National evaluation of breast cancer screening in the Netherlands

NETB XV

National Evaluation Team for Breast Cancer Screening

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Contents

Breast cancer screening – definitions

- Attitude: perspective / a feeling or emotion or opinion in relation to a subject:
  - *explicit attitude:* conscious association that can be articulated;
  - *implicit attitude:* automatic association that may influence behaviour without the person being aware of it.

  A person's implicit attitude does not always align with their explicit attitude;
- Adjuvant therapy: a therapy, such as radiotherapy, chemotherapy, hormone therapy, targeted therapy, or any combination of these, administered as a complementary treatment following surgery;
- Ductal carcinoma in situ (DCIS): ductal carcinoma in situ is considered to be a pre-cancerous stage of breast cancer, which can develop into an invasive breast cancer. The malignant cells are still inside the milk ducts, have not yet started to infiltrate in the surrounding tissue and are not yet able to metastasize;
- Informed decision: when someone has sufficient knowledge, a positive attitude, and participates in the screening programme, or when someone has sufficient knowledge, a negative attitude, and does not participate in the screening programme;
- Efficiency frontier: a curve displaying all cost-effective alternatives;
- Incremental cost-effectiveness ratio (ICER): the difference in costs of the interventions being compared divided by the difference in effects;
- Interval cancer: breast cancer diagnosed after a negative screening result (a result that did not lead to a referral) in the interval (first 2 years or 30 months) after the screening;
- Lumpectomy: breast-conserving surgery in which the tumour is removed from the breast but the breast itself is preserved;
- Mastectomy: amputation of the breast;
- MISCAN model: the MIcrosimulation SCreening ANalysis model is a microsimulation model that simulates the lifespan of women, the progression of breast cancer, and the outcomes of the screening programme;
- Neoadjuvant therapy: systemic therapy administered prior to the surgical removal of a tumour or tumours;
- Overdiagnosis: the diagnosis of breast cancer through screening that would never have caused any harm in the lifetime of the woman concerned. The diagnosis therefore does not confer any benefit to the woman in terms of survival, but it could result in possible adverse effects from treatment;
- Positive predictive value: the likelihood that a woman has breast cancer following a positive screening result;
- Programme sensitivity: sensitivity indicates the probability that a screening test is positive for a woman with breast cancer at the time of screening. The programme sensitivity of screening is indicated by the proportion of true positive results out of all breast cancers (true positive and false negative results combined) detected in screening and in the first two years after screening. True positive results are derived from the detection rate. Interval cancers serve as a proxy for the number of false negative results. Since this includes cancers that were not detectable during screening (fast-growing cancers), but also cancers that were missed or misinterpreted at screening, the programme sensitivity is lower than the test sensitivity of mammography;

- Programme specificity: programme specificity is indicated by the proportion of true negative results out of all screening results without a breast cancer diagnosis (true negative and false positive results combined) in the first two years after screening. The number of true negative results in the screening programme is calculated by subtracting the number of true positive, false positive, and false negative results from the total number of screening examinations;
- QALY: quality-adjusted life-year: a year of life adjusted for quality of life;
- Risk stratification: screening tailored to a woman's individual risk of breast cancer. This could mean that women at higher than average risk are invited for screening more frequently and/or at an earlier/younger age or that they are screened using a different screening modality. Conversely, women at lower than average risk could enter the screening programme at a later age or be invited for screening less frequently;
- Sensitivity: the probability that the screening test is positive for a woman with breast cancer at the time of screening. The sensitivity of a test is thus the percentage of true positive results among women with breast cancer (true positive plus false negative results);
- Systemic therapy: chemotherapy, hormone therapy, and targeted therapy.

Introduction

The Dutch population screening programme for breast cancer has been running for nearly 35 years and has extensively proven its worth. Although there have been no major changes to the programme design in recent years, it is important to continue to closely monitor screening outcomes and evaluate new developments in a timely manner, to see whether the screening programme could be further improved.

The Dutch screening programme is continuously monitored and regularly evaluated. For the past few years, the Netherlands Comprehensive Cancer Organisation (IKNL) has been responsible for assessing/reporting key indicators, enabling short-cycle monitoring of the programme. The Dutch Expert Centre for Screening (LRCB) is responsible for continuous quality assurance and training of professionals with regard to the execution of the screening programme.

The National Evaluation Team for Breast Cancer Screening (NETB), a partnership between Erasmus MC and Radboud university medical center (Radboudumc), regularly evaluates the benefits, harms, costs, and cost-effectiveness of the programme. Based on in-depth analysis of screening and clinical data, the screening programme outcomes are compared with the expected effects. In addition, predictions are made for potentially important developments that might affect the program, such as a new screening test. The expected long-term effects of the screening programme are estimated using a computer simulation model developed by the Erasmus MC Department of Public Health (MGZ).

In this fifteenth report, the NETB provides an overview of the key outcomes of the breast cancer screening programme and describes relevant national and international developments.

Chapters 2 through 5 examine the health benefits achieved through the Dutch screening programme.

Chapter 2 begins by presenting the decline in breast cancer mortality in the Netherlands and estimating the extent to which this can be attributed to screening. These estimates are then compared with international studies.

Chapter 3 provides an overview of the shift in breast cancer disease stage at diagnosis brought about by the screening programme. This stage shift is the basis for all of the effects of the screening programme. This includes the differences in treatment, which are summarised in Chapter 4.

Chapter 5 discusses the differences in long-term outcomes between women with breast cancer detected at screening and women with breast cancer detected clinically, comparing quality of life after treatment, five-year disease-free survival, and mortality from breast cancer.

Chapters 6 through 8 examine participation in and the direct results (benefits and harms) of the screening programme.

Chapter 6 describes the outcomes of the screening programme over the past years. Trends in referrals, detection of breast cancer through screening, and interval cancers are shown for the years 2004 to 2019. The sensitivity, specificity, and false positive referrals are also described and compared with international studies.

In Chapter 7, we explore the recent slight decline in participation in the screening programme. Various analyses are described, including participation in relation to socioeconomic status, participation during the COVID-19 pandemic, and concurrent participation in other screening programmes. This chapter also covers a study that describes women's knowledge about screening and attitudes with regard to participation in the screening programme.

In Chapter 8, we calculate the probability of a person receiving an unfavourable screening result over 11 screening examinations (cumulative referral rate). We also calculate the probability that no breast cancer will be found in further assessment (false positive result). Although the referral rate in the Netherlands is one of the lowest in the world, the cumulative probability is not insignificant across all

screening examinations in a lifetime. The impact of receiving a false positive result can also be seen in the reduced participation in the screening programme of women who received a false positive result in the previous examination.

Chapter 9 describes the costs associated with the screening programme.

Chapter 9 provides an overview of the total cost per screening examination. This has been stable since 2012, with the exception of 2020, due to the temporary halt of the screening programme due to COVID-19. The cost-effectiveness of the screening programme is calculated and compared with alternatives, such as starting at a younger age, three-yearly screening, using MRI for women with extremely dense breast tissue, and tomosynthesis.

Chapter 10 examines possible changes that could be made to the screening programme in the future.

In Chapter 10, we describe both the benefits and harms of the screening programme. We also look to the future and describe a number of important developments that could have an impact on the programme. For example, we describe research into possible further risk stratification, as well as new screening modalities, such as tomosynthesis, MRI, and contrast-enhanced mammography.

2 Breast cancer mortality reduction

Key points

- Breast cancer mortality in the Netherlands has decreased over the past 30 years, partly due to the screening programme.
- Two studies using Dutch data show that population screening can lead to a reduction in breast cancer mortality of 33 to 58%.
- The screening programme is estimated to prevent around 1,300 breast cancer deaths in the Netherlands each year.

2.1
Trends in breast cancer mortality in the Netherlands

Mortality from breast cancer has declined over the past three decades. **Figure 2.1** shows the trends in breast cancer mortality for various age groups over the period 1989-2021. In each of the five-year age groups, mortality from breast cancer decreased by 40 to 60% over the time period concerned. The biggest relative decrease was seen for women in the 50-54 age group. For most groups, the decline in breast cancer mortality has been less prominent in the past five years. In the under-50 age groups, no further decline in the mortality rate can be seen. The effects of the screening programme temporary halt caused by COVID-19 and the extension of the 24-month screening interval due to labour market shortages and COVID-19 restrictions are not reflected in the breast cancer mortality figures for 2020 and 2021.

Based on these trends, it is not possible to determine how much of the decline in mortality rate can be attributed to the screening programme. Alongside the introduction of population screening, breast cancer treatment has improved significantly over the past 30 years. The decrease in breast cancer mortality in the age groups that do not participate in the screening programme confirms this fact. However, even in these age groups, screening plays a role: women under the age of 50, particularly those aged between 45 and 50, are sometimes screened outside of the screening programme. In particular, women who are known to have an increased risk of breast cancer often take part in intensive hospital-run surveillance programmes. Earlier detection of tumours in women over the age of 70 will also have an effect on the breast cancer mortality rate among women aged 75 and over.

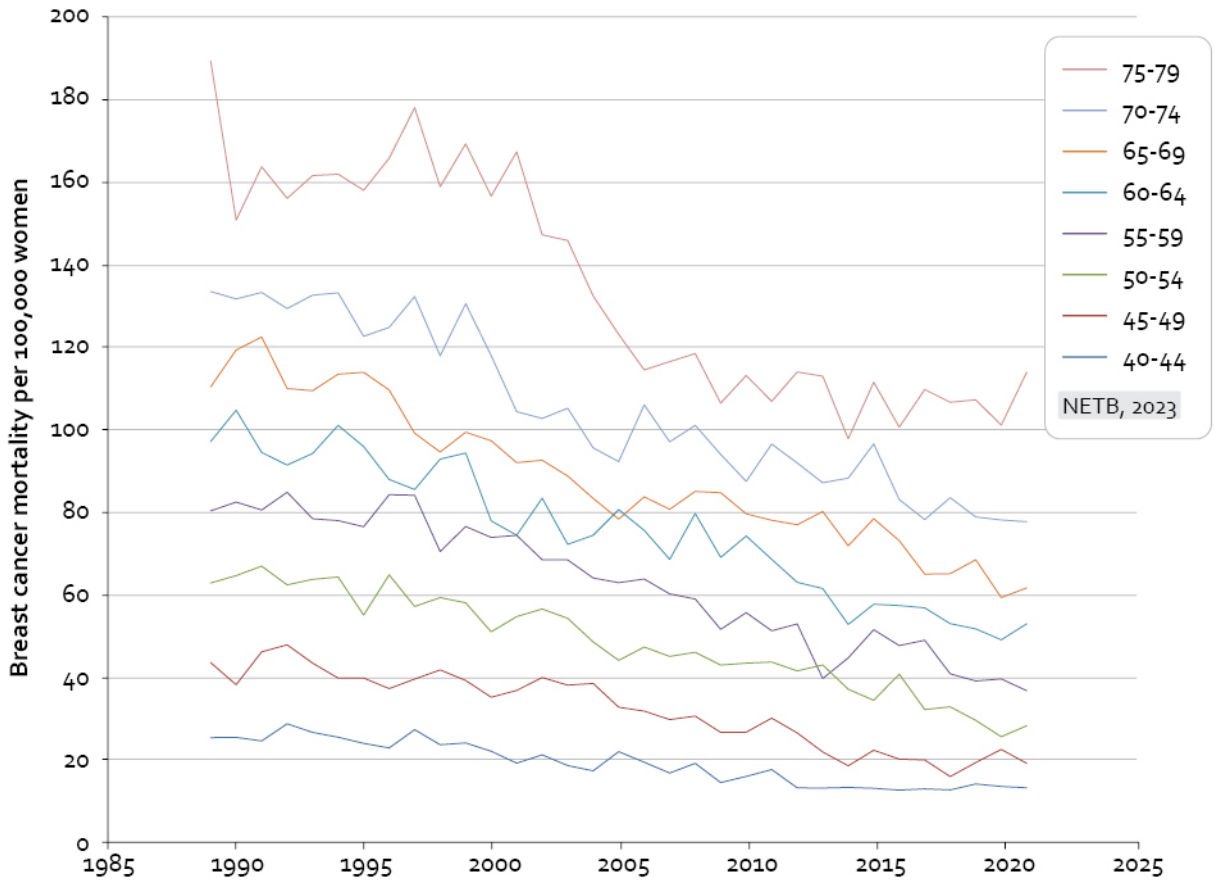

Figure 2.1
Breast cancer mortality rates per 100,000 women over the years 1989-2021 for various age groups.
Source: IKNL. The 2021 figures come from Statistics Netherlands and are provisional.

2.2
Dutch and international studies on breast cancer mortality

Previous studies using Dutch data used other methods to evaluate the effect of the screening programme on breast cancer mortality. The first study showed a 58% drop in the breast cancer mortality rate for participants in the screening programme compared with non-participants (Paap et al., 2014).

The second study evaluated the effect of the screening programme on the trend in breast cancer mortality based on a municipal-level trend analysis (Sankatsing et al., 2017). Women aged between 55 and 74 experienced a 30% decrease in breast cancer mortality 20 years after the introduction of screening. In municipalities that started the screening programme early (between 1987 and 1992), a similar decrease in mortality was found as in municipalities that started later (1995–1997), despite the fact that treatment improved significantly between these periods.

In the past few years, no new studies with Dutch data have been published that examine the effect of the screening programme on breast cancer mortality. However, a systematic review was recently published of all literature relating to the decline in breast cancer mortality as a result of population screening programmes in Europe (Zielonke et al., 2020). Out of 60 published studies, 19 studies of good or adequate quality were selected. Eight of these studies were from Western Europe. These eight studies found a 12-58% decrease in the breast cancer mortality rate among participants in population screening programmes compared with non-participants. For Northern Europe, the decrease was 33-43% (five studies); for Southern Europe, it was 43-45% (two studies).

The MISCAN (MIcrosimulation SCreening ANalysis) model has been used to calculate the long-term effects and costs of the screening programme in the Netherlands. This model simulates the lifespan of women, the progression of breast cancer, the treatment given, and a screening programme. The results show that the current screening programme has reduced breast cancer mortality by 33% compared with a situation without a screening programme (Kregting et al., 2022).

2.3
Predicting the number of breast cancer deaths prevented per year in the period 2023-2029

The MISCAN model has been used to predict breast cancer mortality in the Netherlands over the next few years, based on the current situation with population screening. By comparing these model predictions with a situation in which no population screening is modelled, an estimate was made of the number of breast cancer deaths prevented per year by the screening programme. Due to the impact of the labour market shortages and COVID-19 restrictions, this prediction was based on the situation in 2019-2021 with a participation rate of 76% (with a temporary drop to 66% for part of the period 2020-2021) and a screening interval of 25-31 months in the period 2019-2025 and 24 months in the period 2026-2029.

The model predictions showed that, for the period 2023-2029, in the current situation with a longer screening interval, an estimated 1,285 breast cancer deaths will be prevented each year. If the screening interval had remained at 24 months, this figure would have been 1,336 breast cancer deaths per year. These estimates are higher than in the previous report, due to an estimated increased risk of developing breast cancer and an increase in average age over the next few years.

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3 Tumour size and stage distribution at the time of breast cancer diagnosis

Key points

- Ductal carcinoma in situ (DCIS) is a non-invasive form of breast cancer that is mainly detected in screening participants.
- For those with invasive breast cancer, a breast cancer detected through screening is usually at an early stage (TNM stage 1 or 2). Advanced breast cancer (TNM stage 3 or 4) is most often detected in those who were screened more than 30 months ago or have never been screened.
- The ratio of breast cancer diagnosed at an early stage (stage 1 or 2) to breast cancer diagnosed at an advanced stage (stage 3 or 4) is most favourable for breast cancer detected at screening (22:1). The ratio is less favourable for breast cancer detected in the interval between two screening examinations (5:1), and it is least favourable for those who have never been screened or who were screened > 30 months ago (3:1).

3.1 Introduction and method

This chapter examines the stage distribution of breast cancer at the time of diagnosis. The stage of the tumour is important for the disease prognosis. In this chapter, the differences between screened and non-screened people are described. We distinguish between three groups: participants with breast cancer (1) detected at screening following a positive screening result; (2) diagnosed in a period of 30 months after a negative screening result; and (3) diagnosed without participation or recent participation in the screening programme. The last group comprises people who have never participated and participants who last took part in the screening programme more than 30 months ago. The data were obtained from the Netherlands Comprehensive Cancer Organisation (IKNL) and the screening organisation Bevolkingsonderzoek Nederland. The above distinction can be made from 2006 onwards. Data were provided up to the end of 2017 (i.e., before COVID-19 and before the issues leading to the increased screening interval). For all groups, we looked at the 50-74-year-old age group. The incidence rates were standardised using the European standard population for 2013 (Eurostat). The incidence rates were calculated according to the number of women in the population. Thus, the incidence rate for breast cancer in screening in any given year is the number of people with breast cancer detected at screening *per 100,000 women in the population* in the year in question. That means that an increase or decrease in screening participation affects the incidence rate (the numerator changes, but the denominator does not). For detection rates (the number of people with breast cancer detected at screening *per 1,000 screening examinations*), we refer to Chapter 6: Screening performance. The detection rate is not affected by a change in screening participation (the numerator and denominator change by the same proportion).

3.2 Ductal carcinoma in situ (DCIS) versus invasive breast cancer

Breast cancer can be detected as an invasive cancer or at a pre-cancerous stage as ductal carcinoma in situ (DCIS). The latter form of breast cancer is mainly detected through population screening. This is because DCIS usually manifests as calcifications that are clearly visible on a mammogram but cannot be felt.

This can be seen in **Figure 3.1** by comparing the light blue solid line (DCIS from screening) with the light blue dashed line (interval DCIS) and the overlapping light blue dotted line (DCIS in people who last participated more than 30 months ago or have never participated in the screening programme).

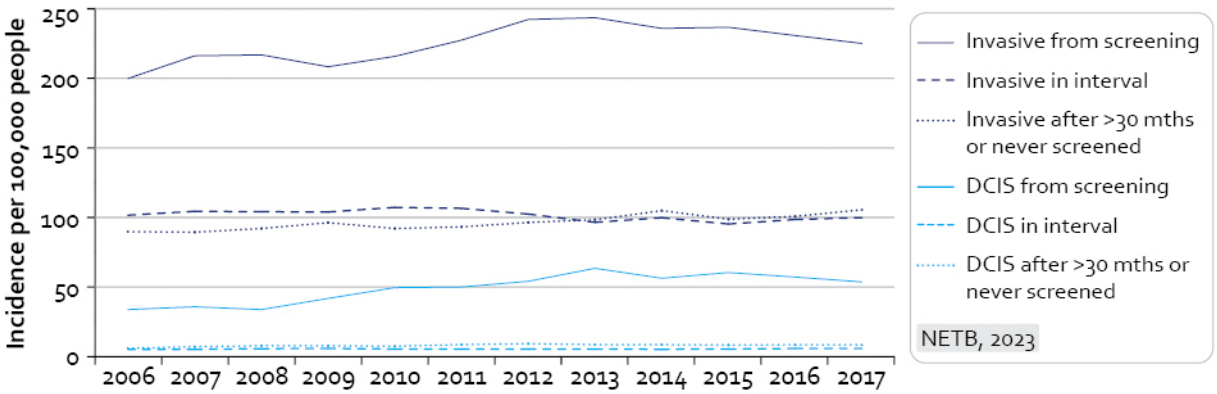

Figure 3.1
Age-adjusted incidence rate of invasive breast cancer and DCIS per 100,000 women in the population, by detection method.

Figure 3.1 also shows that the incidence rates for both invasive breast cancer (dark blue line) and DCIS (light blue line) found through screening follow an upward trend from 2010 before levelling off a few years later. This is a consequence of the transition from film to digital mammography (introduced gradually between 2008 and 2010), which increased the detection of both invasive breast cancer and DCIS. We call this the "prevalence peak". From 2013, the incidence rates were stable or slightly decreasing but still higher than in the period with film mammography. On the one hand, this is because the incidence has passed the prevalence peak. On the other hand, the slight drop in invasive breast cancer and DCIS found through screening after 2013 may be a consequence of the decline in screening participation. This meant the number of breast cancers detected decreased while the population numbers remained the same, resulting in the incidence rate falling.

Because the first round with digital screening will detect a range of breast cancers, from an early stage to almost presenting with symptoms (prevalence peak), a dip occurred in the number of people with invasive breast cancer in the interval between two screening examinations (green line). This stabilised after 2013 at more or less its previous level, before the transition to digital mammography.

Incidence rates for invasive breast cancer were highest for people whose cancer was found through screening in 2017, at 218 per 100,000 women, compared with 100 and 106 per 100,000 for people with an interval cancer or people who were last screened more than 30 months ago or had never been screened. The incidence rate for DCIS found through screening was still significant, at 56 per 100,000 women, but considerably lower than for invasive breast cancer. DCIS plays only a minor role for the other two groups, with rates of 10 and 11 respectively per 100,000 women.

3.3 Stage distribution by detection method

Stage distribution is based on the pTNM classification (the p stands for pathological). In addition to tumour size, this system involves looking at lymph node status and distant metastasis (Brierley et al., 2017). If the pTNM stage cannot be determined (because of neoadjuvant therapy, for example), the cTNM system is used (c for clinical, or "based on clinical findings").
Stage 0 refers to DCIS, which, as described earlier, almost always falls into the group of carcinomas detected at screening (top panel of **Figure 3.2**).

We also distinguish between early tumours, i.e., stage 1 and 2 (middle panel), and advanced tumours, stage III and IV (bottom panel). Tumours with an unknown stage are almost non-existent, because if there is no pTNM (pathological) stage, the cTNM (clinical) stage is used.

Stage I and II tumours (small tumours and/or few affected lymph nodes) are mainly detected through screening and to a lesser extent as interval carcinomas or in people who were last screened more than 30 months ago or have never been screened.

For stage III and IV tumours (advanced tumours), the reverse is true. These tumours are mainly found in the group of people who were last screened more than 30 months ago or have never been screened, or in the interval between two screening examinations. In the last five years (2013-2017), the light blue and red lines have diverged, with the highest incidence of advanced tumours being in the group of people who were last screened more than 30 months ago or have never been screened. The incidence rate for advanced stage breast cancer is lowest in the group detected through screening. Note: the Y axis for the top two panels goes from 0 to 250 breast cancers per 100,000 women, while for the lowest panel, it goes from 0 to 100 breast cancers per 100,000 women; this panel has been enlarged.

The stage distribution ratio of early (stage I and II) versus advanced (stage III and IV) breast cancers is most favourable for breast cancers detected at screening. In 2017, 215 early stage versus 10 advanced stage breast cancers were detected at screening, per 100,000 women. That is a ratio of 22 early stage breast cancers for every advanced stage breast cancer (22:1). For breast cancers detected between

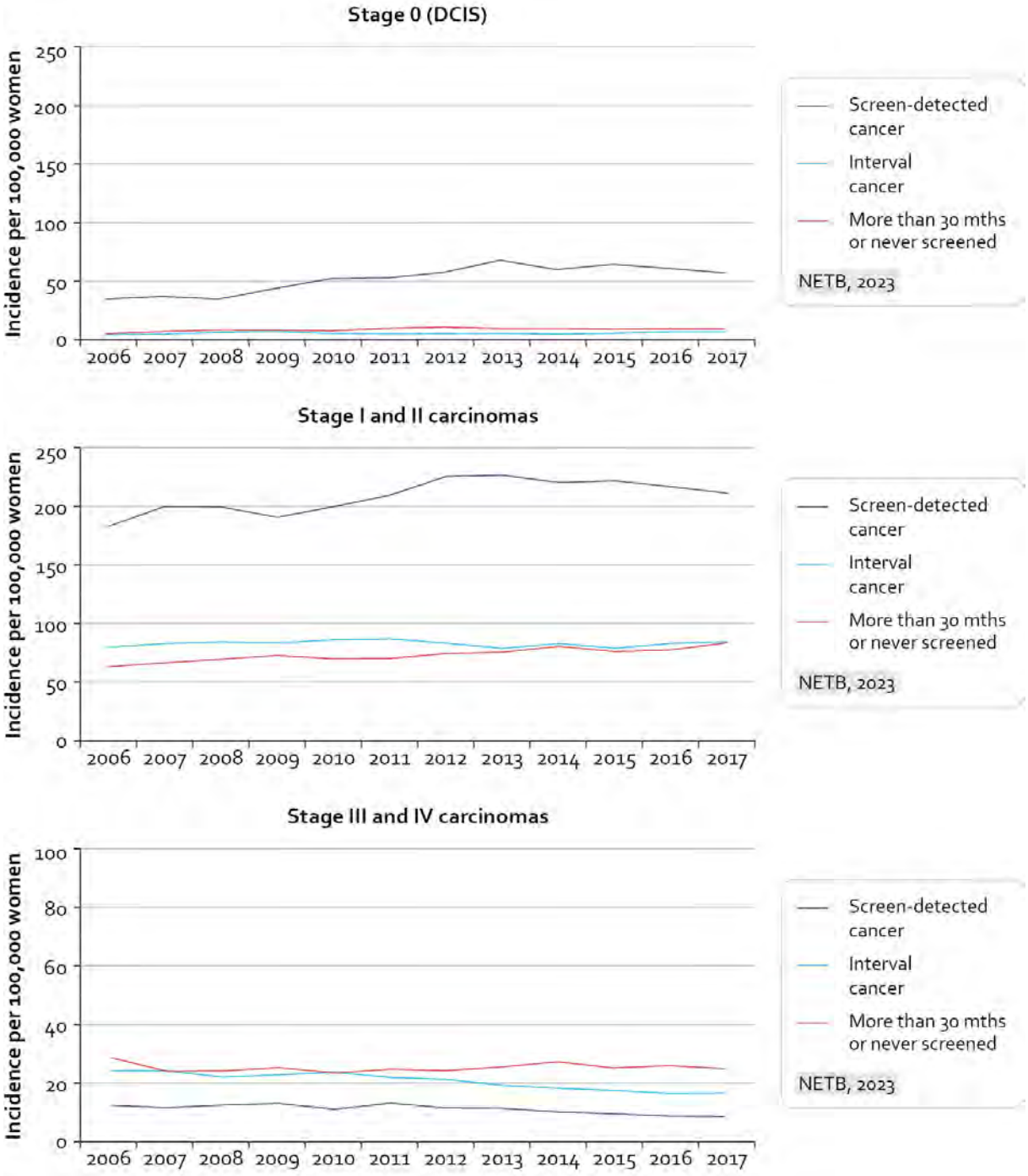

Figure 3.2
Age-adjusted incidence grouped by stage (0 DCIS, early I/II and advanced III/IV) and detection method of breast cancer in the 50-74 age group.
NB: the Y axis scale varies across the panels.

two screening examinations, this ratio is less favourable, at 84 versus 17 per 100,000, or 5:1. For the group screened more than 30 months ago or never, the ratio is least favourable, at 83 versus 25 per 100,000, or 3:1.

The more favourable stage of the invasive breast cancers detected through screening improves the starting point for treatment and the likelihood of survival. On the other hand, in some cases, the detection of DCIS is an overdiagnosis (van Luijt et al., 2016).

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4 Breast cancer treatment

Key points

- The percentage of invasive breast cancers treated with neoadjuvant therapy is on the rise and is particularly high among young women (>50% of women under 40).
- Most invasive breast cancers are removed surgically, increasingly through breast-conserving surgery. Mastectomies are increasingly being followed by reconstructive surgery.
- There were no major shifts in adjuvant therapy in the period 2010-2017.
- DCIS is increasingly being treated with breast-conserving surgery.
- Screen-detected breast cancers are treated less intensively (because they are found at an earlier stage); this applies to neoadjuvant therapy as well as surgery and adjuvant therapy.

4.1 Introduction

This chapter examines the treatment of breast cancer, focusing on women who are aged between 50 and 74 and are thus in the target group for the screening programme. It looks at both screened and non-screened women. Data from the Netherlands Comprehensive Cancer Organisation (IKNL) were linked to data from Bevolkingsonderzoek Nederland, allowing the therapy data to be stratified by screening relationship. Data are available from 2004 through 2017. In this chapter, we describe trends over time for the 50-74 age group (n=120,678) and trends by age for the 2017 calendar year (n=15,719) for neoadjuvant therapy, surgery, and adjuvant therapy. We then look at the treatment of DCIS and at treatment according to detection method.

4.2 Neoadjuvant therapy for invasive breast cancers

The arrival of neoadjuvant therapy around the year 2000 marked the start of a major change in breast cancer treatment. Neoadjuvant therapy means that, following the diagnosis, the breast cancer is first treated systemically, with the aim of shrinking the tumour before it is removed surgically.

The percentage of women who received any form of neoadjuvant therapy increased from 3.0% in 2004 to 17.6% in 2017 (**Figure 4.1**). The majority of these women received only neoadjuvant chemotherapy; a smaller percentage received a combination of neoadjuvant chemotherapy and hormone therapy or only neoadjuvant hormone therapy.

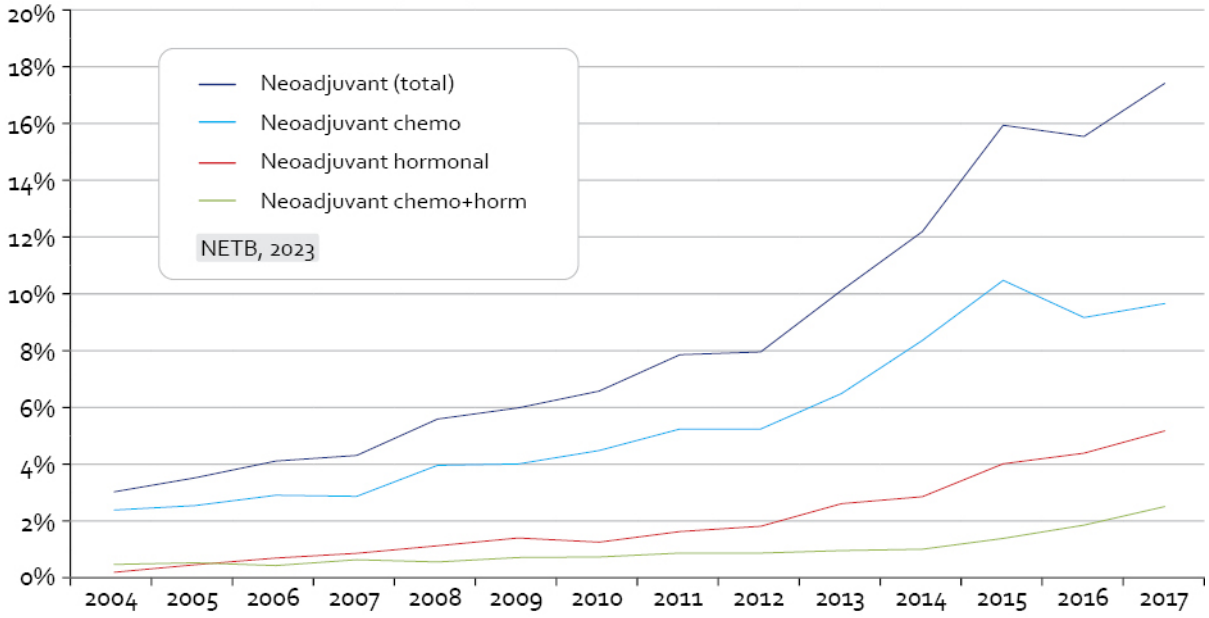

Figure 4.1
Neoadjuvant therapy for invasive breast cancers in women aged 50-74 years in 2004-2017.

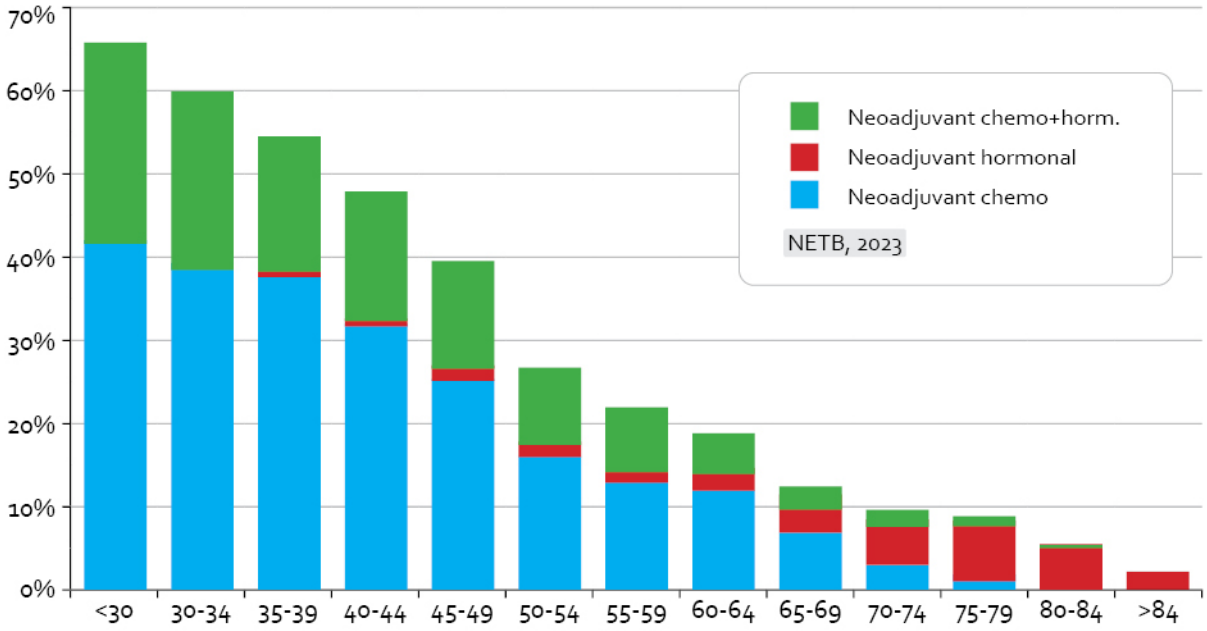

Figure 4.2
Neoadjuvant therapy for invasive breast cancers in 2017 by age.

It is predominantly young women who are eligible for neoadjuvant therapy (**Figure 4.2**). Neoadjuvant therapy is less frequently given to older women, but if it is given, it is relatively more likely to be hormonal therapy.

4.3 Surgical treatment of invasive breast cancers

Most invasive breast cancers are surgically removed: in 2017, 67.4% of invasive breast cancers were treated with breast-conserving surgery (lumpectomy) and 26.9% with a mastectomy, of which 6.0% included reconstruction (**Figure 4.3**). In a mastectomy, all mammary gland tissue is removed. About 5.8% of women did not undergo surgery. This percentage increased significantly after the age of 75, to 67.6% of women in the oldest age category (84+, see **Figure 4.4**).

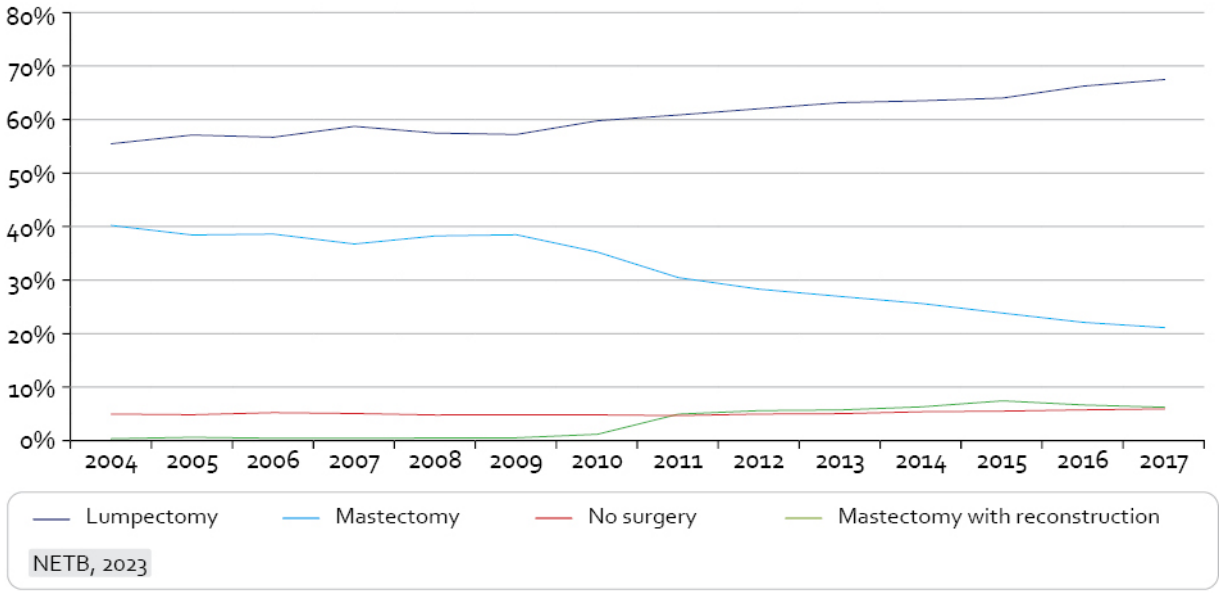

Figure 4.3
Surgery for invasive breast cancers in women aged 50-74 years in 2004-2017.

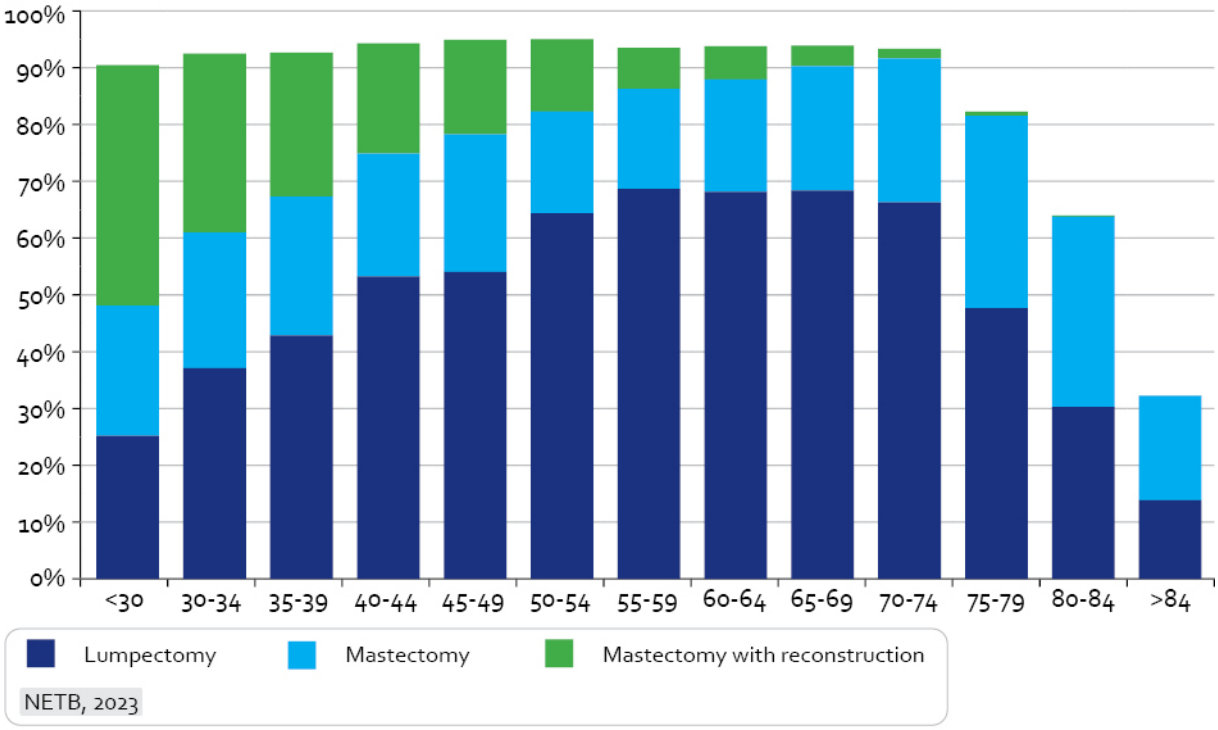

Figure 4.4
Surgery for invasive breast cancers in 2017 by age.

4.4 Adjuvant therapy for invasive breast cancers

The vast majority of all women with invasive breast cancer receive further treatment after surgery in the form of adjuvant therapy, i.e., radiotherapy, chemotherapy, hormone therapy, targeted therapy, or any combination of these. In recent years, around 28% of women with invasive breast cancer have been treated with radiotherapy alone and 35% with a combination of radiotherapy and hormone therapy (see **Figure 4.5**). The percentage of women with invasive breast cancer who received no further treatment in the form of adjuvant therapy fell from around 19% in 2004 to less than 12% in the period 2011-2013 before rising slightly to 14% in 2017. In general, there were no major shifts in adjuvant therapy in the period 2010-2017.

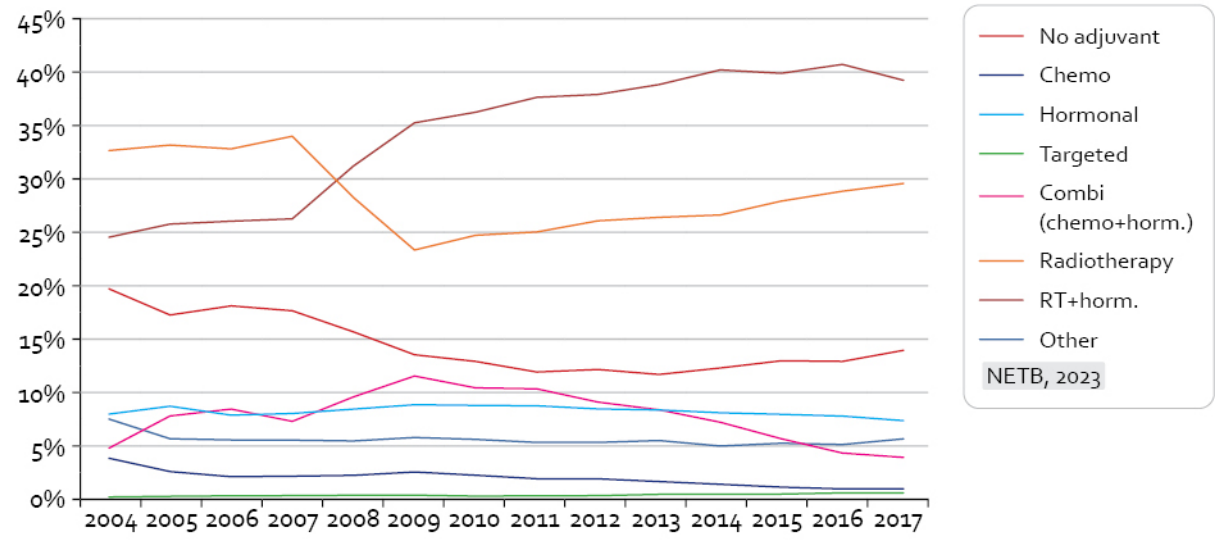

Figure 4.5
Adjuvant therapy for invasive breast cancers in women aged 50-74 years in 2004-2017.

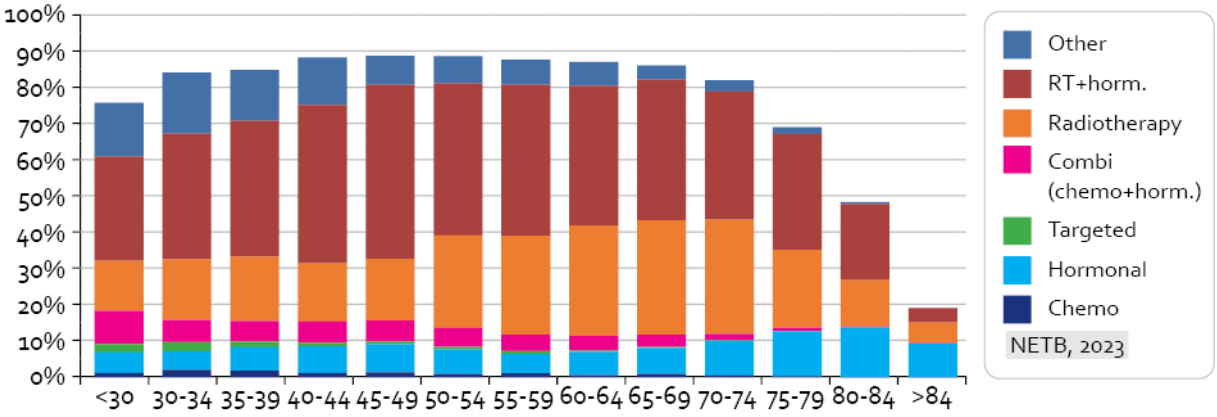

Figure 4.6
Adjuvant therapy for invasive breast cancers in 2017 by age.

Younger women are less likely to be given adjuvant therapy (**Figure 4.6**). However, a significant proportion of this group will have received neoadjuvant therapy. Elderly women are less likely to receive adjuvant therapy; if they do receive it, it is less likely to be radiotherapy and slightly more likely to be hormone therapy.

4.5 DCIS

In the period 2004-2017, neoadjuvant therapy was rarely given for ductal carcinoma in situ (DCIS) (fewer than 0.1% of cases). The overwhelming majority of DCIS cases were treated with surgery: 96.5% of DCIS in women aged 50-74 years in 2017. Over time, the percentage of cases treated with breast-conserving surgery has increased, and the percentage treated with mastectomy (without reconstruction) has decreased (**Figure 4.7**). Younger women receive reconstructive surgery more frequently than older women (**Figure 4.8**). In 78.4% of DCIS cases treated with breast-conserving surgery, subsequent radiotherapy was administered.

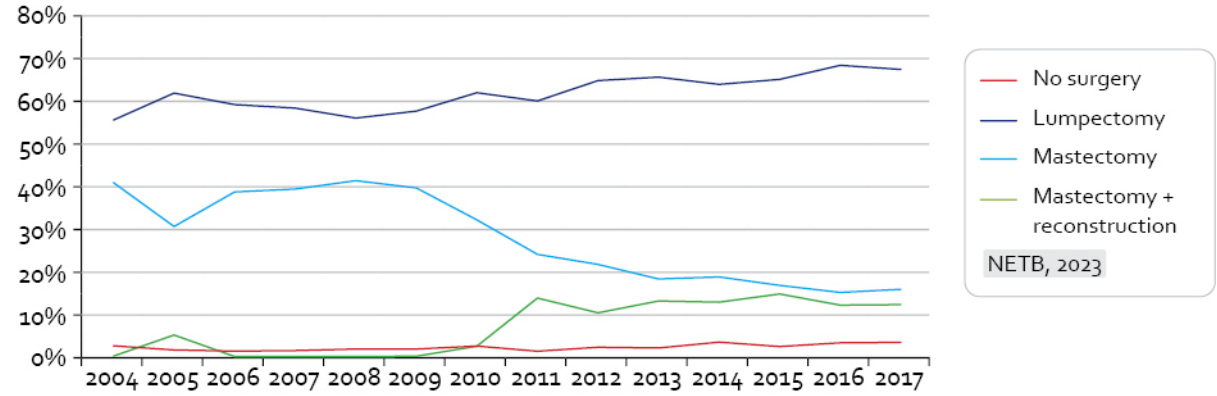

Figure 4.7
Surgical treatment for DCIS in women aged 50-74 years in 2004-2017.

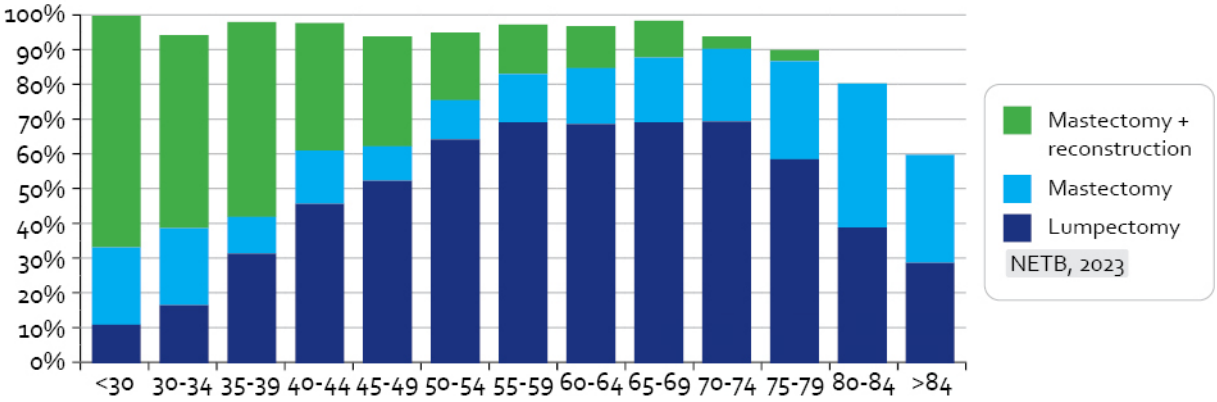

Figure 4.8
Surgical treatment for DCIS in women in 2017 by age.

4.6 Treatment according to detection method

In Chapter 3, we explained that screen-detected breast cancers are typically smaller than interval cancers or breast cancers in women who did not participate in the screening programme. This difference in tumour stage distribution results in a different therapy distribution of screen-detected tumours compared with clinically detected breast cancers, as can be seen in **Figures 4.9 through 4.11**. A distinction is drawn here between screen-detected cancers, interval cancers discovered within 30 months of the last screening, and cancers detected clinically more than 30 months after the last screening or in non-participants.

In general, screen-detected cancers are treated less intensively than interval cancers or breast cancers in women who did not participate in the screening programme. For example, screen-detected cancers are treated with neoadjuvant therapy less often (10% versus 24%), with breast-conserving surgery more often (lumpectomy) (80% versus 47%) and with just radiotherapy more often (40% versus 18%) than breast cancers in women who were last screened more than 30 months ago or have never been screened.

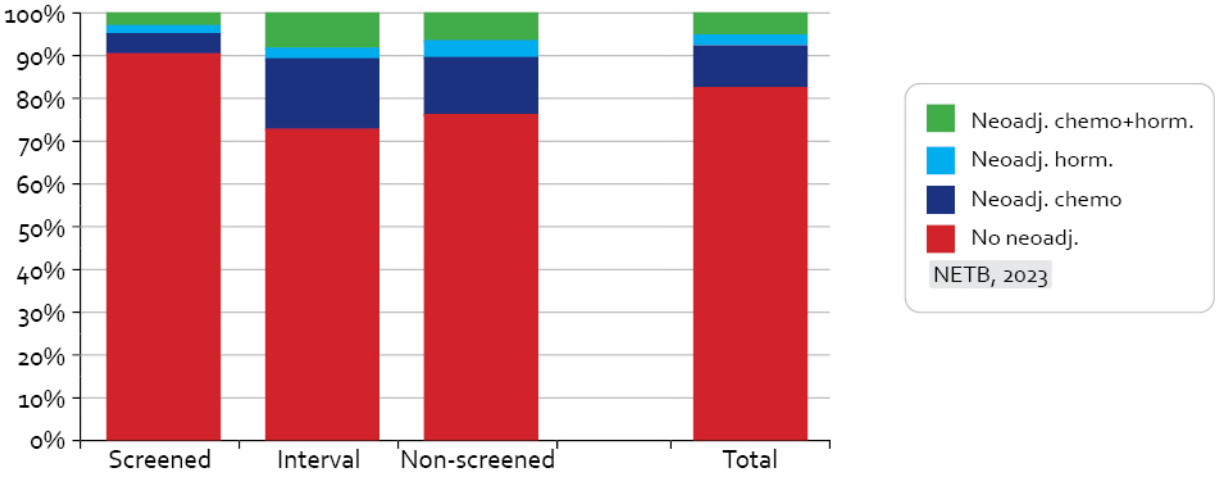

Figure 4.9
Neoadjuvant therapy for invasive breast cancers in 2017, broken down by detection method

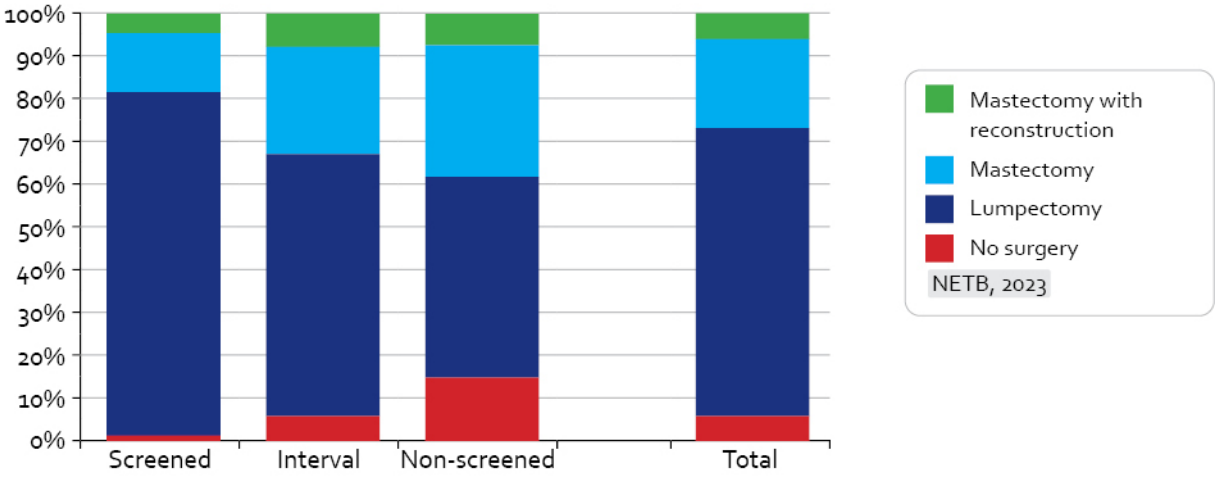

Figure 4.10
Surgery for invasive breast cancers in 2017, broken down by detection method

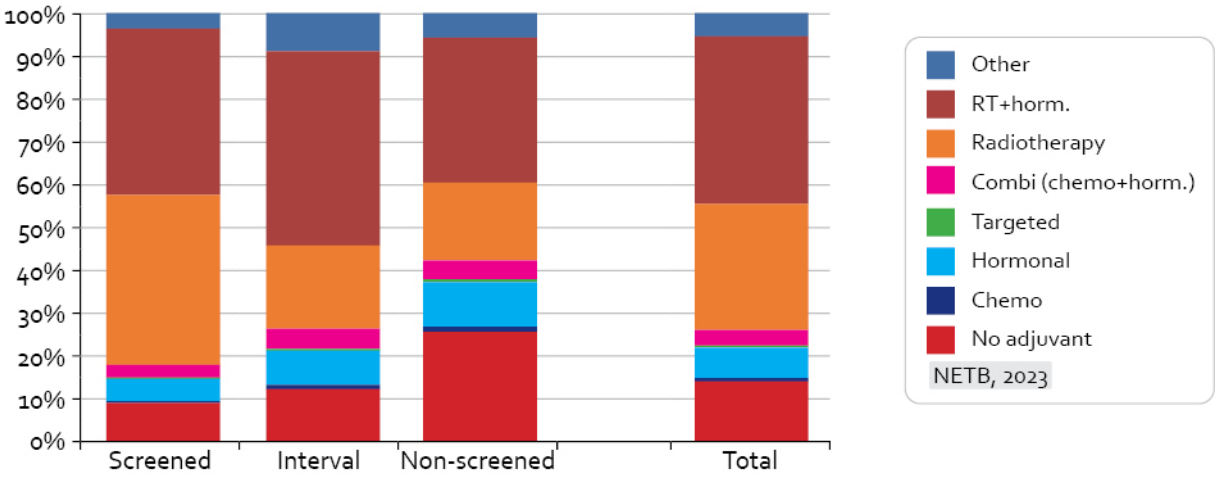

Figure 4.11
Adjuvant therapy for invasive breast cancers in 2017, broken down by detection method

5 Screening outcomes

Key points

- Women treated for breast cancer after referral from the screening programme have a slightly higher quality of life and fewer symptoms than women diagnosed outside of the screening programme.
- Women with breast cancer detected through screening have a more favourable stage distribution, lower chance of metastasis, and lower chance of recurrence of the disease than women with an interval cancer or clinically detected breast cancer.
- The overall mortality rate and breast cancer mortality rate are higher among breast cancer patients than in the general population. This excess mortality, both overall and breast cancer specific, is considerably lower – by around half – in patients with breast cancer detected through screening than in patients diagnosed outside of the screening programme.

5.1 Introduction

The breast cancer screening programme has decreased the breast cancer mortality rate (see Chapter 2). In addition to the effect on the mortality rate, other outcomes are also influenced by the screening programme. For example, tumours are detected at an earlier stage, the treatment is less intensive, and quality of life may be better. On the other hand, breast cancer detection can also have undesirable effects, such as anxiety, depression, and adverse effects from the breast cancer treatment. Accordingly, as well as considering the effect on the mortality rate, it is important to look at the quality of life. A second question is whether, after treatment, breast cancer found through the screening programme recurs or spreads to other organs less frequently. Finally, it is important to determine whether the long-term adverse effects of treatment lead to a higher rate of mortality from other causes. These three different outcome measures (quality of life, disease-free survival, and causes of death) will be examined in this chapter. A summary of three relevant studies is set out below (Otten et al., 2020a, Otten et al., 2020b, Otten et al., 2021).

5.2 Quality of life

In the UMBRELLA study, questionnaires (EORTC QLQ-C30 and QLQ-BR23) were completed by 1,327 breast cancer patients, of whom 775 (58%) had had their tumour detected through the screening programme (screening group) and 552 (42%) were diagnosed after experiencing symptoms (clinical group) (Gal et al., 2019). The patients were diagnosed during the period 2013-2017. The screening group was slightly older (61.3 versus 60.1 years), had a more favourable stage distribution (66% versus 37% had stage I), and had undergone less intensive treatment than the clinical group. For instance, 7% of the patients in the screening group had had a mastectomy, compared with 18% in the clinical group. The EORTC QLQ-C30 is a questionnaire comprising 30 questions about function (physical, role, cognitive, emotional, and social), general health, and symptoms (fatigue, pain, nausea and vomiting, shortness of breath, insomnia, loss of appetite, constipation, diarrhea, and financial problems). The EORTC QLQ-BR23 is an expanded version of the QLQ-C30 that specifically focuses on treatment-specific problems with breast cancer; it comprises 23 questions. The higher the score given to symptoms, the worse the symptoms are.

The results showed that 17-24% of all patients had problems with anxiety and/or depressive symptoms, which were still present one year after diagnosis. There was a very small difference in anxiety and depression between the screening group and the clinical group, and the stage at diagnosis had little effect on the severity of the anxiety or depression.

The quality of life was higher, and there were fewer symptoms in the screening group than in the clinical group, but the differences in scores between the two groups were small (**Figure 5.1**). The differences between the two groups of breast cancer patients and a group of women without breast cancer (norm population) were also small, with the exception of symptoms such as shortness of breath, insomnia, and fatigue, which may relate to the treatment. These symptoms were more common in the clinical group. The quality of life measured after one year was better than shortly after diagnosis. The quality of life was lower for patients with a stage III tumour than for patients with a tumour at a better stage.

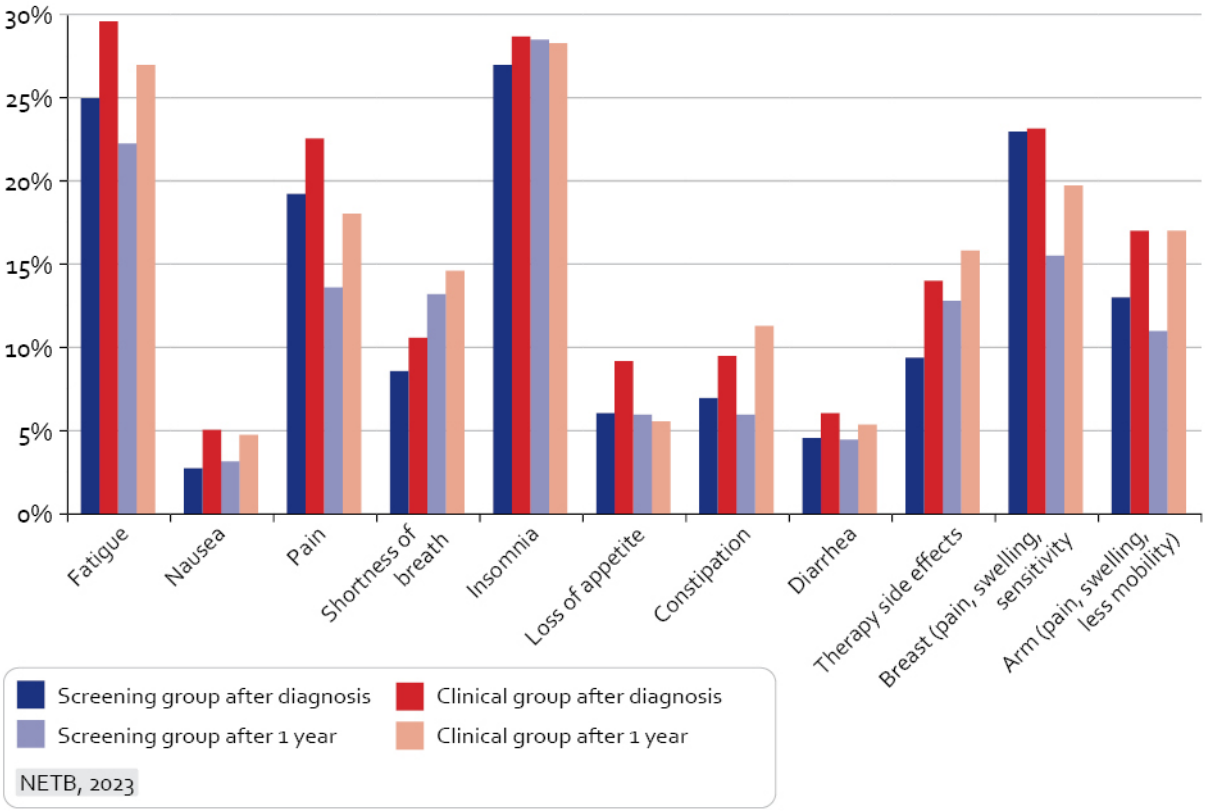

Figure 5.1.
QLQ-C30 and QLQ-BR23 questionnaire scores for the screening and clinical groups.

Breast cancer patients who had received neoadjuvant therapy (Chapter 4) mainly experienced side effects during treatment, while patients who had received chemotherapy reported a lower quality of life due to side effects one year after diagnosis. Breast cancer patients who underwent mastectomy had a considerably more negative body image than patients treated with breast-conserving surgery. Patients who had undergone axillary lymph node dissection in which more than three lymph nodes were removed had significantly more arm problems (such as oedema).

5.3 Disease-free survival

To determine whether there is a difference in disease-free survival between patients with invasive breast cancer diagnosed through the screening programme and diagnosed clinically, a Netherlands Comprehensive Cancer Organisation (IKNL) dataset was used. This dataset contains data from 28,179 patients with invasive breast cancer from the period 2004-2008. In 55% of these patients, the breast cancer was detected via the screening programme (screening group). For 45%, it was clinically detected (clinical group). The screening group was slightly older (62.2 versus 60.6 years), had a more favourable stage distribution (63% versus 34% had stage 1), and had undergone less intensive treatment (30% versus 49% had undergone mastectomy) than the clinical group. The groups were monitored for five years, and the probabilities of locoregional recurrence, distant metastasis, and a second breast tumour were calculated and adjusted for age. For the period 2006-2008, the IKNL distinguished between patients with an interval cancer (tumour diagnosed clinically between two screening rounds) and those with other clinically diagnosed tumours (tumours in non-participants or women who had skipped one or more screening rounds).

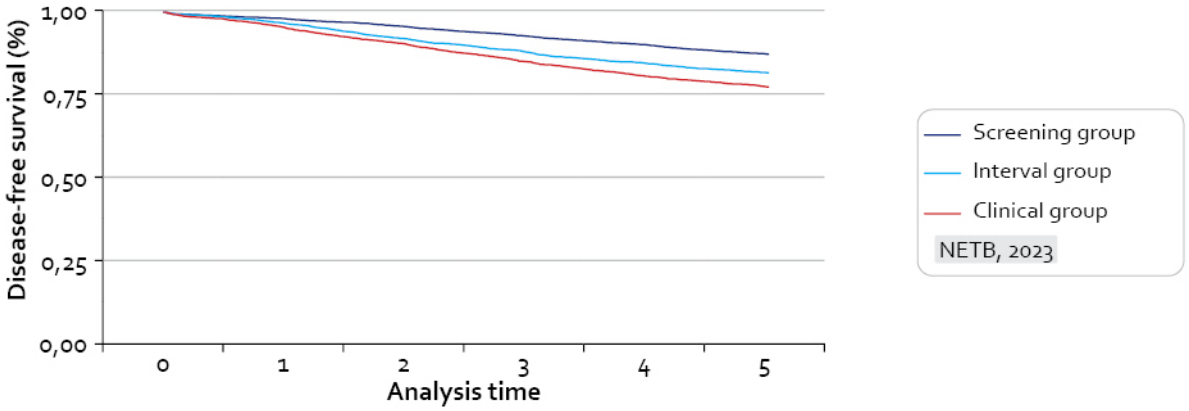

Figure 5.2.
Disease-free survival for patients whose cancer was detected through screening (screening group), the interval group, and the clinical group, at the five-year follow-up.

Figure 5.2 shows a clear difference between the groups in terms of five-year disease-free survival. The survival rate is more favourable for patients in the screening group (87%) and interval group (81%) than for those in the clinical group (76%). The mortality rate was 1.4 times higher in the clinical group (10.6 per 1,000 patients) than in the screening group (8.7 per 1,000 patients).

Where disease-free survival was interrupted, this was in most cases due to metastasis, followed by a second tumour and recurrence. Patients in the screening group were less likely to develop a metastasis (8.9 versus 22.8 per 1,000 woman-years) and less likely to experience a recurrence (3.0 versus 6.4 per 1,000 person-years) than patients in the clinical group. There was no difference between the two groups in terms of the occurrence of a second tumour.

Metastasis occurred 2.5 times more often in both the clinical group and the interval cancer group than in the screening group. The mortality rate was 80% higher in the clinical group than in either of the other two groups. Diagnosis of a second primary breast tumour was virtually the same in all three groups (around 33 per 1,000 patients).

5.4 Causes of death

To determine whether there were any differences in cause of death between patients with invasive breast cancer detected through the screening programme and detected clinically, the same IKNL data file was linked to data from the Causes of Death Register held by Statistics Netherlands. Of the 26,166 breast cancer patients whose data could be linked, 8,310 (32%) patients had died, 182 (1%) had migrated, and 17,674 (67%) were still alive on January 1, 2020.

Compared with the general population, the overall mortality rate among the breast cancer patients was significantly higher (excess mortality) in both the screening group (1.4 times higher) and the clinical group (2.3 times higher, **Table 5.1**).

Cancer was the most common cause of death among the breast cancer patients; compared with the general population, it occurred more than twice as frequently in the screening group and four times as frequently in the clinical group. As expected, breast cancer was the most common specific cause of death: it was nearly 9 times more frequent in the screening group and 20 times more frequent in the clinical group than in the general population. Lung cancer was a relatively common cause of death for both groups, with a mortality rate approximately 20% higher than in the general population. This could be related to the radiation therapy administered for breast cancer but could also be connected to related risk factors such as smoking behaviour.

Table 5.1.
Most common main and specific groups of causes of death of 26,166 breast cancer patients, by detection method, in the period 2004-2008.

	Detected through screening (N = 14,546)			Clinically diagnosed (N = 11,620)		
	Number (N)	Expected (E)	N/E	Number (N)	Expected (E)	N/E
Vital status						
Deceased	4,125	2,917	1.41	4,185	1,846	2.27
Specific cause of death						
Cancer	2,434	1,089	2.23	2,942	728	4.04
Breast cancer	1,383	155	8.92	2,174	107	20.23
Lung cancer	291	249	1.17	210	172	1.21
Pancreatic cancer	86	79	1.08	76	51	1.46
Colon cancer	86	99	0.86	64	64	0.99
Ovarian cancer	61	62	0.98	63	41	1.50
Cardiovascular disease	693	701	0.99	464	426	1.09
Myocardial infarction	97	106	0.91	118	66	1.77
Decompensated heart failure	91	101	0.89	54	59	0.91
Stroke	69	79	0.87	64	46	1.37
Respiratory disease	228	255	0.89	194	159	1.22
COPD	130	158	0.82	118	100	1.18
Psychological and behavioural disorders	153	178	0.88	84	102	0.82
Dementia	131	145	0.90	72	82	0.87

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The other most common causes of death in the screening group – cardiovascular disease (myocardial infarction, decompensated HF, and stroke), respiratory disease, and psychological and behavioural disorders such as dementia – matched the expected mortality rate in the general population. Accordingly, in terms of the other causes of death, it appears that the screening group was "just as healthy" as the general population.

In the clinical group, death from respiratory disease occurred more frequently than in the general population. Death from myocardial infarction (77% higher mortality rate), stroke (37% higher), and pancreatic (46% higher) and ovarian cancer (50% higher) occurred more frequently in the clinical group than in the general population. These excess mortality rates do not appear to be a direct consequence of breast cancer treatment. Rather, it appears that the clinical group was less healthy overall.

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Otten JDM, de Koning HJ, van Ravesteyn NT, et al. 2020b. Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker. Rapport II Uitkomstmaten bij borstkankerscreening – ziektevrije overleving. https://pure.eur.nl/en/publications/landelijk-evaluatie-team-voor-bevolkingsonderzoek-naar-borstkanke-3

Otten JDM, de Koning HJ, van Ravesteyn NT, et al. 2021. Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker. Rapport III Uitkomstmaten bij borstkankerscreening - doodsoorzaken. https://pure.eur.nl/en/publications/landelijk-evaluatie-team-voor-bevolkingsonderzoek-naar-borstkanke

6 Screening performance

Key points

- Screening performance was virtually stable in the period 2013-2017 (following the introduction of digital mammography)
- In the Dutch screening programme, the balance between breast cancer detection and false positive referrals is relatively favourable compared with other countries
- The ratio is less favourable for the initial examination than for subsequent examinations
- With a longer interval between examinations, breast cancer is detected later and the detection rate is higher: it increases by around 0.15 for each additional month in the screening interval.

6.1 Screening performance

To obtain an overview of screening performance, we used national figures for this chapter based on a defined set of indicators from the breast cancer data warehouse of the Netherlands Comprehensive Cancer Organisation (IKNL). The data are complete up to the end of 2017 (screening year), but some data are missing for more recent years, such as data relating to interval cancers. In the most recent five-year period for which data are available (2013-2017), more than five million screening examinations were performed. More than 122,000 women were referred for additional assessment, and breast cancer was found through screening in 35,000 women. More than 11,000 breast cancers were diagnosed outside of the screening programme (**Table 6.1**).

In the period from 2004 to 2013, the detection rate rose gradually from 5.1 per 1,000 to 6.9 per 1,000 participants. In the period 2013-2017, the detection rate was nearly 7 per 1,000 and fairly stable (Figure 6.1). The interval cancer rate was also fairly stable throughout the period 2004-2017, at 2.2 per 1,000.

Table 6.1.
Screening performance in the period 2013-2017

Test result	Breast cancer +	Breast cancer –	Screened		
Screening +	35,001[1]	87,200	122,201	*PPV (%)*	28.6%
Screening –	11,053[2]	4,947,286	4,958,339	*Referral rate/1000*	24.1
	46,054	5,034,486	5,080,540	*False positives/1000*	17.2
	Prog. sensitivity 76.0%	*Prog. specificity* 98.3%		*Detection rate/1000*	6.9
				Interval cancers/1000	2.18
				Prevalence/1000	9.1

PPV: Positive Predictive Value
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[1] Breast cancer detected through screening
[2] Breast cancer detected outside of the screening programme

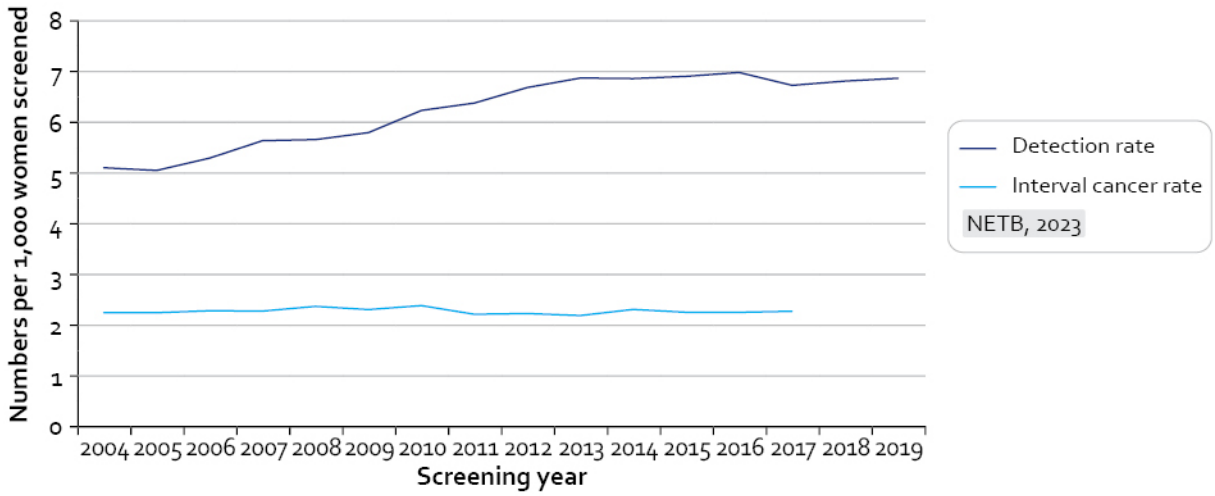

Figure 6.1.
Breast cancer detection and interval cancer rate per 1,000 women screened over time

6.2
Screening performance for initial versus regular subsequent examinations

It is important to make a distinction in terms of screening performance between initial and subsequent examinations. In initial examinations, there are relatively more breast cancers present, because the women concerned have never been screened before. At the same time, there is no previous mammogram with which the current mammogram can be compared. Accordingly, screening performance for initial examinations will be different than for regular subsequent examinations (within 30 months of the previous examination).

The referral rate for all examinations has risen over time, from 14 per 1,000 in 2004 to 24 per 1,000 in 2019 (**Figure 6.2**). The increase is highest for initial examinations, with the rate more than doubling (from 26 per 1,000 in 2004 to 59 per 1,000 in 2019), but there has also been a substantial increase for subsequent examinations (from 12 per 1,000 to 18 per 1,000). Here, too, we can see the trends stabilizing from 2013 onwards.

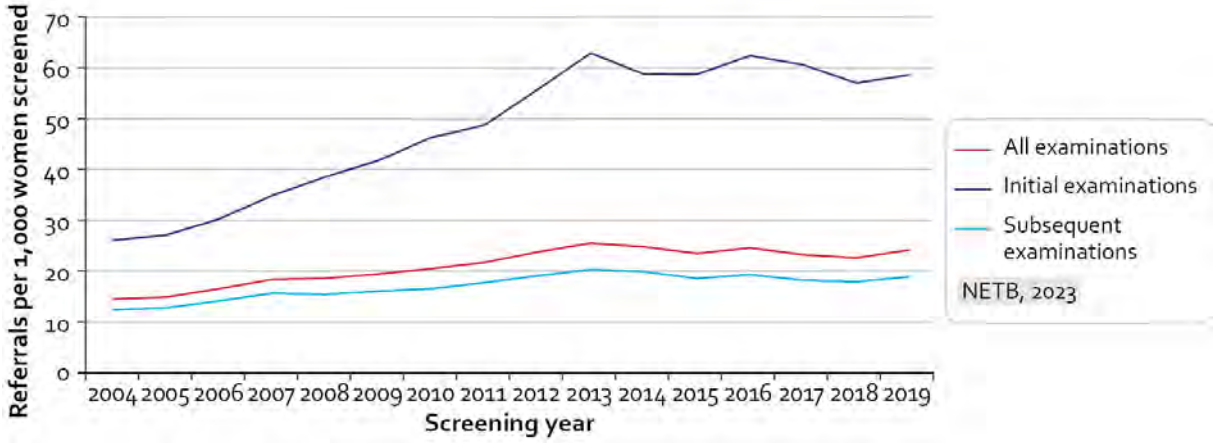

Figure 6.2.
Referral rate for initial examinations, subsequent examinations, and all examinations over time

As the referral rate increases, so do the breast cancer detection rate and the rate of false positive referrals over time (**Figures 6.3 and 6.4**). Here, too, the increase is greatest for initial examinations. The increasing trends in the referral rate, the number of false positive referrals, and the detection rate are largely due to the transition to digital mammography. The revision of the radiological guidelines for referral and an increase in the background incidence of breast cancer have also contributed to the increase in referral and detection rates.

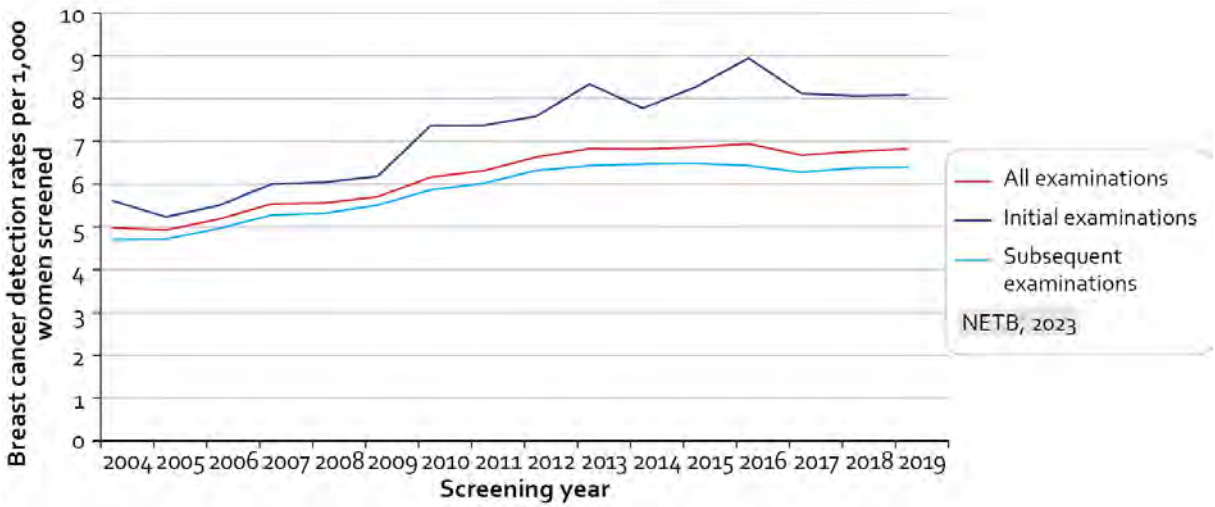

Figure 6.3.
Breast cancer detection rate in initial examinations, subsequent examinations, and all examinations over time

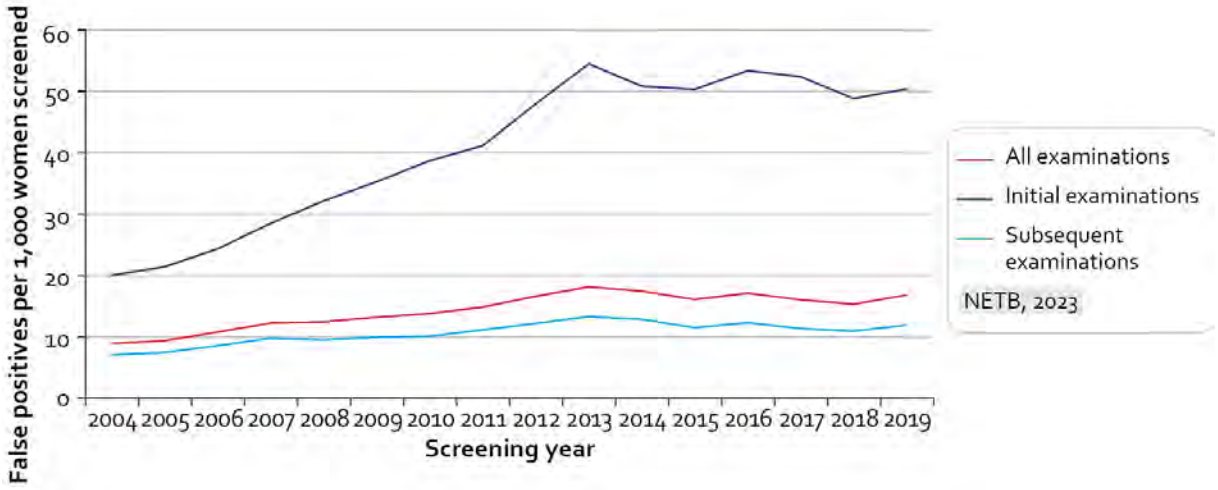

Figure 6.4.
False positive rate for initial examinations, subsequent examinations, and all examinations over time

Due to the relatively high referral rate for initial examinations, the programme specificity was lower than for subsequent examinations (in the period 2013-2017: 94.7% versus 98.7%). The specificity for initial examinations also fell comparatively more sharply than that for subsequent examinations, from 98.0% in 2004 to 94.4% in 2013. In the subsequent period, the specificity was around 95% (**Figure 6.5**).

In the period 2013-2017, the programme sensitivity for initial examinations was comparable to the programme sensitivity for subsequent examinations: 76.9% for initial examinations and 75.4% for subsequent examinations (**Figure 6.6**).

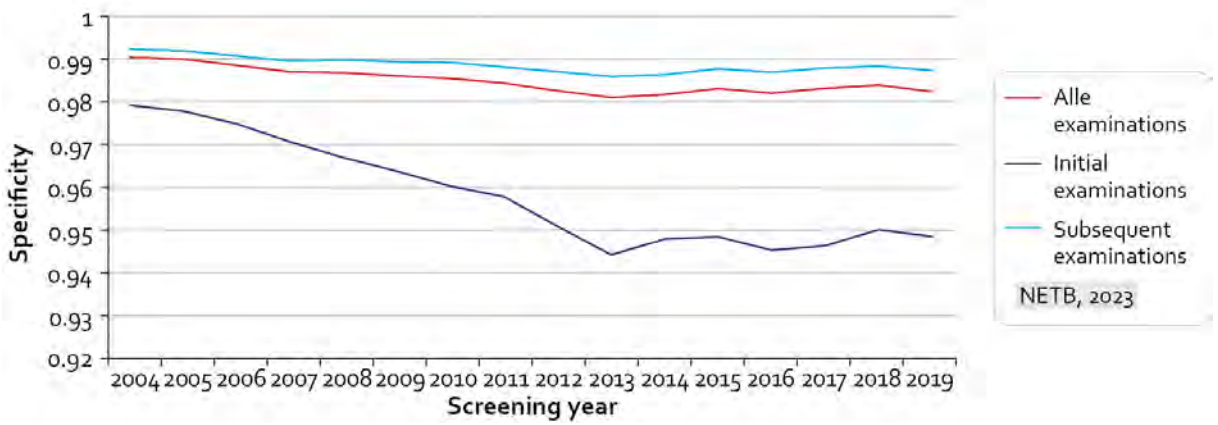

Figure 6.5.
Specificity for initial examinations, subsequent examinations, and all examinations over time

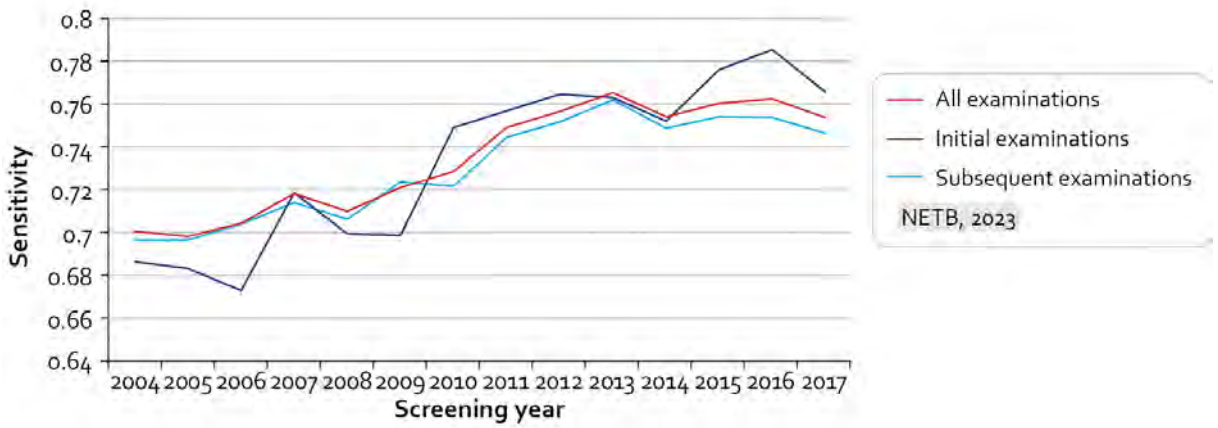

Figure 6.6.
Sensitivity for initial examinations, subsequent examinations, and all examinations over time

If we look at all examinations in the period 2013-2017, the breast cancer detection rate (true positives (TP)) is 6.9 per 1,000 and the rate of false positives (FP) is 17.2 per 1,000 (**Tables 6.1 and 6.2**). Accordingly, the ratio between the breast cancer detection rate and false positive referrals for all examinations is 2.5 (**Table 6.2**). That means that, for each breast cancer detected, there were 2.5 referrals that were subsequently found to be unnecessary. The ratio is less favourable for initial examinations (6.3 false positives per breast cancer detected) than for subsequent examinations (1.9 false positives per breast cancer detected). The ratio has also worsened slightly over time, from 1.8 in 2004 to 2.4 in 2017. However, the ratio is still favourable from an international perspective. For example, various European studies have reported FP:TP ratios varying from 2.8 (based on data from before the introduction of digital mammography) to 6.7 (Singh et al., 2016, Paci 2012, ECIBC, 2019). The Dutch ratio of 2.5 for all examinations is lower, indicating that, in the Netherlands, relatively fewer women are subsequently found to have been referred unnecessarily.

Table 6.2.
Breast cancer detection rate (TP), false positive rate (FP), and FP:TP ratio for initial examinations in the period 2013-2017

	FP/1000	TP/1000	FP:TP
All examinations	17.2	6.9	2.5
Initial examinations	52.7	8.3	6.3
Subsequent examinations	12.4	6.5	1.9

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6.3 Impact of extended intervals on detection

For the past few years, there has been a shortage of radiographers within the health sector in general and within the breast cancer screening programme in particular. As a consequence, fewer women have been able to have mammograms, women are receiving their mammogram invitations later, and the screening interval has increased. **Table 6.3** shows that, over the years, the percentage of subsequent examinations with an interval of between 22 and 26 months has fluctuated around 80%. In the period 2014-2018, this percentage was around 85%, but in 2019, it decreased significantly to 65%. In 2020 and 2021, this percentage was considerably lower, due to the programme being shut down because of COVID-19. Between 2013 and 2017, the number of screening examinations with an interval of between 27 and 30 months was less than 5%. This percentage increased slightly in 2018 and was substantially higher in 2019, at 25%. The percentage of screening examinations that took place after an interval of more than 30 months was also slightly higher in 2019 than in previous years and substantially higher in 2020 and 2021.

To assess the impact of a longer interval on the breast cancer detection rate, we used data from IKNL for all subsequent examinations that took place between 2005 and 2018. The data for 2019 could not be used, because the detection data were not yet complete. **Figure 6.7** shows that the detection rate (the number of TP screening results per 1,000 screening examinations) increases as the interval between two screening examinations increases. Examinations with an interval of less than 20 months have the lowest detection rate. Examinations with an interval of between 22 and 26 months appear to have a similar or slightly higher detection rate of around 6 per 1,000. For intervals of between 26 and 55 months, the detection rate gradually increases from 6 to 10 breast cancers per 1,000 examinations. On average, the detection rate increases by 0.15 for each additional month in the screening interval. A longer interval is also expected to result in more interval cancers, higher stage at diagnosis, and, in due course, fewer prevented deaths.

Table 6.3
Screening intervals by calendar year (2005-2021)

	2005	2006	2007	2008	2009	2010	2011	2012	2013
n	780,255	773,639	802,187	807,000	805,404	849,494	875,770	893,072	908,400
<22 mths	6%	6%	3%	4%	3%	4%	7%	10%	9%
22-26 mths	83%	82%	81%	79%	81%	78%	77%	79%	81%
27-30 mths	7%	8%	11%	13%	12%	13%	11%	6%	5%
>30 mths	4%	4%	5%	4%	4%	5%	5%	4%	4%

	2014	2015	2016	2017	2018	2019	2020	2021
n	883,965	910,858	909,326	918,275	875,029	819,142	*	*
<22 mths	6%	6%	7%	6%	5%	3%	3%	1%
22-26 mths	87%	86%	84%	86%	84%	65%	15%	1%
27-30 mths	3%	4%	4%	4%	6%	25%	33%	11%
>30 mths	4%	4%	5%	5%	5%	6%	49%	87%

* Data from 2020/2021 monitor relating to the invitation interval. NETB, 2023
Breast Cancer Screening Monitor 2020-2021 | RIVM

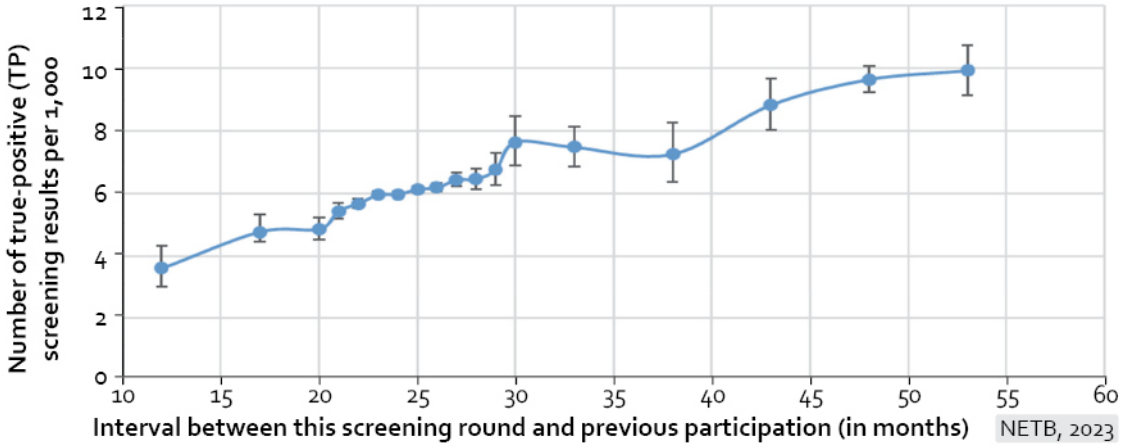

Figure 6.7.
Detection rate (per 1,000 screening examinations) by screening interval with associated confidence interval (95% CI)

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7 Participation

Key points

- Participation in the breast cancer screening programme has fallen slightly in recent years, to 76.0% in 2019.
- The participation rate is lower among women with a lower socioeconomic status.
- During the pandemic, participation dropped to 71.2% of invited women in 2020 and 72.5% of invited women in 2021.
- At the ages of 55 and 60, 54% of Dutch women take part in screening for breast, cervical and colorectal cancer.
- The information leaflet enclosed with the screening invitation improves knowledge about the breast cancer screening programme and leads to more positive attitudes. This in turn leads to more informed decisions, particularly among women who have been invited to participate in the screening programme for the first time.
- Implicit attitudes do not appear to have any effect on the decision of whether or not to participate in the breast cancer screening programme.

7.1 Invitations and participation

Participation in the breast cancer screening programme is voluntary. Between 2015 and 2019, approximately 1.3 million invitations were sent out per year for the screening programme. In an international context, participation in the Dutch screening programme is relatively high, but in recent years, a declining trend can be seen. **Figure 7.1** shows that participation has slowly dropped from around 82% between 2005 and 2008 to 76% in 2019. Between 2015 and 2019, around one million screening examinations per year were performed. The declining participation trend was also observed in previous evaluation reports and has continued in recent years. As a result, the participation rate is approaching the minimum desired participation rate of 75%, as recommended by European guidelines (Perry et al., 2006).

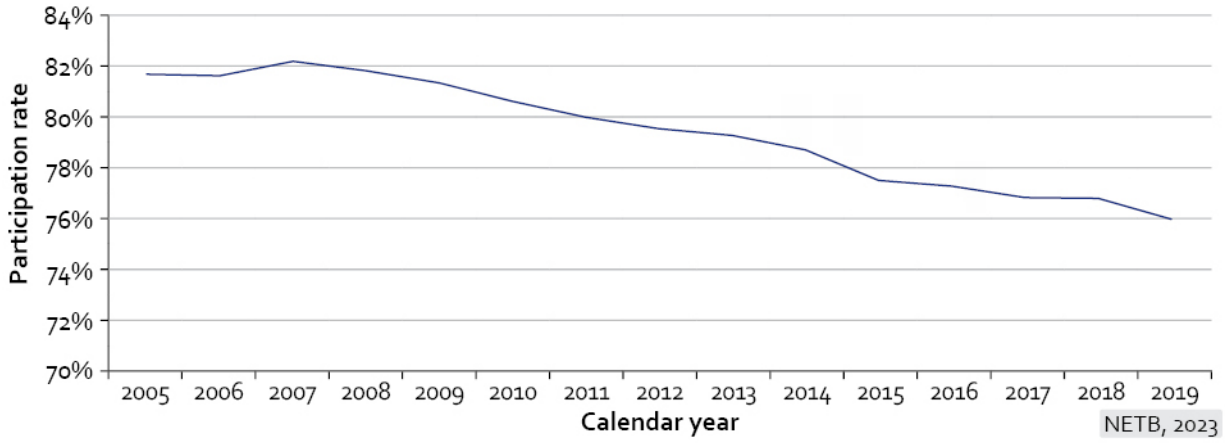

Figure 7.1
Participation rate in the breast cancer screening programme from 2005 through 2019

Previous research has shown that women who have previously participated in the breast cancer screening programme are more likely to participate when they receive an invitation for a later round than women who have not previously participated (Scaf-Klomp et al., 1995, Setz-Pels et al., 2013). This is reflected in the high percentages for re-attendance cited in the national monitor (>90%). It is suspected that women do not make an explicit decision regarding participation with every new invitation; they act based on the decision they made previously. This underscores the importance of decisions made by the group of women being invited to participate in the screening programme for the first time, since these decisions could lead to serial participation (or non-participation) in the future.

7.1.1 Socioeconomic status

Participation in the breast cancer screening programme differs between groups with different socioeconomic status (SES). A 2011 study in the Southern screening region looked at participation among various SES groups (Aarts et al, 2011). Individual SES data from Statistics Netherlands, such as property values and household incomes, were used to calculate an SES for each PC6 postcode area. This study found that, between 1998 and 2005, the participation rate was 79% among women with a low SES score, 85% among women with an average SES score, and 87% among women with a high SES score ($p<0.001$). This difference in participation rate was still visible after adjusting for age and calendar year.

More recent data (2017-2019) regarding participation at the ages of 55, 60, and 65 were also used to examine the differences in participation between SES groups. SES was calculated using median household incomes in the larger (PC4) postcode areas (Kregting et al., 2022). Women were divided into five SES groups, from low to high, for which the participation rates were 67%, 70%, 80%, 81%,

and 75% respectively. The same trend can be seen as in the previous study, with the exception of the lower participation in the highest SES group. This group is extremely small (<1%) and lives in a postcode area where the median household income is extremely high. The 'high SES' group from the previous study corresponds to the two highest SES groups in this more recent analysis.

7.1.2 COVID-19

On March 16, 2020, the breast cancer screening programme was suspended, effective immediately, due to the COVID-19 pandemic. It gradually started up again from mid-June, albeit with significantly reduced capacity due to the distancing and hygiene measures. By the autumn of 2020, capacity had gradually increased to around 80%. After that, capacity only increased slowly, due to the other COVID-19-related measures and a shortage of personnel. The consequence of all this was that fewer invitations were sent out, fewer mammograms were able to be performed, and the screening interval between two invitations rose from an average of two years to closer to three years by 2022. In 2020, only 55.1% of the target population has been invited, only 539,000 mammograms were performed, and the participation rate dropped to 71.2% (source: IKNL). In 2021, the number of invitations increased to 87.6% of the target population, and 886,000 mammograms were performed. The participation rate for 2021 increased slightly to 72.5% (Source: IKNL).

7.2 Participation in multiple screening programmes

In addition to the breast cancer screening programme, women in the Netherlands are also invited to participate in screening programmes for cervical and colorectal cancer at various points in their lives. Women are invited to take part in all three screening programmes around the ages of 55 and 60 (**Figure 7.2**). An LETB study in collaboration with LEBA (National Evaluation Team for Cervical Cancer Screening) and LECO (National Evaluation Team for Colorectal Cancer Screening) examined the overlap in participation in the three screening programmes at these ages (Kregting et al., 2022).

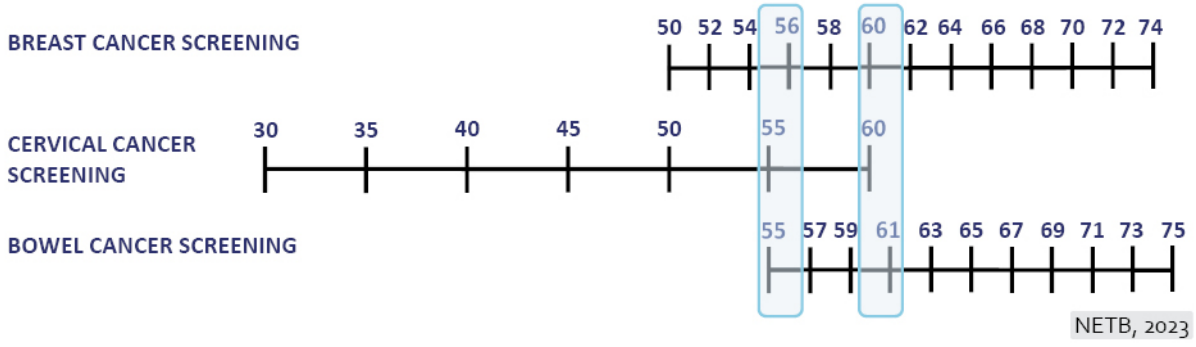

Figure 7.2
Ages at which women are invited for a screening test as part of a screening programme. The light blue bars show the age bands in which women receive invitations for all three screening programmes.

Data for all women who received invitations between 2017 and 2019 for all three screening programmes around the ages of 55 or 60 show that 54% participated in all three programmes (**Table 7.1**). A further 22% participated in two screening programmes, nearly 12% in just one, and around 12% of each age group participated in none of the screening programmes. Participation in the cervical cancer screening programme alone was the lowest, at 1.6%.

Table 7.1
Participation rate for each possible combination of the three screening programmes for women aged 55 and 60

Participation	Breast	Cervical	Bowel	%	
				Aged 55	Aged 60
Three programmes	x	x	x	53.7%	54.1%
Two programmes	x	x	-	5.3%	5.6%
	x	-	x	10.5%	11.9%
	-	x	x	6.3%	5.2%
One programme	x	-	-	5.6%	6.1%
	-	x	-	1.6%	1.6%
	-	-	x	4.5%	4.0%
No participation	-	-	-	12.6%	11.6%

NETB, 2023

Additional analysis showed that concurrent participation was lowest in the Southwest and West-Central screening regions, and in the cities. Concurrent participation was also lower in postcode areas where median household incomes were lower. This analysis provided an indication that participation in multiple screening programmes is lower among women with a lower SES. No differences in concurrent participation were seen when the three invitations were received shortly after each other (within three months) compared with the invitations being received at greater intervals (more than six months apart).

7.3 Informed decisions and implicit attitudes

It is important that everyone who is invited to participate in a screening programme makes an informed decision about whether to participate. According to the multidimensional model for informed decisions produced by Marteau et al., an informed decision is when someone has sufficient knowledge, a positive attitude, and participates in the screening programme, or when someone has sufficient knowledge, a negative attitude, and does not participate in the screening programme (Marteau et al., 2001).

In an Erasmus MC study in collaboration with the Southwest screening region (BOZW), 988 women (50-75 years of age) were surveyed to investigate whether they had made an informed decision in relation to their participation in the breast cancer screening programme (Kregting et al., 2020). Questionnaires were used to ascertain their knowledge and attitude regarding the screening programme. Participation data were also available for the next screening round for which they received an invitation.

Out of all respondents, 89% were found to have sufficient knowledge about the breast cancer screening programme. This can be seen in the big square at the front in **Figure 7.3** (78%, 1%, 7%, and 2%). This figure also shows that 78% made an informed decision to participate (i.e., they had sufficient knowledge, a positive attitude to the screening programme, and participated), while 2% made an informed decision

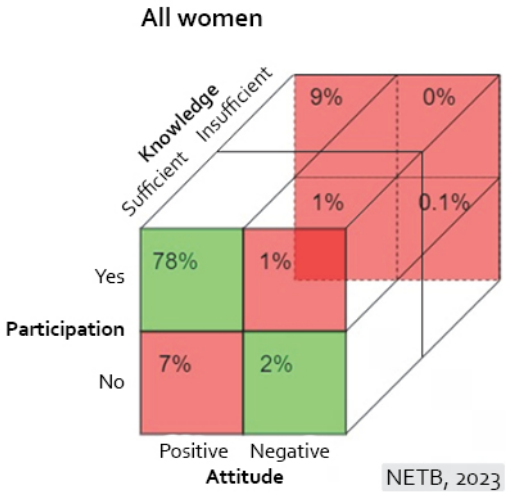

Figure 7.3
Multivariable figure of informed decisions
(Green: informed decision, Red: no informed decision)
Due to rounding, the percentages do not add up to 100%.

to not participate (they had sufficient knowledge, a negative attitude, and did not participate). A further 8% made a participation decision that did not correspond to their attitude (1% participation: yes, attitude: negative, and 7% participation: no, attitude: positive), while 11% (rounded up) had insufficient knowledge to make an informed decision (9%, 0%, 1%, and 0.1%).

7.3.1 Information leaflet

As part of this study, some of the respondents were shown the 2018 RIVM information leaflet about the breast cancer screening programme. After reading the leaflet, 94% of them had sufficient knowledge about the screening programme. It was also striking that this group more often had a positive attitude than the group that was not shown the leaflet. This resulted in a higher percentage of informed decisions: 84% decided to participate, while 2% decided not to participate. There was no difference between the groups in terms of actual participation, but this could be due to the fact that everyone ultimately received the leaflet with their screening invitation.

7.3.2 Initial invitation

Before they received the information leaflet, women who were invited for the first time were less likely to have sufficient knowledge than women who had been invited previously (80% instead of 89%). Partly for this reason, the percentage of informed decisions in first attenders was only 66% (64% decided to participate and 2% decided not to participate). The left panel of **Figure 7.4** shows that 21% had insufficient knowledge (16%, 0%, 5%, and 0%), while 11% had sufficient knowledge but made a decision that did not correspond to their attitude (10% and 1%). After being given the information leaflet, the percentage of women receiving their first invitation who had sufficient knowledge increased to 93% (81%, 12%, 0%, and 0%), and all of them had a positive attitude (right panel of **Figure 7.4**). This lifted the percentage of informed decisions to 81%.

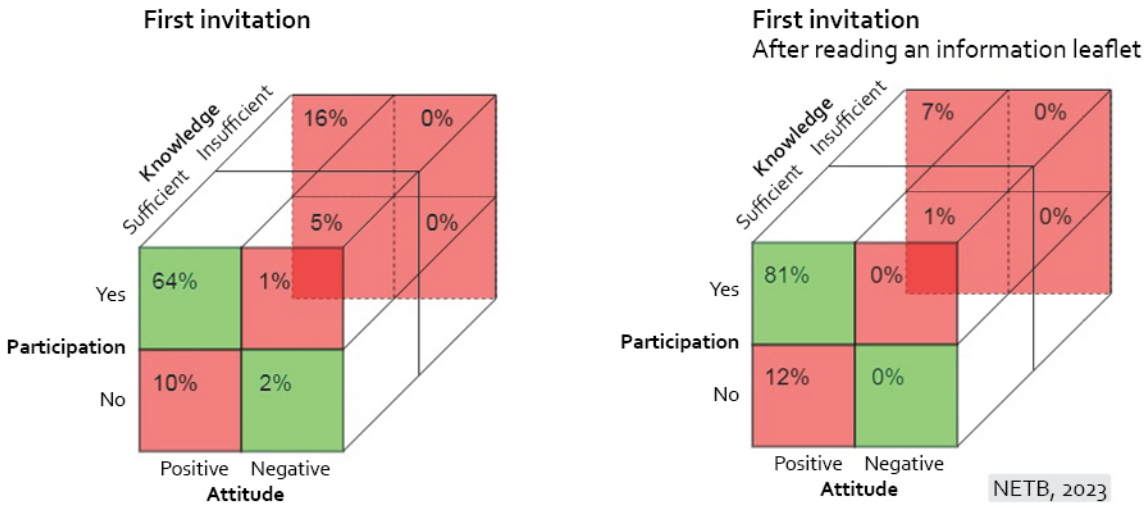

Figure 7.4
Informed decisions by the group of women receiving their first invitation, before (left) and after (right) reading the leaflet.
(Green: informed decision, Red: no informed decision)
Due to rounding, the percentages do not add up to 100%.

7.3.3 Explicit and implicit attitude

Attitudes can be divided into two types: explicit and implicit. People are aware of their explicit attitude to a certain subject and can speak about it. An implicit attitude is more latent and has to do with an automatic response to a subject. Implicit attitudes can influence behaviour without the person being aware of it and can be responsible for spontaneous and automatic behaviours. A person's implicit attitude does not always align with their explicit attitude.

The above study also looked at whether there was a link between explicit and implicit attitudes and intention to participate, actual participation, screening programme-related knowledge, educational level, a history of previous invitations, previous participation, and a previous referral in the context of the screening programme. Explicit attitude was found to have a strong correlation with intention to participate and a moderate correlation with actual participation. Educational level had only a weak link to explicit attitude. Implicit attitude was not found to be associated with either intention to participate or actual participation. This seems to indicate that the decision to participate is influenced only by explicit attitude, not by implicit attitude. This would imply that people have a "conscious" opinion about participation and that this opinion can be rationally influenced, for example by providing information.

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8 Cumulative risk of screening outcomes

Key points

- After participation in the first seven screening examinations, the cumulative risk of a false positive (FP) result is 9.1% and the cumulative risk of a true positive (TP) result is 3.7%.
- Over 11 screening examinations, the expected cumulative risks are 13.5% for a FP result and 7.1% for a TP result.
- In an international context, the cumulative risk of a FP result is relatively low, while the cumulative risk of a TP result is comparable. This indicates a favourable balance between FP and TP results.
- Participants who receive a FP result are less likely to participate in the next screening examination. This effect is most visible when the FP result is received in the first examination and less strong when the FP result is received in a subsequent examination.
- Participants who had previously received a FP result were subsequently more likely to have screen-detected breast cancer, interval cancer, or another FP result than participants who had previously received true negative results.

8.1 Introduction

The risk of a particular screening outcome is often described in relation to participation in a single examination. However, the full screening programme comprises 13 consecutive screening examinations. Women often seem to make a fundamental decision about whether or not to participate in relation to the first examination and stick with that decision for subsequent examinations (see Chapter 7). It is therefore important to inform them of the risks of participating in multiple examinations. This can be done by looking at the cumulative risks of false positive (FP) and true positive (TP: screen-detected breast cancer) results after multiple screening examinations.

In addition, it can be investigated whether these cumulative risks are higher for participants who had a FP result in a previous examination, compared with participants who have always received true negative (TN) results.

Screening outcomes

TP: true positive test result, also known as screen-detected breast cancer. An abnormality is observed on the mammogram, after which breast cancer is diagnosed in the further assessment.

FP: false positive test result. An abnormality is observed on the mammogram, but no breast cancer is diagnosed in the further assessment.

FN: false negative test result. The woman is not referred based on the mammogram, but breast cancer is diagnosed later. The number of FN results is often measured as the number of cancers diagnosed within 30 months after a negative screening mammogram.

TN: true negative test result. The woman is not referred based on the mammogram and no breast cancer is diagnosed later.

8.2 Cumulative risk of a FP or TP result

For this study, data were obtained for successive examinations in the screening programme since 2005 (Kregting et al., 2023). The population in this dataset consisted of women who were aged between 49 and 59 in 2005. These data made it possible to calculate the cumulative risks of screening outcomes over up to seven examinations of breast cancer screening, specifically for the Dutch screening programme. Through extrapolation, this could be extended to 11 examinations.

The analysis showed that, after seven screening examinations, the cumulative probability of a FP referral was 9.1%, while it was 3.7% for a TP referral (**Figure 8.1**). After 11 examinations, the estimated

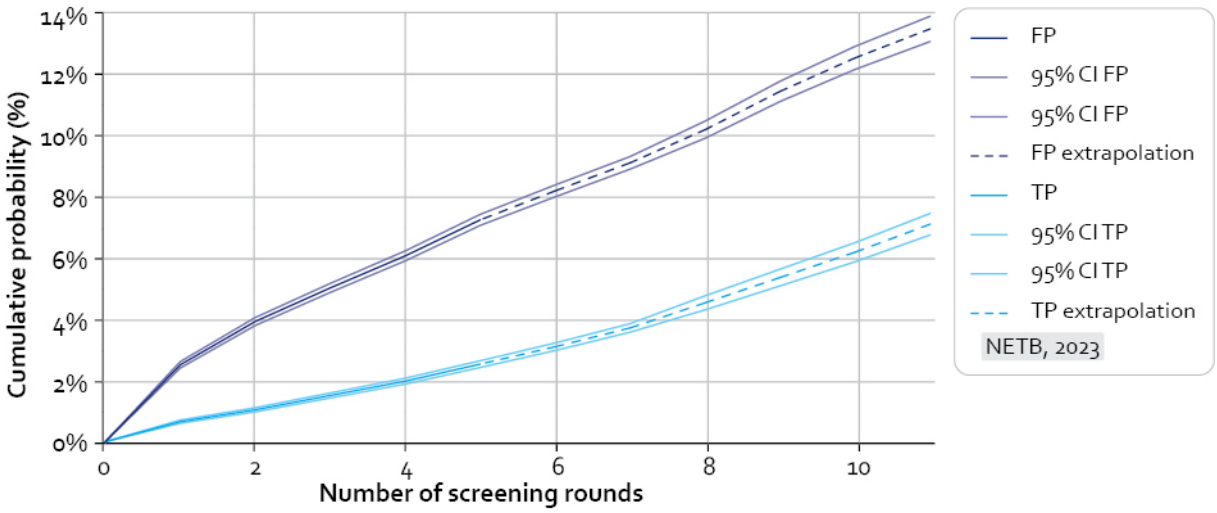

Figure 8.1
Cumulative risks over multiple rounds of breast cancer screening

cumulative risks were 13.5% for a FP result and 7.1% for a TP result. These risks are a bit higher than in the earlier analyses published in NETB Report XIV in 2019. This difference can be explained by the fact that a different analysis technique was used this time, in which only the data of people who had participated in all examinations were analysed. A study by Otten et al. predicted cumulative risks of 16.1% for a FP result and 7.1% for a TP result after 13 screening examinations (Otten et al., 2013). The current analysis shows a risk of 13.5% for a FP result after 11 examinations, which appears to be in line with a risk of 16.1% after 13 examinations. However, the risk of a TP result after 11 examinations in the current study is as high as after 13 examinations in the Otten study. This difference appears to be attributable to an increase in the incidence of breast cancer in the current population compared with the population in the Otten study.

In an international context, the cumulative risk of a FP result, as calculated in the current study, is relatively low. For example, European studies have found cumulative risks over 10 screening examinations of between 8% and 23% (Singh et al., 2016, Roman et al., 2014, Salas et al., 2011, Njor et al., 2007). Only the cumulative risk of 8% from a study in Funen, Denmark, was lower than the 12.6% found in the current study after 10 examinations (Njor et al., 2013). The other studies, conducted in Finland, Norway, Spain, and Copenhagen, Denmark, found higher percentages. The likely explanation is that the referral rate in the Netherlands is lower than in those countries and regions, resulting in fewer FP results.

The Finnish study also looked at the cumulative risks of a TP result and found a risk of 3.4% after 7 examinations and 5.7% after 10 examinations (Singh et al., 2016). A Spanish study found that the cumulative risk of a TP result after seven screening examinations varied between 2.6% and 6.1%, depending on a family history of breast cancer and previous benign breast abnormality (Román et al., 2014). The weighted average of these groups produced a cumulative risk of 3.0%. The risk of a screen-detected breast cancer diagnosis in Finland or Spain is thus slightly lower than in the Netherlands. The combination of a relatively low cumulative risk of a FP result and a relatively high cumulative risk of a TP result from screening produces a favourable ratio between FP and TP results, which is positive for the balance between advantages and disadvantages.

8.3 Participation and screening outcomes following a previous FP result

Of the participants who receive a FP result, only 72-81% participate in the following examination, while 91-93% of participants with a TN result take part. We observed that the difference in participation is greatest when the FP result was received in the first examination of the breast cancer screening programme and becomes smaller for FP results received in each subsequent examination (**Figure 8.2**). An earlier study by Setz-Pels showed that some of the people who stopped participating in the

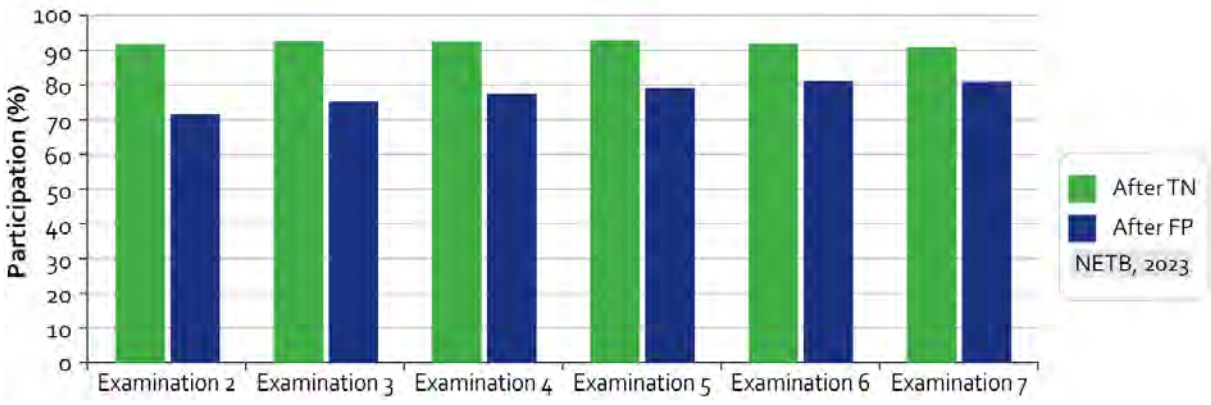

Figure 8.2
Participation in breast cancer screening stratified by previous screening result

screening programme after receiving a FP result still underwent regular breast examinations in the hospital. It is therefore possible that some of the non-participating FP population are being screened opportunistically.

However, people with a FP result who continue to participate in the screening programme are 1.59 times more likely to receive a TP result and 1.66 times more likely to have an interval cancer (FN result) (see **Table 8.1**). They are also almost twice as likely to receive a FP result in these subsequent examinations (factor of 1.96). This shows that participants who have had a FP result appear to have a higher risk of later being diagnosed with breast cancer. However, this group is less likely to take part in later examinations, which means a breast cancer may not be diagnosed until later.

Table 8.1
Screening results in screening examinations following a TN or FP result

Result in examinations 2 through 7 per 1,000 screening tests	**FP**	**TP**	**Interval cancer**	**Breast cancer** (TP + interval cancer)
After TN	34.6	16.5	5.0	21.5
After FP	67.8	26.1	8.2	34.3
***Factor** (FP/TN)*	*1.96*	*1.59*	*1.66*	*1.60*

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9 Cost-effectiveness

Key points

- In the period 2013-2019, a screening examination for breast cancer cost around €65-€70.
- In 2020, due to COVID-19, significantly fewer examinations were performed, which meant the cost per examination were much higher that year, at €111.
- The current programme has a favourable ratio between costs and effects, but in retrospect, from a cost-effectiveness perspective, even better alternatives are available.
- Possible alternatives to the current programme include switching to a longer interval, combined with an earlier starting age. For the subgroup of women with extremely dense breast tissue (around 8% of the screening population), screening with MRI would lead to a substantial decrease in the number of breast cancer deaths, for a reasonable cost.

9.1 Breast cancer screening costs

The number of screening examinations increased slightly between 2012 and 2017. In 2018 and 2019, fewer screening examinations were performed, due to a shortage of personnel. In 2020, considerably fewer examinations were performed, owing to the temporary suspension of the programme due to COVID-19.

Between 2012 and 2019, the cost per examination was fairly stable, varying between €65 and €70 (**Table 9.1**). In 2020, the cost per examination suddenly became much higher (€111), because of the smaller number of examinations performed in that year.

The total cost of screening increased between 2012 and 2017 from €64.6 to €69.8 million, before falling slightly to €66.0 million in 2019. In 2020, the total cost was €59.2 million. Over the same period (2012-2020), the consumer price index increased by 13% (source: Statistics Netherlands).

Table 9.1.
Average costs per screening examination, number of examinations, and total costs

	2012	2013	2014	2015	2016	2017	2018	2019	2020
Cost per examination (€)	64.05	65.05	66.06	66.30	67.01	67.82	70.11	66.26	110.96
Number of examinations	1,007,966	1,017,596	996,080	1,023,449	1,021,388	1,029,097	978,833	996,447	533,256
Total cost of screening (€m)	64.6	66.2	65.8	67.9	68.4	69.8	68.6	66.0	59.2

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9.2 Effects (utilities)

To determine cost-effectiveness, it is important to consider not only the costs but also the effects. Effects can be expressed in terms of life-years and quality-adjusted life-years (QALYs) gained. QALYs express the number of additional years of life yielded by an intervention, adjusted for quality of life during those years. QALYs are calculated on the basis of utility scores. The life-years gained are multiplied by the utility. Utility scores are determined using questionnaires. The utility is the rating given to the quality of the person's state of health. The utility score can vary from 0 (dead) to 1 (perfect health). Disutilities indicate the reduction from a perfect state of health (1-utility).

To calculate QALYs, various utilities, with associated durations, were used as input in the MIcrosimulation SCreening ANalysis (MISCAN) model. For the state of health without breast cancer, a utility of 0.858 was used, based on a study by Versteegh et al. (2016). Based on a study by Stout et al. (2006), disutilities of 10%, 25%, and 40% were used for DCIS/small tumours, larger tumours, and metastasis respectively (**Table 9.2**). For screening participation, a disutility of 0.006 for 1 week was applied. For a positive result, a disutility of 0.105 for 5 weeks was applied (de Haes et al., 1994).

Table 9.2.
Utilities and associated durations

State of health	Utility	Duration
No breast cancer	0.858	N/A
After undergoing screening	0.853*	1 week
After a positive screening result	0.768#	5 weeks
DCIS/small tumours	0.772	2 years
Larger tumours	0.644	2 years
Metastasis	0.515	Until death
Dead	0	

* Based on a disutility of 0.006: (0.858-0.006*0.858)
# Based on a disutility of 0.105: (0.858-0.105*0.858)

NETB, 2023

9.3 Cost-effectiveness of the current programme and alternative scenarios

To determine how the costs of screening relate to the effects, a cost-effectiveness analysis can be performed. In this cost-effectiveness analysis, the costs and effects of a situation with screening and a situation without screening are compared. The result is expressed as the cost of one life-year (or QALY) gained. The lower this amount, the more cost-effective the screening.

The cost-effectiveness of the breast cancer screening programme was previously estimated at around €5,000 per life-year gained (with both costs and effects discounted by 3.5% per year) (NETB Report XIV). This estimate was made using the MISCAN model. Recent changes in breast cancer risk and improvements in treatment and screening may mean that the balance between the benefits and harms of screening has changed and that the current screening strategy is no longer optimal. Accordingly, the MISCAN model was used to simulate a comprehensive set of 920 screening strategies for the current situation in the Netherlands and determine their cost-effectiveness.

Based on a conservative willingness-to-pay threshold of €20,000 per QALY gained, two-yearly screening from the ages of 40 to 76 is the most cost-effective. However, this strategy would result in more overdiagnosis and false positive (FP) results and require a higher screening capacity than the current strategy. The current Dutch strategy (two-yearly screening for 50 to 74-year-olds) was close to but not on the efficiency frontier (**Figure 9.1**). This means that there are other strategies that would deliver a greater impact and cost less money. These alternatives include three-yearly screening from 44 to 71 or 74 years of age. These strategies resulted in 5% or 7% more QALYs gained respectively, while the costs were 5% and 1% lower (Kregting et al., 2022).

In conclusion, the current programme has a favourable ratio between costs and effects, but it is not optimal from a cost-effectiveness perspective. Possible alternatives for the entire population include switching to a longer interval, combined with an earlier starting age.

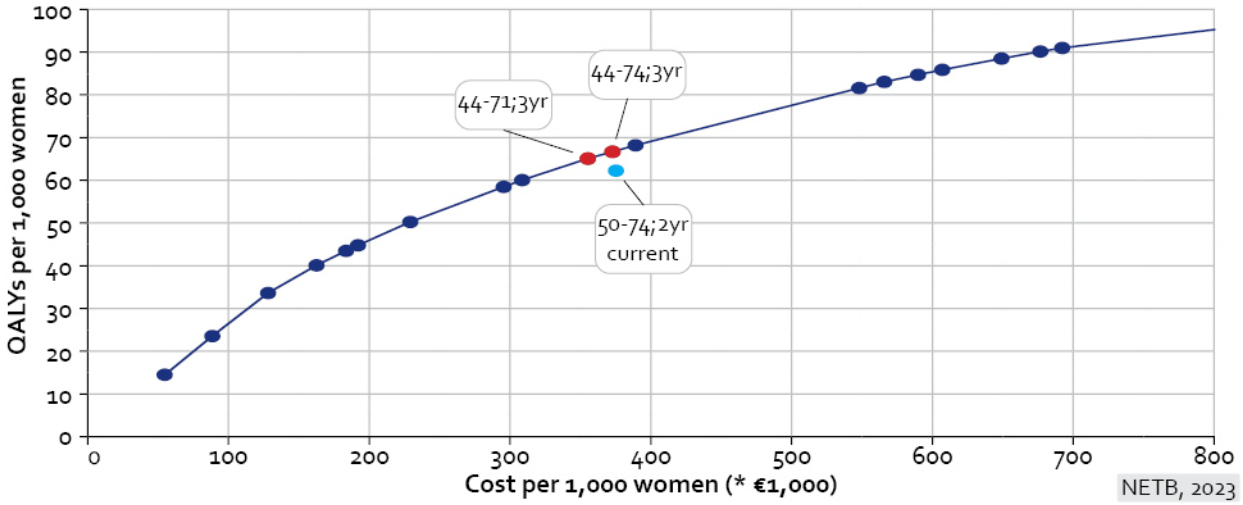

Figure 9.1
Effects (QALYs gained) and costs of various screening scenarios per 1,000 women
3yr: three-yearly screening
2yr: two-yearly screening

9.4 Women with extremely dense breast tissue

Both nationally and internationally, there has been a great deal of attention in recent years on additional screening for women with dense or extremely dense breast tissue, using MRI or another imaging modality. The DENSE study investigated additional screening with MRI for women with extremely dense breast tissue and a negative mammogram (Veenhuizen et al., 2021, Bakker et al., 2019, Emaus et al., 2015). Significantly fewer interval cancers were found in the MRI group than in the control group (Bakker et al., 2019). However, there were also more false positive referrals in the MRI group than in the control group, and the cost of performing an MRI scan is higher (€272).

The results of the first and second round of the DENSE study were used in the MISCAN model to estimate the cost-effectiveness of exclusive or supplementary MRI screening (Geuzinge et al., 2021). Data from the DENSE study were used to calibrate the MISCAN model and to model a group of women with extremely dense breast tissue, with a higher risk of developing breast cancer and a lower sensitivity of mammography. Screening strategies with varying intervals and combinations of mammography and MRI were modeled, all beginning at the age of 50 and stopping at the age of 74. For these women, the current screening policy would result in 69 screen-detected tumours and 43 breast cancer deaths (11 prevented deaths) per 1,000 women. If MRI were added, there would be 28 additional screen-detected tumours and 8 fewer breast cancer deaths (so 19 prevented deaths in total). All strategies that are considered "efficient" consist of MRI screening only, with no mammography. If we apply a threshold value of €20,000 per QALY gained, MRI at four-yearly intervals is the most cost-effective screening strategy. For this strategy, the incremental effects versus the incremental costs (ICER) are estimated to be €15,620 per QALY gained. If a higher threshold value is applied, MRI at three-yearly intervals is also cost-effective (ICER: €37,181 per QALY gained). If there is a preference to keep a two-year screening interval, alternating mammography and MRI would be a good alternative, although this strategy is considered less efficient. The cost of MRI screening had the biggest influence on the cost-effectiveness ratios.

In short, for the subgroup of women with extremely dense breast tissue, screening with MRI would lead to a substantial decrease in the number of breast cancer deaths, for a reasonable cost.

9.5 Tomosynthesis

The mammographs currently in use in the screening programme are able to perform both 2D mammography and tomosynthesis (3D mammography). Tomosynthesis appears to be a promising technique that could be introduced to the existing screening programme as a replacement for digital mammography. A recent meta-analysis found a higher cancer detection rate with tomosynthesis than with digital mammography, but the effect on interval cancers is unclear (Houssami et al., 2021). Moreover, data on the long-term effects are still very scarce.

After expanding the MISCAN model with tomosynthesis-specific parameters (derived from the literature and experts), the cost-effectiveness of tomosynthesis compared with the current screening using digital mammography was calculated (Sankatsing et al., 2020). The calculations were based on a two-year screening interval and tomosynthesis screening between the ages of 50 and 74, as in the current programme.

With model analyses, we estimate that, compared with digital mammography, screening with tomosynthesis once every two years between the ages of 50 and 74 would lead to an additional 13 life-years gained per 1,000 women (7% increase), 0.9 additional breast cancer deaths prevented per 1,000 women (6% increase), and 4 fewer false positive findings per 1,000 women (2% decrease).

The importance attached to costs and effects decreases the further in the future they lie. This was taken into account by discounting the outcomes. The average additional costs of tomosynthesis, compared with digital mammography, is €137,555 per 1,000 women (discounted by 3.5% per year). The average additional effects (also discounted by 3.5% per year) amount to 5 life-years gained per 1,000 women. Both outcomes show significant spread (**Figure 9.2**) and result in an average ICER of €27,023 per life-year gained.

Our analysis supports the conclusion that the introduction of tomosynthesis in the Netherlands could lead to an increase in the number of deaths prevented and life-years gained. However, it is likely that the introduction would be accompanied by an increase in costs. The cost of tomosynthesis screening in particular accounts for a large part of the uncertain increase in total costs.

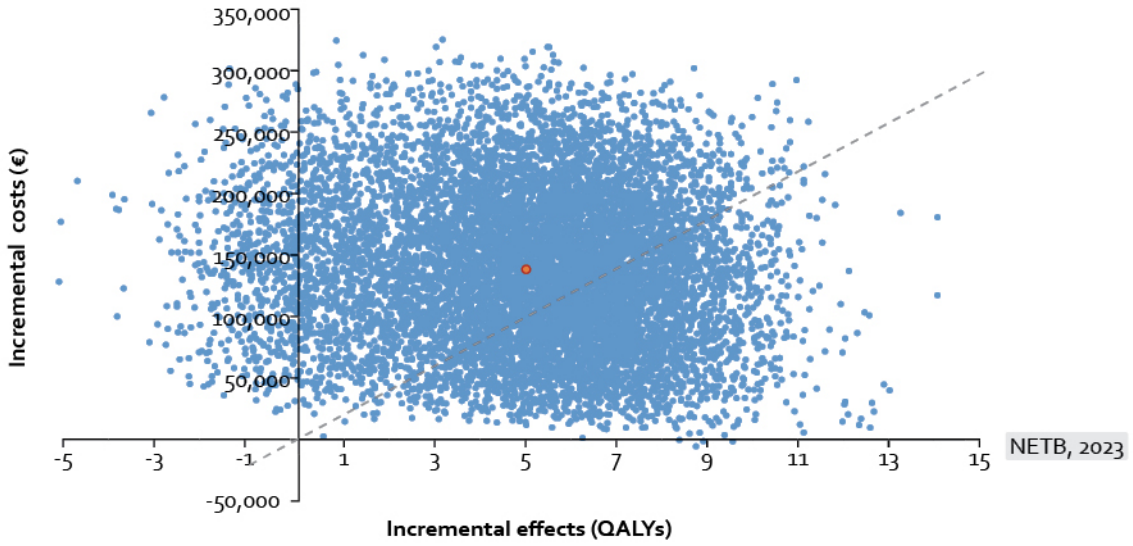

Figure 9.2.
Additional costs and effects of tomosynthesis versus digital mammography. The X axis shows the incremental effect (QALYs), and the Y axis shows the incremental costs (both discounted by 3.5%). Each dot represents the result of one model run with a particular combination of input parameters. There are 10,000 dots (model runs) in total. The red dot indicates the average result. The estimated outcomes of dots (model runs) in the area below and to the right of the grey dashed line are cost-effective.

In short, there is still considerable uncertainty around the costs and effects of breast cancer screening with tomosynthesis. Additional research that produces a better picture of the costs of tomosynthesis in a screening setting, investigates various reading strategies, and includes multiple screening rounds to better determine the effectiveness of tomosynthesis is therefore important and will be performed over the next few years.

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10 Epilogue – striking the balance & future developments

10.1
Effects of the current breast cancer screening programme

10.1.1 Screening performance

Each year in the Netherlands, around 1.3 million women between the ages of 50 and 75 are invited to participate in the screening programme. In the pre-pandemic years (2013 to 2019), around 78% of women who received an invitation attended, and approximately 1 million screening tests were performed each year. Chapter 7 described how participation has fallen slightly in recent years, reaching 76% in 2019, and how participation is lower among women with a lower socioeconomic status. In that chapter, we also described a study into informed decisions regarding screening participation. The vast majority of invited women have sufficient knowledge (89%) and make informed decisions about participation (80%). This 80% comprises 78% who made an informed decision to participate (i.e., they had a positive attitude in regard to the screening programme and attended) and 2% who made an informed decision to not participate (they had a negative attitude and did not attend).

In Chapter 6, we described the screening performance. In the period 2013-2017, for every 1,000 participants, breast cancer was detected (at an early stage) in 7, while 17 were referred for further assessment that was in retrospect found to be unnecessary. In addition, breast cancer was clinically diagnosed in two participants during the screening interval (interval cancer), despite the fact that the screening examination had not prompted a referral (**Table 10.1**). This report includes data from a relatively stable period; the figures for the next report will clearly show the impact of COVID-19.

The numbers in **Table 10.1** provide a good overview of what invited women can expect from participation in a single screening examination. However, re-attendance is high, and most invited women undergo multiple screening examinations in their lives. Accordingly, it is also important to communicate the risk of various screening outcomes over multiple screening examinations. In Chapter 8, we described the risks based on participation in multiple screening examinations. People who participate in 11 examinations have, over those 11 examinations, a cumulative risk of 13.5% of receiving one or more referrals that were in retrospect unnecessary, and a 7.1% cumulative risk of having breast cancer detected through screening. This is an extremely favourable ratio from an international perspective, mainly due to the low referral rate in the Netherlands.

Table 10.1.
Screening results in the period 2013-2017, in the first two years after a screening examination, scaled to 1,000 participants

	Breast cancer	No breast cancer	Screened
Positive test	7	17	24
Negative test	2	974	976
Total	9	991	1,000
	Prog. sens. 76.0%	Prog. spec. 98.3%	

NETB, 2023

Prog. sens.: programme sensitivity: the proportion of true positive results out of all breast cancers (true positive and false negative results combined) detected in screening and in the first two years after the screening examination.
Prog. spec.: programme specificity: the proportion of true negative results out of all screening examinations with no breast cancer diagnosis in the first two years after the screening examination.

10.1.2 Benefits of the screening programme

Participants in whom breast cancer is detected through screening have a more favourable stage distribution (Chapter 3), lower chance of metastasis, and lower chance of recurrence of the disease than participants with an interval cancer or women with clinically detected breast cancer (Chapter 5). Screen-detected breast cancers require less intensive treatment, since they are found at an earlier stage. As a result, participants in whom breast cancer is detected through screening are less likely to receive neoadjuvant therapy and are more likely to be treated with breast-conserving surgery (Chapter 4). We further noted that women treated for breast cancer after referral from the screening programme have a slightly higher quality of life and fewer symptoms than those diagnosed outside of the screening programme (Chapter 5). The most important benefit and the goal of the screening programme is the reduction in the risk of dying from breast cancer. At an individual level, it cannot be determined for whom death due to breast cancer has been prevented, but model calculations show that population screening is estimated to prevent around 1,300 breast cancer deaths in the Netherlands each year.

10.1.3 Harms of the screening programme

Alongside these benefits, there are also harms connected with the screening programme, including false positive results, overdiagnosis, and overtreatment. As described earlier, the cumulative risk (over 11 examinations) of a false positive result is 13.5%. Out of all the women who participate in any given screening examination, 91-93% will participate in the next examination. For those who receive a false positive result, this proportion is only 72-81%. This may be one of the reasons why the participation rate has gradually fallen from 82% in 2007 to 76% in 2019.

The main harm for a small number of participants in the screening programme, namely overdiagnosis, is directly related to the high quality of the screening programme. A good test enables early stage breast cancer to be detected in women without symptoms. This means ductal carcinoma in situ (DCIS) is frequently detected, particularly since it is characterised by clear abnormalities on the mammogram. However, there are women who, following detection and treatment of a DCIS, die of other diseases. Overdiagnosis, and treatment that is found to be unnecessary in retrospect, also occurs with invasive breast cancers, but it is much less common (Chootipongchaivat, et al., 2020).

When a DCIS is detected through screening and treated, for some women, invasive breast cancer is prevented. However, for a substantial percentage of other women (estimated to be around 50%, varying according to histological grade), detection of a DCIS constitutes overdiagnosis, i.e., without screening, there would have been no symptoms and no diagnosis (van Luijt, et al., 2016).

Several major clinical trials have been set up to monitor women with DCIS, study its natural progression, and adjust therapy as necessary. In the Netherlands, the Low-Risk DCIS (LORD) trial (Elshof et al., 2015) is investigating whether the standard treatment for low-risk (grade I/II) DCIS, comprising surgery potentially followed by radiation and/or hormone therapy, can safely be omitted. This could avoid unnecessary operations, radiation and/or hormone therapy. Determining whether these can be safely dispensed with requires close monitoring. This means that women receive an annual mammogram to ascertain whether there have been any changes in the DCIS. In the future, the results of this and similar international studies will make an important contribution to our understanding of DCIS and its treatment.

As with the prevention of breast cancer deaths, overdiagnosis also cannot be determined at the individual level. However, using the MISCAN model, we can produce an estimate at a population level. The model is continually updated based on the latest insights in relation to both screening and treatment. With the most recent version, it is estimated that, for every 1,000 women who participate in every screening examination and are monitored throughout their lives, there are 16 prevented deaths and 5 overdiagnoses (Kregting, et al., 2022).

10.1.4 Cost-effectiveness

A breast cancer screening examination costs €65-€70, and in 2019, the total cost of the screening programme was €66 million. If we take those costs and look at the screening programme as a whole, we can estimate the balance between effects (both benefits and harms) and costs. We express the effects in terms of 'quality-adjusted life-years' (QALYs), where one QALY is equal to one year of life in perfect health. In terms of costs, as well as considering the costs of the screening programme, we also take into account the costs of further assessment and treatment. For the screening programme in its current form, this results in an estimated ratio of €6,000 per QALY gained (with both costs and effects discounted by 3.5%). In an international context, preventative interventions with costs of up to €35,000 per life-year or QALY gained are considered cost-effective. The screening programme is therefore well below this threshold. In Chapter 9, the cost-effectiveness of the screening programme was calculated and compared with other screening strategies. The results showed that switching to a longer (three-yearly) interval, combined with an earlier starting age, would be a favourable alternative.

10.2 Future developments

10.2.1 Risk stratification

Since the start in 1989, the breast cancer screening programme has been offered to women in a specific age category. This is the group for whom breast cancer is seen as a significant health problem and for whom early detection of breast cancer can make a difference in prognosis. Over the past years, the question has increasingly been asked whether such a uniform programme is also the best possible programme. The selection of the 50-to-74 age group was based on the average breast cancer risk and the balance between benefits and harms of screening for this group. But does it actually deliver a good balance for all women in this age group? Even within this age group, women have different levels of breast cancer risk. Can we tailor the screening program to different levels of risk, to make it more effective and efficient?

To provide insights on the balance between the benefits and harms of screening for groups with an above-average or below-average breast cancer risk, MISCAN was used to simulate a screening programme in which the target population was stratified in three subgroups (low, medium, and high risk) (Sankatsing, et al., 2020). The results showed that optimal screening for low-risk women involves a longer screening interval (3 years) and an earlier stopping age (71 years). With a three-year interval, low-risk women retain much of the benefit of screening, while the harms – particularly false positive referrals – and costs are reduced. For high-risk women, an earlier starting age (40 years) appears to be particularly important.

The study by Sankatsing et al. made assumptions for the purpose of the simulation with regard to the higher or lower risks in the subgroups, based mainly on the literature (Sankatsing, et al., 2020). In recent years, the PRISMA study has gathered a wealth of information regarding risk factors among participants in the breast cancer screening programme. These data make it possible to estimate how many women in the Dutch target group fall into particular risk groups. When determining breast cancer risk, it is also important to consider breast density, i.e., the amount of glandular tissue in the breast. As well as being a risk factor for breast cancer, high breast density makes it harder to see breast cancer on a mammogram. Differences in risk and density mean that the current 'one-size-fits-all' strategy leads to variable outcomes in the different subgroups, indicating that improvements could be achieved if screening were personalised. Future work will find out more about the benefits and harms of more stratified strategies.

Outside the Netherlands, there are other screening cohorts like PRISMA in which information about breast cancer risk factors is being gathered from screening participants. Examples include the KARMA cohort in Sweden and the PROCAS cohort in the UK. In addition, two randomised trials

are being conducted: WISDOM (Women Informed to Screen Depending on Measures of Risk) in the United States and MyPEBS (My Personal Breast Cancer Screening) in Europe. The latter trial is the most relevant for the Dutch screening programme. This trial, being conducted in six European countries, compares a personalised screening programme with the current breast cancer screening programme. Inclusion in MyPeBS ground to a halt during the pandemic, and the trial has suffered delays as a result. By December 31, 2022, out of the target of 56,435 participants, 43,456 participants had been included (77%). The participants have been stratified into risk groups based on their risk of developing an invasive breast cancer within five years. The screening strategies offered are based on the participants' risk and breast density (see **Table 10.2**). The key outcome measure in MyPeBS is the difference in the detection rate of advanced breast cancers. MyPeBS is also looking at the acceptability and personal experiences of participants and the economic aspects of personalised screening.

Table 10.2.
Risk groups and screening strategies offered in MyPeBS

Breast cancer risk	Low risk	Average risk	High risk	Extremely high risk
Definition of risk (Risk of an invasive breast cancer within five years)	<1%	1-1.66%	1.67 - 6%	≥6%
Mammogram	1 at the end of the study	Every 2 years	Annually	Annually
Additional	Annual "breast cancer awareness" reminder	For high density (D): ultrasound or 3D ultrasound every 2 years	For high density (D): ultrasound or 3D ultrasound every 2 years	Annual MRI until the age of 60

NETB, 2023

10.2.2 Estimating breast cancer risk

In order to offer a risk-based screening programme, it is first necessary to estimate the individual breast cancer risk of each participant. Over the past 10 years, a great deal of energy has been spent on adjusting and extending risk prediction models, which were developed in a clinical genetic setting, so that they can be applied in screening practice. Examples of these models include IBIS, Gail, BOADICEA, and BCSC (Louro, et al., 2019). To improve the discriminatory performance of these models, researchers looked at adding a measure for breast density and a polygenic risk score based on small variations in genes (SNPs). This did indeed improve the ability of these models to distinguish between women with and without breast cancer, but the models did not substantially improve (Clift, et al., 2021). In parallel with the research on classic risk prediction models, research groups are also working on predicting breast cancer risk based on information in the mammogram with the help of computer algorithms (machine learning/deep learning). The outcomes of these studies are promising and are often already producing a better prediction than the classic risk prediction models (Lehman, et al., 2022). Furthermore, recent developments show a shift from prediction of a 5 or 10-year breast cancer risk to a shorter-term risk, such as a two-year risk, in line with the current screening interval (Eriksson, et al., 2017). A short-term risk primarily provides insight into the risk that a participant will be diagnosed with an interval cancer between two screening rounds. It is clear that breast cancer risk prediction is a rapidly developing field. No method or model has so far been identified that could be regarded as the gold standard. At present, no European countries are offering personalised breast cancer screening as standard screening policy.

10.2.3 New screening modalities

Tomosynthesis

In the current screening programme, the screening examination consists of two digital X-rays of each breast. These X-rays provide a two-dimensional image of the breast. The downside is that structures in the breast may be projected on top of each other, making it appear as if an abnormality is present,

or resulting in an abnormality being overlooked. This can lead to participants being referred to the hospital for further assessment, after which no breast cancer is found, or it can lead to breast cancers being missed. Digital tomosynthesis is an x-ray technique that creates a three-dimensional image of the breast. For an average breast, 5 to 6 cm thick, around 50 images, each approximately 1 mm thick, are taken with a low radiation dose. These images are combined to create a three-dimensional image with no overlap between structures, giving the screening radiologist more information about possible abnormalities. European studies in screening programmes have shown that tomosynthesis can detect more breast cancers than digital mammography. Tomosynthesis increases the detection rate from 6 to 9 breast cancers per 1,000 participants, at a referral rate of between 3.5 and 4%. Since the Netherlands has a low referral rate for digital mammography (2.4%), the number of referrals, and thus the number of false positive outcomes, could increase. It is not yet clear whether the extra breast cancers found would lead to health benefits and a lower number of breast cancers being diagnosed between screening rounds (interval cancers) or at an advanced stage. To determine whether tomosynthesis has added value for the Dutch screening programme, the STREAM study was launched on January 1, 2023. The goals of this study are to determine the effect of tomosynthesis on screening outcomes in the short, medium, and long term, to determine acceptability of this screening modality for clients, screening radiographers and screening radiologists, and identify the optimal reading strategy for tomosynthesis.

MRI or contrast-enhanced mammography

Mammograms are a good screening test for many women in the target group. However, we know that mammograms are much less effective for women with high breast density. For this group, MRI, or possibly contrast-enhanced mammography (CEM), could provide a solution.

In the DENSE study, screening participants with a negative mammogram and extremely dense breast tissue are offered MRI. The results show that, for this group, MRI leads to the detection of more breast cancers through screening and a reduction in the number of interval cancers (Bakker, et al., 2019; Veenhuizen, et al., 2021). However, there are also harms to MRI. Compared with mammograms, more of the women referred to the hospital for further assessment are found not to have breast cancer. In addition, MRI leads to overdiagnosis and overtreatment more often than the current programme. It was primarily these harms, as well as the higher costs, that led the Minister of Health, Welfare, and Sport to decide that the time is not yet right to include MRI in the screening programme for women with extremely dense breast tissue. Instead of MRI, the Minister, following the advice of the Health Council of the Netherlands, would first like to know whether a mammogram using a contrast medium could be a viable alternative for this group. This approach is very similar to the mammograms we already use, with the difference that a contrast medium is injected first, as is done with MRI. As with MRI, this contrast medium can show where a cancer may be located in the breast. However, this type of examination also has its harms. More importantly, no research has yet been conducted into the use of contrast-enhanced mammography in the screening population. In February 2023, ZonMw issued a call for grant applications to change this situation.

Artificial intelligence

For mammography, but also for new screening modalities, artificial intelligence, in the form of computer algorithms, offers new possibilities to make reading of screening examinations more effective and/or more efficient. Artificial intelligence could play a role in various places in the screening process. Based on images, algorithms can estimate the breast cancer risk in the short or longer term (as described in Section 10.2.2). Algorithms can also be used to:

1. select screening examinations that do not have to be read by a radiologist because there is a very low risk of breast cancer being present (pre-screening);
2. support the radiologist in reading of images;
3. replace one or more radiologists in reading of images;

4. assess screening examinations that have been assessed as negative by a radiologist, with or without a consensus reading (post-screening) (Freeman, et al., 2021).

If artificial intelligence is to be used for pre-screening, there must be agreement on how many breast cancers the algorithm is allowed to miss (Hickmann, et al., 2022). Algorithms are not perfect, just as radiologists are not perfect. Recent literature reviews show that performance of radiologists improves with AI support (Anderson, et al., 2022). Algorithms used as independent readers do not yet always achieve the level of a radiologist (Hickmann, et al., 2022). To date, only very limited research has been done into post-screening with artificial intelligence (Freeman, et al., 2021).

It is important to bear in mind that all studies performed to date have used previously collected data (i.e., they are all retrospective studies). In addition, many of these studies have used enriched datasets, i.e., datasets in which more breast cancers are present than in the screening population. This means that we still know very little about the application of these kinds of algorithms in day-to-day screening practice. It is important for prospective studies to be performed that also provide insight into the effect of artificial intelligence on the reading behaviour of radiologists.

The use of artificial intelligence in the screening programme as a source of information also raises new questions. Can and should an algorithm assess a mammogram on its own? Or should a radiologist always take a look as well? How certain do we want to be that the algorithm is providing correct information? Prospective studies could find the best way for a computer and a radiologist to work together. How acceptable it is for an algorithm to make decisions in the screening process must also be investigated.

10.2.4 Opportunities in the longer term

In the longer term, other imaging techniques may be considered, such as breast CT. In the Netherlands, this technique is being investigated at Leiden University Medical Center (LUMC). The first results are promising, but according to the LUMC it is still too early to say whether this type of examination could have a place in the breast cancer screening programme. Other techniques have been raised by the media that are not yet being investigated in scientific studies, such as the Early Warning Scan.

A great deal of research is being conducted into biological characteristics (biomarkers) that could reveal the presence of breast cancer, as well as other forms of cancer. These biomarkers could help predict the risk of breast cancer. In the future, it might be possible to use them as a screening test as well. Biomarkers, such as fragments of tumour DNA, can appear in the blood if tumour cells are present anywhere in the body. Breath and urine biomarker tests are also being developed (Duque, et al., 2022). These biomarkers are often investiged first in smaller studies involving patients. The studies examine the ability of the biomarker to distinguish between women with and without breast cancer. This is an important first step in studying biomarkers. However, before any possible application in population screening, it must be investigated whether a biomarker can also detect breast cancer at an early stage, possibly even earlier than the current screening programme. That can only be investigated in women who do not yet have any symptoms of the disease. However, very few of these types of studies are being performed.

10.3 In conclusion

The Dutch breast cancer screening programme is in a steady phase. The results show a favourable ratio between the benefits and harms of the programme for participants. This provides room to investigate whether the programme can be further improved, and if so, how. Especially since we are aware that the current screening policy is not optimal for certain subgroups. New developments in imaging and artificial intelligence are offering opportunities to tailor screening to the individual breast cancer risk of participants. Over the next few years, more scientific evidence with regard to these

new developments will become available. Decisions will then have to be made about which of the new developments will be integrated into the screening programme. Policymakers, the screening organisation, and clients must be prepared for those decisions.

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