/ 1000	N	/ 1000	N	FU PJ / *PY*	/1000 PJ	Sensit-tiviteit	Specifi-citeit	N	FU PJ / *PY*	/1000 PJ	Sensit-*tivity*	Speci-*ficity*	N	FU PJ / *PY*	A / 1000	B / 1000	C /1000 PJ	sd/ivca	Sensit-tiviteit	Specifi-citeit
1990	9	49-70	967	0	0,0	1	1,0	0	927	0,00	100,0%	100,1%	1	572	1,75	50,0%	100,1%	1	1.499	1,03	1,03	0,67	1,0	50,0%	100,1%
1991	9	49-70	2.499	15	6,0	10	4,0	1	2.485	0,40	90,9%	99,8%	119	1.967	60,50	7,8%	99,8%	2	4.452	0,80	0,81	0,45	5,0	83,3%	99,8%
1992	9	49-70	1.886	15	8,0	9	4,8	3	1.871	1,60	75,0%	99,7%	2	1.573	1,27	81,8%	99,7%	5	3.445	2,65	2,67	1,45	1,8	64,3%	99,7%
1993	9	49-70	3.293	20	6,1	10	3,0	0	3.278	0,00	100,0%	99,7%	3	3.001	1,00	76,9%	99,7%	3	6.280	0,91	0,92	0,48	3,3	76,9%	99,7%
1994	8	49-70	3.042	34	11,2	15	4,9	2	3.013	0,66	88,2%	99,4%	5	2.641	1,89	75,0%	99,4%	7	5.654	2,30	2,33	1,24	2,1	68,2%	99,4%
1995	8	49-70	5.828	68	11,7	37	6,3	0	5.771	0,00	100,0%	99,5%	9	5.439	1,65	80,4%	99,5%	9	11.209	1,54	1,56	0,80	4,1	80,4%	99,5%
1996	8	49-70	13.349	130	9,7	68	5,1	15	13.226	1,13	81,9%	99,5%	11	12.533	0,88	86,1%	99,5%	26	25.759	1,95	1,97	1,01	2,6	72,3%	99,5%
1997	8	49-75	16.747	200	11,9	97	5,8	11	16.585	0,66	89,8%	99,4%	32	15.588	2,05	75,2%	99,4%	43	32.173	2,57	2,60	1,34	2,3	69,3%	99,4%
1998	8	49-75	26.954	448	16,6	235	8,7	12	26.614	0,45	95,1%	99,2%	46	24.794	1,86	83,6%	99,2%	58	51.408	2,15	2,19	1,13	4,1	80,2%	99,2%
1999	8	49-75	65.544	1.189	18,1	642	9,8	38	64.584	0,59	94,4%	99,2%	88	60.699	1,45	87,9%	99,2%	126	125.283	1,92	1,96	1,01	5,1	83,6%	99,2%
2000	7	49-75	71.061	1.339	18,8	662	9,3	48	69.912	0,69	93,2%	99,0%	76	63.863	1,19	89,7%	99,0%	124	133.776	1,74	1,78	0,93	5,3	84,2%	99,0%
2001	7	49-75	39.026	838	21,5	336	8,6	30	38.360	0,78	91,8%	98,7%	49	34.651	1,41	87,3%	98,7%	79	73.011	2,02	2,07	1,08	4,3	81,0%	98,7%
2002	6	49-75	30.420	591	19,4	261	8,6	27	29.841	0,90	90,6%	98,9%	43	27.003	1,59	85,9%	98,9%	70	56.843	2,30	2,35	1,23	3,7	78,9%	98,9%
2003	5	49-75	21.914	412	18,8	163	7,4	13	21.461	0,61	92,6%	98,9%	25	19.813	1,26	86,7%	98,9%	38	41.273	1,73	1,77	0,92	4,3	81,1%	98,9%
2004	9	49-75	42.059	872	20,7	353	8,4	39	41.078	0,95	90,1%	98,8%	62	37.243	1,66	85,1%	98,8%	101	78.321	**2,40**	2,45	**1,29**	3,5	**77,8%**	**98,8%**
2005	9	49-75	38.067	844	22,2	317	8,3	34	37.115	0,92	90,3%	98,6%	71	34.485	2,06	81,7%	98,6%	105	71.600	**2,76**	2,82	**1,47**	3,0	**75,1%**	**98,6%**
2006	9	49-75	37.324	923	24,7	322	8,6	24	36.291	0,66	93,1%	98,4%	66	33.727	1,96	83,0%	98,4%	90	70.018	**2,41**	2,47	**1,29**	3,6	**78,2%**	**98,4%**
2007	9	49-75	38.143	1.042	27,3	364	9,5	34	37.010	0,92	91,5%	98,2%	67	34.759	1,93	84,5%	98,2%	101	71.769	**2,65**	2,72	**1,41**	3,6	**78,3%**	**98,2%**
2008	9	49-75	36.807	979	26,6	341	9,3	30	35.726	0,84	91,9%	98,2%	65	33.325	1,95	84,0%	98,2%	95	69.051	**2,58**	2,65	**1,38**	3,6	**78,2%**	**98,2%**
2009	9	49-75	36.108	952	26,4	312	8,6	30	35.019	0,86	91,2%	98,2%	77	31.142	2,47	80,2%	98,2%	107	66.161	**2,96**	3,04	**1,62**	2,9	**74,5%**	**98,2%**
1990-2003	5-9	49-75	302.530	5.299	17,5	2.546	8,4	200	297.929	0,67	92,7%	99,1%	509	274.137	1,86	83,3%	99,1%	591	572.066	1,95	1,99	1,03	4,3	81,2%	99,1%
2004-2009	9	49-75	228.508	5.612	24,6	2.009	8,8	191	222.238	0,86	91,3%	98,4%	408	204.681	1,99	83,1%	98,4%	599	426.919	2,62	2,69	1,40	3,4	77,0%	98,4%
1990-2009		49-75	531.038	10.911	20,5	4.555	8,6	391	520.167	0,75	92,1%	98,8%	799	478.818	1,67	85,1%	98,8%	1.190	998.985	2,24	2,29	1,19	3,8	79,3%	98,8%

PJ: Persoonsjaren (vrouwjaren) / *PJ: Person-years*

LETB/*NETB*, 2014

A: per 1000 gescreende vrouwen / *per 1000 women screened*

B: per 1000 negatief gescreende vrouwen (na eventueel aanvullende diagnostiek) */per 1000 women screened negatively (after possible assessment)*

C: per 1000 vrouwjaren (PJ) at-risk / *per 1000 woman-years (PY) at risk*

Evaluation tables

Aggregated annual data (evaluation tables) supplied by the regional screening organisations are used for the national evaluation of the breast cancer screening programme. After checking this data for completeness and consistency, the National Evaluation Team for Breast Cancer Screening in the Netherlands (NETB) imports it into a national database, for further analysis.

The *A tables* contain regional-level data on the target population, and on the numbers of invitations issued, together with details about participation and non-participation. The A tables are based on the *invitations to screening tests scheduled to take place in the reporting year in question*. The A-tables draw a distinction between initial and subsequent screening rounds. Subsequent screening rounds involve women who have received two or more invitations to the screening programme. This is independent of any previous participation.

The *B-tables* are based on the *actual number of tests carried out by the regions in the reporting year in question* and the subsequent screening results (recommendations for referral, further diagnosis, size and lymph node status of the detected breast tumours). Screening tests are classified into initial screening tests (independent of the number of previous invitations) and *subsequent screening tests,* in which the previous test took place less than 2.5 years before (= regular subsequent screening tests) or subsequent screening tests at intervals of 2.5 years or more.

Definition of age and target group

The national evaluation uses the same age classification system as Statistics Netherlands (CBS), which is based on an individual's age at 0:00 on 1 January of a given year. Until 1997, the target group was defined as women who, in the reporting year in question, are at least 50 years of age and no older than 69. From 1998 onwards, women aged from 70 to 75 were included (3 rounds of screening). The current target group consists of all women from 50 to 75 years of age. At the beginning of the reporting year in question, these women must be at least 49 years of age and no more than 74 (the age used for evaluation purposes). Screening does not strictly correspond to calendar years, moreover women have the option of rescheduling their appointment. As a result, it often happens that some women are screened at the age of 75.

Participation rate

Calculations of the participation rate are based on the number of invitations sent (excluding reminder invitations, so only the original invitations are counted). In the initial round of screening, this number corresponds to the number of women in the target group (give or take a few individuals) whose invitations were not sent, as the organisation was notified of their death before the invitations were actually posted. In the subsequent rounds (screening rounds 2 and later), a relatively larger number of women were not sent an invitation. These were women who, in an earlier round, had indicated (for various reasons) that they did not wish to receive any further invitations. This means that the group of women who are actually invited for further testing is smaller than the target group. As a result, in comparison with the invitations for an initial screening test, there is a slight bias in favour of the participation rate.

Tracing interval cancers

Interval cancers are detected by linking the files of those women who have been screened in a given year to the Cancer Registry's database. In connection with the official 2-year screening interval, this linkage can only take place in the third year after the end of the screening year (reporting year) in question. If a positive correlation is found between linked records, a check is made to determine whether or not these do indeed relate to the same woman, and whether an interval cancer or a screen-detected cancer is involved. The breast cancer in question is then tagged in the Cancer Registry database with a code 'I' or 'S'. In the case of interval cancers, the period (in months) since the last screening test is recorded.

Evaluation tables on the incidence and treatment of breast cancer

Each year, with the help of the regional screening organisations, the regional cancer registries fill in separate evaluation tables for data from the Cancer Registry. These *C tables* give details of new cases of breast cancer (incidence) by age and, where applicable, by relationship with the breast cancer screening programme ('screening relationship'). *D tables* give details of the primary and adjuvant therapy of mammary carcinomas, by age and screening relationship. It is necessary to link the population screening file to that of the Cancer Registry (see also interval cancers) in order to assess whether the registered breast cancer was detected by screening or whether it was di-

agnosed in a woman who had been screened at some time in the past (interval cancer).
Given that this linkage is primarily intended for tracing interval cancers, and that allowance has to be made for a screening interval of at least two years, the C and D tables cannot be completely filled in until approximately three years after the reporting year in question.

Unlike the Cancer Registry, the national evaluation is not based on a subject's actual age at diagnosis ('incidence date' Cancer Registry), but on their age at 0:00 on 1 January of a given year, in analogy with the other evaluation tables. In addition, the definition of mammary carcinomas used by the National Evaluation Team for Breast Cancer Screening in the Netherlands (NETB) may differ slightly from that used by the Netherlands Cancer Registry, in terms of a few, rare morphological types.

TNM-classification

The NETB uses a simplified classification system for breast cancer tumour size and lymph node status, derived from the TNM classification system developed by the Union for International Cancer Control (UICC). The 'T' stands for the size of the primary tumour ('size'), the 'N' for the regional lymph nodes and the 'M' for the occurrence of tumour tissue elsewhere in the body (distant metastases).

***T** categories used:*

Tis (DCIS)	Primary tumour only (Ductal) Carcinoma in situ
T1a	Invasive tumour, largest diameter <= 0.5 cm
T1b	Invasive tumour, largest diameter >0.5 cm and <= 1 cm
T1c	Invasive tumour, largest diameter >1 cm and <= 2 cm
T1r	Invasive tumour, largest diameter <= 2 cm (no classification into T1a, T1b or T1c)
T2	Invasive tumour, largest diameter >2 cm and <= 5 cm
T3	Invasive tumour, largest diameter >5 cm
T4	Invasive tumour, all sizes with invasion of chest wall and/or skin
Tx	Size of primary tumour cannot be determined

***N** categories used (involves invasive tumours):*

N- (or N0)	No tumour tissue in the regional lymph nodes
Nsn	No tumour tissue (metastases) in sentinel node
N+	Tumour tissue (metastasis) in regional lymph nodes / sentinel node
Nx	No lymph nodes examined

***M** categories used (in accordance with the UICC's TNM classification):*

M0	No distant metastasis
M1	Demonstrable distant metastasis

In general, pTNM (the post-surgical or pathological TNM) is used. If this is not available, then cTNM (the clinical TNM) is used instead. That involves the determination of tumour size and lymph node status during diagnosis.

The first decade of the 21st century witnessed the rise of neo-adjuvant therapy, which is designed to achieve a pre-operative reduction in tumour volume. If such volume reduction is successful, however, pT and pN will no longer reliably indicate the tumour's size and lymph node status during screening tests. Up until the end of 2011, this may have led to an underestimation of average tumour size. With effect from the start of 2012, cTNM was used instead of pTNM in these cases.

The Dutch nation-wide breast cancer screening programme

The screening programme is co-ordinated by the Centre for Population-based 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 (NETC) and the National Evaluation Team for Breast cancer screening (NETB). The five (up to 2010 nine) screening regionsare responsible for actually performing the screens. Each region boasts 2 to 4 reading 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. Before the implementation of digital mammography, an initial screen consisted of two-view mammography, whereas in subsequent rounds an oblique view was taken only as a standard; additional cranio-caudal views were taken only on indication Since 2013 all screening examinations consist of a two-view mammography. 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 within ten working days; 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, participation (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 a file of screened women to the file of the national cancer registry. (In the past linkage was carried out at regional level which may have led to some underreporting of interval cancers in women diagnosed and treated in another region than were screening took place). 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. Demographic and (breast cancer) mortality data are provided by Statistics Netherlands. The most common of these data can be downloaded directly from their website (http://statline.cbs.nl/StatWeb).

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 participation*
  The screening round corresponds with the number of invitations for screening of the individual woman regardless of her participation at the previous round(s). The participation 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 the interval cancer, to the date of the following screening examination, 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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