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Breast cancer: screening, stage, and outcome

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BREAST CANCER: SCREENING, STAGE, *and* OUTCOME

Studies based on
the Netherlands Cancer Registry

Linda de Munck

Breast cancer: screening, stage, and outcome

Studies based on the Netherlands Cancer Registry

PhD thesis, University of Groningen, The Netherlands

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Studies based on the Netherlands Cancer Registry

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TABLE OF CONTENTS

Chapter 1	General introduction	7
Part I	Impact of screening on breast cancer detection and stage	23
Chapter 2	Impact of mammographic screening and advanced cancer definition on the percentage of advanced stage cancers in a steady-state breast screening programme in the Netherlands	25
Chapter 3	Is the incidence of advanced-stage breast cancer affected by whether women attend a steady-state screening programme?	47
Chapter 4	Digital vs screen-film mammography in population-based breast cancer screening: performance indicators and tumour characteristics of screen-detected and interval cancers	77
Part II	Outcome and follow-up up to 10 years after diagnosis	95
Chapter 5	Do screen-detected breast cancers have positive margins less often than clinically detected breast cancers?	97
Chapter 6	10-year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study	113
Chapter 7	Attending the breast screening programme after breast cancer treatment: a population-based study	153
Chapter 8	Evaluating the age-based recommendations for long-term follow-up in breast cancer	167
Part III	General discussion	189
Chapter 9	General discussion	191
Appendices	Nederlandse samenvatting	211
	List of publications	219
	Research Institute SHARE	229
	Curriculum vitae	233
	Dankwoord	237

1

General introduction

BREAST CANCER EPIDEMIOLOGY

Breast cancer is the most common cancer in women both worldwide and in the Netherlands [1,2]. Reports indicate that more than 17,000 Dutch women are diagnosed with breast cancer (invasive carcinoma or ductal carcinoma in situ [DCIS]) each year and that 1 in 7 women will develop breast cancer in their lives [3]. The incidence of breast cancer has increased over recent decades from 109 to 199 per 100,000 women in 1990 and 2018, respectively (Figure 1). This increase has been seen most prominently in small localised invasive tumours, measuring less than 2 cm and without positive lymph nodes (Stage I), as well as in DCIS. Despite being pre- or non-invasive, DCIS is often seen as a non-obligate precursor of invasive breast cancer [4]. Its incidence amongst women also increased from 4 per 100,000 in 1990 to 27 per 100,000 in 2018, with most cases occurring among women aged 50-74 years (Figure 2). For invasive breast cancer, an increase has been seen in all ages other than in women aged 75-79 years (Figure 3). Although the incidence of breast cancer remained low in men between 1990 and 2018, there has been an increase from 0.5 to 1.5 per 100,000 men.

Figure 1. Breast cancer incidence by stage (Source: NKR-cijfers / IKNL)

Figure 2. Age-specific incidence of ductal carcinoma in situ (DCIS) (Source: NKR-cijfers / IKNL)

Figure 3. Age-specific incidence of invasive breast cancer (Source: NKR-cijfers / IKNL)

Several factors have been proposed to explain the increased incidence of breast cancer. The population of older women is increasing, and women are tending to live longer on average. Furthermore, post-menopausal obesity, and changes in hormonal and reproductive factors, such as increased age at first birth and lower parity, can increase the incidence of breast cancer [5-7]. The introduction of the national breast cancer screening programme also had an effect on case identification, as did increased awareness among women in general. Furthermore, women with a known positive family history or who are gene carriers are routinely offered specific surveillance to detect breast cancer at an early stage. It is expected that this will lead to a shift in diagnosis from advanced to early stage breast cancer for these women.

Survival from breast cancer has improved substantially over the last few decades, with the 10-year overall survival increasing from 68% for women diagnosed in the period 1990-2000 to 76% for women diagnosed in the period 2001-2010 [2]. Although improved treatment options will have played a role in this, it is clear that the shift toward early detection has been crucial. A tumour diagnosed at an earlier stage has a lower chance of developing distant metastasis and as such, will be more likely to have favourable outcomes [6]. For example, patients diagnosed with small localised tumours now have 5-year overall survival rates of approximately 99% (Figure 4). By contrast, patients with lymph node involvement at the time of diagnosis have a 5-year overall survival of 77%, while those with distant metastasis at the time of diagnosis (about 5% of new diagnosis annually) have an even worse 5-year overall survival of 28%.

Figure 4. Breast cancer survival by stage (Source: NKR-cijfers / IKNL)

Survival has increased over the years, which might be partly due to an earlier diagnosis. Therefore, it is important to look at mortality rates as well. Breast cancer mortality has decreased over time, with around 3,500 deaths due to breast cancer in the period 2001-2010 to around 3,100 deaths in recent years.

Consistent with the increased incidence and survival rate, the 10-year prevalence rate (which includes all patients alive at a moment in time who were diagnosed with breast cancer in the previous 10 years) has also increased. In 2018, there was an estimated 135,000 women alive in the Netherlands after being diagnosed with breast cancer (Figure 5) [2].

Figure 5. The 10-year prevalence of invasive breast cancer and DCIS among women (Source: NKR-cijfers / IKNL)

BREAST CANCER SCREENING PROGRAMME

Early detection has become an important aspect in the management of breast cancer by decreasing the associated mortality [6,8]. The main goal of a breast screening programme is to reduce mortality related to breast cancer. Several studies and trials have been performed into the effectiveness of detecting breast cancer early through a screening programme. The first were published in 1963 (New York) and 1977 (Sweden) and these showed that there was a reduction in breast cancer deaths among screened populations [9,10]. In the Netherlands, pilot projects started in 1975 in Utrecht and Nijmegen [11,12]. Based on the results of this early research, in 1989 it was decided that a nationwide breast cancer screening programme would be implemented gradually in the Netherlands. This initially offered biennial mammography screening to women aged

50-70 [13]. It was fully implemented from 1996 and from 1998 the age limit was extended to 75 years. In 2003, the first pilots were performed using digital screening to replace screen-film mammography, and after gradual implementation, digital screening was fully implemented from 2010.

The screening programme has been monitored using several performance indicators since its inception. Those used most often are the referral rate (i.e. the number of women referred for clinical follow-up per 1000 screened women), the detection rate (i.e. the number of women diagnosed with breast cancer per 1000 screened women), and the positive predictive value (i.e. the percentage of women diagnosed with breast cancer among all referred women).

Another method of evaluation has been to compare the characteristics of different groups by attendance at the screening programme and by their result. A positive screening result necessitates a referral to hospital for further check-up, whereas a negative result requires only further screening in another 2 years. When a woman has a positive screening result and is diagnosed with breast cancer within 1 or 2 years, she is diagnosed as having a **screen-detected cancer**. If a woman has a negative screening result, but is diagnosed with breast cancer within 2 years, she is diagnosed as having an **interval cancer**. This latter group arises when a small tumour is not yet visible on mammography, or was missed by the reviewing radiologists. The ratio of screen-detected to interval cancers is currently three to one [14].

Finally, there is a group of women who will not have attended screening for at least two years, either because they attend irregularly (e.g. skipped an invitation) or because they never attended. Cancers diagnosed in these women are considered **non-screened breast cancers** because they are detected in a way unrelated to the screening programme. Finally, any cancers detected on clinical grounds in hospital after a woman presents with complaints may be either interval or non-screened cancers.

The breast cancer screening programme and the Netherlands Cancer Registry (NCR) both started around the same time, which makes it difficult to see the effect of the programme on the incidence of invasive breast cancer and DCIS (Figure 2 and 3). However, there was an increase in DCIS in the age ranges invited for screening. In those aged 70-74 years, this increase can be seen after 1998, when the screening programme was introduced in this age group. The increase in invasive cancers has been less specific, but there was

evidence of a decrease in those just over the upper age limit of the programme (aged 75-79 years).

TREATMENT

The treatment of breast cancer depends on patient characteristics, the stage of the tumour, and other tumour characteristics (such as receptor status), with recommendations on treatment options provided in the Dutch NABON (Nationaal Borstkanker Overleg Nederland) Guidelines [15]. Moreover, the effective treatment of breast cancer requires good communication between many disciplines with a need for each treatment plan to be discussed in a multidisciplinary team. Treatment can include surgery, lymph node dissection, radiation therapy, chemotherapy, hormonal therapy, targeted therapy or a combination of these options. In the Netherlands, breast conserving therapy is the most used option in cases of small localised breast cancer. This involves breast conserving surgery, which removes the tumour while keeping part of the breast tissue, followed by radiotherapy. Mastectomy is the other surgical option and this requires the entire breast to be removed along with the tumour. Both options are reported to be equally safe [16-18]. However, it is important for both options that the entire tumour is removed with clear tumour-free margins. Non-surgical treatment can be given as neo-adjuvant or adjuvant therapy (i.e. before or after surgery), and the available options have improved substantially over time (e.g. chemotherapy, hormonal therapy, and the implementation of targeted therapy with trastuzumab).

FOLLOW-UP

After treatment, patients receive aftercare for a minimum of 5 years through annual follow-up visits at hospital in which clinical examination and mammography are performed [15]. According to the Dutch NABON Guideline, the first year of follow-up should focus on side effects, quality of life, and psychosocial complaints, but from the second year onwards, the priority should be to detect local and regional recurrences or to detect a second primary breast cancer. After 5 years, recommendation is to adopt an age-based follow-up policy on the basis that clinical cure is assumed: women aged <60 years should be seen annually and women 60-75 years biennially in the screening programme. However, in women older than 75 years, it may be appropriate to end all follow-up.

A recurrence can be either a local or regional recurrence, or a distant metastasis which develops in another organ. It is important to detect local or regional recurrences early

because these can be treated with curative intent. By contrast, distant metastases are still associated with a poor prognosis. Of all patients diagnosed in 2005 and treated with curative intent, 4.7% experienced local recurrence and 3.0% experienced regional recurrence within 10 years, while 15.0% were diagnosed with metastases over that period [19]. Most recurrences appear in the second year after treatment, and 1.9% of patients experienced further recurrence after a first recurrence has been treated [20].

An effect of the increased survival and prevalence is that more women are at risk of recurrence or late side effects and may require follow-up. This has increased the burden on the health care system and on health care professionals, which has led to a need for research into whether the content and time schedule of follow-up care can be improved after treatment.

DEBATE

To gain the optimal outcome of early detection, and subsequently the best treatment options, follow-up schedules and ultimately decrease mortality, a screening programme has to be monitored and adapted to new developments with continuous reviews. Such an approach allows screening programmes to meet their main goal of reducing disease related mortality. However, there are two sides to the debate about breast cancer screening programmes, with evidence of both benefit and harm.

The main benefits of the breast cancer screening programme arise from the fact that it can detect cancer early, which is expected to result in cases with more favourable characteristics and prognoses resulting eventually in less deaths due to breast cancer. Moreover, a small localised tumour can be treated less invasively and with fewer side effects for the patient. Additionally, it may be possible to perform breast conserving therapy while ensuring complete removal of the primary breast cancer with adequate tumour-free margins. By diagnosing more cases of breast cancer at early stages metastasis should also present less often. Survival and mortality are therefore expected to improve in women diagnosed at earlier stages.

Despite the positive outcomes reported in trials and later population-based studies, the effectiveness of breast cancer screening has always been subject to debate. The most prominent argument against the screening programme was that the expected decrease in the incidence of advanced stage disease was not shown in some population-based studies [21,22]. Furthermore, although the mortality rate did decrease over time (in line with the

main goal of the screening programme), decreases were also seen in other age groups that were not invited for screening. As such, the observed effects on the rates of advanced stage disease and mortality have been attributed to a combination of the screening programme and the improved staging and treatment options for breast cancer [23,24].

Furthermore, potential harms for the screening programme are the rate of false positive recalls, overdiagnosis, overtreatment and the occurrence of interval cancers. A false positive recall occurs when a woman receives a positive result from the screening examination when she should have received a negative result. It leads to unnecessary hospital follow-up and anxiety, and it contributes to the problems of overdiagnosis and overtreatment. Overdiagnosis can be defined as the detection of a breast cancer (DCIS or invasive carcinoma) by screening that would never have presented clinically during a woman's lifetime [6]. Overtreatment refers to treatment that is excessive [25] and exposes a woman to adverse effects without reasonable expectation of benefit. The issue of overtreatment appears to be especially relevant to DCIS, for which 80% of all cases are diagnosed by screening, with its incidence increasing rapidly since screening was introduced (Figure 2) [26]. Despite the non-invasive nature of DCIS, the treatment of choice is breast conserving therapy or mastectomy. However, there is ongoing debate as to whether such extensive treatment is actually necessary, and this is currently being investigated in a randomised trial [27].

In 2014 the Health Council of the Netherlands (Gezondheidsraad) decided that population-based breast cancer screening was still worthwhile [28]. However, there has been a shift in society that has led to informed decision making becoming more important. Women must therefore be informed of the benefits and harms of screening to allow them to make a well informed decision about whether they should attend the programme. If we are to ensure that we provide up-to-date information on the effectiveness of screening in the setting of continuing improvements in treatment options, we must continue research in this field. Although the most objective information would be obtained from randomised trials, this is not possible because the screening programme is already in place. Therefore, observational studies based on data from daily practice offer the next-best option, providing key information about the screening programme in a population-based setting. However, several issues must be considered with such research.

Notably, observational studies are hampered by lead-time bias and length-time bias. Lead-time bias occurs when a tumour is detected earlier (by screening), but the life span remains similar. Therefore, screening will appear to increase the survival time without

having an actual effect on survival: the additional survival time (lead-time) is actually the time between a tumour being detected by screening and otherwise presenting clinically. By contrast, length-time bias refers to fact that screening detects more slow-growing rather than fast-growing tumours, and that the former are usually associated with better outcomes. This results in longer survival due to the preferential selection of tumours with a better prognosis, rather than showing that screening per se is beneficial. Despite these issues, observational studies can offer valid outcome estimates for cancer populations in many circumstances, provided the study is adequately designed and properly addresses its limitations [29].

AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis was to describe the impact of the Dutch screening programme in the context of increasing breast cancer incidence. The contribution of the screening programme to the detection of early stage cancers and smaller tumours was studied, as was its effects on the disease-free interval (including tumour-free margins and breast cancer recurrence) and overall survival.

This thesis is broadly split into three parts. **Part 1** comprises **Chapters 2-4** and covers the impact of the screening programme on the detection of breast cancer, the stage at detection, and describes several key performance indicators. **Part 2** then comprises **Chapters 5-8** and covers the extended follow-up from breast cancer treatment to 10 year after diagnosis. Finally, **Part 3** concludes this thesis with a general discussion in **Chapter 9**. The content of each chapter is now summarized.

In **Chapter 2**, the proportions of advanced stage disease among screen-detected, interval, and non-screened cancers are compared using three definitions of advanced stage and assuming an amount of overdiagnosis. This is necessary because several researchers have described the effect of breast cancer screening on the stage distribution of breast cancer, but they have done so using different definitions of advanced stage. Thus, the impact of these definitions on the proportion of advanced stage cancers needs to be described.

In **Chapter 3**, the age-specific incidence rates of advanced breast cancer are assessed in women attending and not attending the breast cancer screening programme. These data clarify the contribution of screening mammography to the reduced rate of advanced breast cancer at a population level, which is still matter of debate.

In **Chapter 4**, performance indicators during the transition from screen-film mammography to full-field digital mammography are described together with the characteristics of screen-detected and interval cancers. This is important if we are to clarify the impact of technological advantages (i.e. better image quality, the ability to adjust contrast, and transfer capabilities) on outcomes since full-field digital mammography has replaced screen-film mammography in the Dutch breast cancer screening programme.

In **Chapter 5**, whether breast conserving surgery for screen-detected breast cancer produces positive margins less often compared with that for clinically detected breast cancer is evaluated. Breast conserving therapy is the most common treatment for breast cancer, and the presence of positive tumour margins is a major quality criterion against which successful surgical treatment of localised primary breast cancer is measured. National guidance states that the rate of positive margins should not exceed 30% for DCIS and 15% for invasive cancers. Furthermore, the choice of subsequent therapy is studied when margins were positive after initial breast conserving surgery.

In **Chapter 6**, the 10-year overall survival and breast cancer-specific survival rates are evaluated and compared between patients treated with breast conserving therapy and mastectomy for different tumour stages.

In **Chapter 7**, the potential factors affecting screening attendance during outpatient follow-up (overlap) and the (re-)attendance after 5 years of outpatient follow-up are described. As previously stated, patients receive standard follow-up for the first 5 years after diagnoses and treatment, before subsequent follow-up needs are determined by age. However, the relation between outpatient follow-up visits and the screening programme in the 5 years after treatment is not well established, even though attending both screening and scheduled outpatient follow-up is undesirable.

In **Chapter 8**, to take the first steps toward an adapted follow-up schedule that is based on risk, the patterns of long-term breast cancer recurrence are described and the age-based hazards of recurrence are modelled.

In **Chapter 9**, the thesis concludes with a general discussion of the main findings, implications for current and future patients, and a discussion on future perspectives.

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Part I

**Impact of screening on
breast cancer detection and stage**

2

Impact of mammographic screening and advanced cancer definition on the percentage of advanced stage cancers in a steady-state breast screening programme in the Netherlands

Linda de Munck

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ABSTRACT

Background

To estimate the percentages of advanced stage breast cancers (BCs) detected during the course of a steady-state screening programme when using different definitions of advanced BC.

Methods

Data of women aged 49–74 years, diagnosed with BC in 2006–2015, were selected from the Netherlands Cancer Registry and linked to the screening registry. BCs were classified as screen-detected, interval or non-screened. Three definitions of advanced BC were used for comparison: TNM stage (III–IV), NM stage (N+ and/or M+) and T size (invasive tumour ≥ 15 mm). Analyses were performed assuming a 10% overdiagnosis rate. In sensitivity analyses, this assumption varied from 0 to 30%.

Results

We included 46,734 screen-detected, 17,362 interval and 24,189 non-screened BCs. By TNM stage, 4.9% of screen-detected BCs were advanced, compared with 19.4% and 22.8% of interval and non-screened BCs, respectively ($p < 0.001$). Applying the other definitions led to higher percentages of advanced BC being detected. Depending on the definition interval, non-screened BCs had a 2–5-times risk of being advanced.

Conclusion

Irrespective of the definition, screen-detected BCs were less frequently in the advanced stage. These findings provide evidence of a stage shift to early detection and support the potential of mammographic screening to reduce treatment related burdens and the mortality associated with BC.

BACKGROUND

Breast cancer (BC) is the most common cancer among women, and tumour stage at diagnosis is important to overall survival [1-3]. Early diagnosis results in a mean lower tumour stage, which allows for better treatment options and ultimately reduces mortality. Although BC screening by mammography was introduced based on these arguments, there is ongoing debate as to whether screening affects the occurrence of advanced stage BC [4-6].

In a previous study, we studied the incidence rates of advanced stage, and found that there was a lower incidence of advanced BCs in screened women than in non-screened women, with estimates of 38 and 94 BCs per 100,000 women, respectively [7]. Most other studies have assessed the rates of advanced BCs in the total target population and/or have compared the percentages of early and advanced BCs in screen-detected versus other cancers [8-11]. However, these studies used different definitions for BC staging, making the true differences in percentage difficult to compare. Comparison has been further complicated by the potential for overdiagnosis. This is defined as the detection by screening of a BC (ductal carcinoma in situ or invasive carcinoma) that would never have presented clinically during a woman's lifetime [12]. A more favourable ratio between tumours of early and advanced stages can result not only from a reduction in the number of advanced BCs because of early detection and treatment, but also from an increase in overdiagnosis. At present, the extent of this overdiagnosis is unclear, with estimates ranging from 0 to 52% [13-18], and levels sitting at ~10% in the Netherlands [13,18].

When comparing the published percentages of advanced BCs, reported differences in the impact of mammographic screening might, at least partly, be attributable to the varying definitions of advanced tumours. Therefore, we aimed to estimate the percentages of advanced BC in a steady-state biennial screening programme when using different definitions for advanced stage. We also wanted to assess the impact of different assumptions of overdiagnosis on the estimated percentages of advanced BC. These results will contribute to a clear perspective of what already has been published on this topic.

METHODS

Study design

This population-based study included all women aged 49–74 years diagnosed with BC (invasive cancers and ductal carcinomas in situ) between January 1, 2006, and December 31, 2015. We used data from the Netherlands Cancer Registry (NCR), hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) [1], and linked them to data from the Netherlands Breast Cancer Screening Registry. Percentages were compared between screen-detected, interval and non-screened cases of BC, using three definitions of advanced BC (i.e., TNM, NM and T-size staging). The Central Committee on Research involving Human Subjects determined that this study did not require approval from an ethics committee. The study was approved by the Privacy Review Board of the NCR.

Study population

We selected women aged 49–74 years who were diagnosed with BC (invasive and ductal carcinoma in situ) between January 1, 2006, and December 31, 2015 from the NCR. Their data were linked to those in the Netherlands Breast Cancer Screening Program. The linkage data identified women screened between January 1, 2004, and December 31, 2015, to cover a period of at least 24 months before BC diagnosis. Given that the screening programme invited women for biennial screening, the 24-month threshold before diagnosis was considered important when defining the detection mode (i.e., the relation between BC diagnosis and the screening programme). For example, a woman diagnosed with BC in 2006 could have been screened in 2004 or 2005 and categorized with interval cancer, whereas if she had not attended the screening programme, the cancer would be categorised as a non-screened BC.

We excluded women diagnosed after their prevalent screen on the basis that screening is not a once-only event. Furthermore, we excluded women with lobular carcinoma in situ because this is not considered malignant. Women diagnosed with BC in 5 years before the current diagnosis were also excluded to minimize interference from hospital follow-up visits. For women with synchronous BC, only the most advanced cancer was included.

Definitions of BC groups and cases

We defined three groups of BC: screen-detected, interval and non-screened. Screen-detected BCs included cases diagnosed within 24 months after being recalled for further diagnostic workup due to a positive screening result; interval BCs included cases diagnosed within 24 months after a negative screening result, which indicates no recall

necessary. Non-screened BCs included those diagnosed in women at a screening interval beyond the planned 24 months (i.e., not recently screened) or never attended screening, as we were not able to divide these two groups.

Cases of advanced BC were identified using three definitions: TNM-staging, NM-staging and T-size staging. Using the TNM classification, stages III–IV were defined as advanced cancer, and stages 0–II were defined as early cancer [19,20]. Based on NM-staging, tumours with positive lymph nodes and/or metastasis (N+ and/or M+) were defined as advanced NM-stage, and tumours without positive lymph nodes or metastasis (N0M0) were defined as early NM-stage [21]. When using the tumour size only, an advanced T-size stage was defined as the presence of an invasive tumour measuring ≥ 15 mm, whereas an early T-size stage was defined as either a tumour measuring < 15 mm or as a ductal carcinoma in situ (regardless of size) [22]. For each definition, BCs of unknown stage are included in the description of the cohort characteristics, but not in the statistical analyses. Furthermore, in sensitivity analyses, additional definitions of advanced TNM-stage were included, in which advanced TNM-stage was defined as stage IIB–IV (compared with 0–IIA) or as stage II–IV (compared with stage 0–I).

Data sources

Data were accessed from the NCR and the Netherlands Breast Cancer Screening Programme. In the Netherlands, all new cancer cases are registered in the NCR, which contains data on patient, tumour and treatment characteristics for all in situ and invasive malignancies diagnosed since 1989. The main source of notification for the NCR is the Nationwide Histopathology and Cytopathology Data Network and Archive (PALGA) [23]. After the NCR has been notified, specially trained registration clerks visit hospitals to collect information on patient and tumour characteristics, including the stage and treatment data, directly from patient records. Tumour topography, morphology and grade were coded according to the International Classification of Diseases for Oncology, 3rd edition [24]. Staging is classified according to the TNM Classification of Malignant Tumours, using the sixth edition until 2009 and the seventh edition thereafter [19,20].

The population-based Netherlands Breast Cancer Screening Programme has been operational since 1990, initially inviting women aged 49–69 years for a biennial screening examination, but including women aged 70–74 years from 1998 onwards [25]. All mammographic examinations are performed by specialist radiographers and are double-read by accredited radiologists. Recall for further diagnostic workup is indicated if the screening examination is incomplete (i.e., Breast imaging reporting and data system

[BI-RADS] 0) or if there are suspicious or malignant findings (i.e., BIRADS 4 or 5) [26,27]. Between 2003 and 2010, screen-film mammography has gradually been replaced by full-field digital mammography [28]. Permission for linkage to the NCR was requested from women when they attended screening. This was based on an optout option, which was used by 0.02% of all women screened [29].

The impact of overdiagnosis

To consider the impact of possible overdiagnosis in our main analysis, we assumed an overdiagnosis estimate of 10%, consistent with that reported in the Netherlands [13,18]. By definition, overdiagnosis only occurs in BCs that are detected by screening in an early stage. For all three definitions of advanced BC, we performed separate calculations to correct for overdiagnosis and performed separate analyses. For all screen-detected BCs, we assumed that 10% of the total sample was overdiagnosed, and then excluded this number at random from the early screen-detected BCs. However, given that the true overdiagnosis rate is unknown, and that published estimates differ substantially, we performed sensitivity analyses in which the assumed overdiagnosis estimates were 0 and 30% [30]. The adjustments for overdiagnosis resulted in a lower total number of screen-detected BCs and in a higher percentage of advanced screen-detected BCs. To check whether exclusion was performed at random, the baseline characteristics of the remaining screen-detected BCs were compared with the original sample (Supplementary Table 1).

Statistical methods

The percentage of advanced cancers in the screen-detected, interval and non-screened BC groups was compared by the Chi-squared test. Univariable and multivariable logistic regression analyses were used to estimate differences in the percentage of advanced disease among the three subgroups, controlling for age at diagnosis, year of diagnosis and socioeconomic status (SES). Data for the multivariable analyses are reported as odds ratios (ORs) with their 95% confidence intervals (95% CIs). Age at the time of diagnosis was categorised as 49–59, 60–69 and 70–74 years, with the age category 60–69 years defined as the reference group. SES was determined by education, household income and labour market status, based on postal codes, and categorised as high (reference), medium and low SES [31]. Statistical significance was set at a p-value of <0.05, and all tests were two-sided. Analyses were performed using the STATA Software Package, Version 14.1 for Windows (Stata Corporation LP, College Station, TX, USA).

RESULTS

Participants

In our main analysis, we included 88,285 BC cases, of which 46,734 were screen-detected, 17,362 were interval and 24,189 were non-screened (Figure 1). Note that among the 51,927 initial cases of screen-detected BCs, we excluded 5,193 cases based on the assumption of a 10% overdiagnosis rate, leaving 46,734 screen-detected cases. Median time between a negative screening result and interval cancer diagnosis was 14 months (interquartile range 10 months). The baseline characteristics are shown in Table 1.

Figure 1. Flow chart of included patients.

We included 88,285 BC cases, of which 46,734 were screen-detected, 17,362 were interval, and 24,189 were non-screened. We excluded 5,193 cases from the 51,927 initial cases of screen-detected BCs based on the assumption of a 10% overdiagnosis rate.

Table 1. Breast cancer characteristics for each detection cohort

	Screen-detected		Interval		Non-screened		Total	p-value*
	N	%	N	%	N	%	N	
Age								
- mean (IQR)	63 (58-68)		61 (56-67)		60 (53-67)			
49-59	15,610	33.4	6,989	40.3	11,211	46.3	33,810	<0.001
60-69	22,192	47.5	7,795	44.9	9,107	37.6	39,094	
70-74	8,932	19.1	2,578	14.8	3,871	16.0	15,381	
Year								
2006	3,631	7.8	1,598	9.2	2,156	8.9	7,385	<0.001
2007	3,976	8.5	1,618	9.3	2,261	9.3	7,855	
2008	4,051	8.7	1,661	9.6	2,393	9.9	8,105	
2009	4,127	8.8	1,698	9.8	2,467	10.2	8,292	
2010	4,526	9.7	1,756	10.1	2,301	9.5	8,583	
2011	4,850	10.4	1,832	10.6	2,354	9.7	9,036	
2012	5,241	11.2	1,825	10.5	2,415	10.0	9,481	
2013	5,490	11.7	1,737	10.0	2,513	10.4	9,740	
2014	5,349	11.4	1,865	10.7	2,691	11.1	9,905	
2015	5,493	11.8	1,772	10.2	2,638	10.9	9,903	
SES								
High (8-9-10)	14,486	31.0	5,562	32.0	7,623	31.5	27,671	<0.001
Medium (4-5-6-7)	18,681	40.0	7,014	40.4	9,472	39.2	35,167	
Low (1-2-3)	13,567	29.0	4,786	27.6	7,094	29.3	25,447	
Total	46,734	100	17,362	100	24,189	100	88,285	

* Chi-squared test.

Abbreviations: IQR: interquartile range; SES: socioeconomic status

Table 2. Percentages of early and advanced disease in each detection cohort, reported by definition of advanced stage breast cancer

	Screen-detected		Interval		Non-screened		Total	p-value*
	N	%	N	%	N	%	N	
TNM-Stage								
Early stage (St 0-I-II)	44,368	95.1	13,953	80.6	18,578	77.2	76,899	<0.001
Advanced stage (St III- IV)	2,272	4.9	3,353	19.4	5,491	22.8	11,116	
Unknown	94		56		120		270	
NM-Stage								
Early stage (N0M0)	35,391	78.8	9,012	59.0	12,886	60.9	57,289	<0.001
Advanced stage (N+ and/or M+)	9,514	21.2	6,270	41.0	8,285	39.1	24,069	

Table 2. (continued)

	Screen-detected		Interval		Non-screened		Total	p-value*
	N	%	N	%	N	%	N	
Unknown	1,829		2,080		3,018		6,927	
T-stage								
Early stage (<15mm)	28,467	62.4	4,976	30.9	8,858	41.8	42,301	<0.001
Advanced stage (invasive ≥15mm)	17,133	37.6	11,107	69.1	12,353	58.2	40,593	
Unknown	1,134		1,279		2,978		5,391	
Total	46,734		17,362		24,189		88,285	

* Chi-squared test.

Advanced TNM-stage (stages III and IV)

Based on TNM-staging, 4.9% of screen-detected BCs were advanced (Table 2, Figure 2). More cancers were diagnosed as being advanced stage in the interval (19.4%) and non-screened (22.8%) cohorts ($p < 0.001$). Multivariable logistic regression indicated that compared with screen-detected BC, there was an increased risk of the interval and non-screened BCs being advanced, with ORs of 4.67 (95% CI, 4.41–4.94) and 5.76 (95% CI, 5.47–6.07), respectively (Figure 3). In sensitivity analyses using additional definitions of advanced TNM-stage, the results remained similar (Supplementary Figures 1 and 2).

Figure 2. Percentages of advanced breast cancers over time in the screen-detected, interval, and non-screened cohorts by three definitions of advanced stage.

The solid line indicates the screen-detected cancers assuming 10% overdiagnosis. The shaded area then indicates the percentage assuming 0% overdiagnosis (lower limit) to 30% overdiagnosis (upper limit).

Advanced NM-stage (N+ and/or M+)

Based on NM-staging, 21.2% of BCs were advanced in the screen-detected cohort, compared with 41.0% and 39.1% in the interval and non-screened cohorts, respectively ($p < 0.001$, Table 2). Analysis confirmed that interval and non-screened BCs were more often advanced, with the respective ORs of 2.53 (95% CI, 2.44–2.64) and 2.34 (95% CI, 2.26–2.43) (Figure 2). Compared with TNM-staging, the percentage of advanced cancers based on NM-staging was higher for all detection modes, and the ORs for advanced BC were almost halved in the interval and non-screened cohorts (Figures 2 and 3).

Figure 3. Odds ratios for advanced breast cancer between different cohorts by the three definitions of advanced stage.

Data are for the interval and non-screened cohorts compared with the screen-detected cohort.

* Multivariable analyses corrected for age, year of diagnosis, socioeconomic status.

Abbreviations: 95%CI: 95% Confidence Interval

Advanced T-size (invasive tumours ≥ 15 mm)

When defining advanced BCs as invasive disease measuring ≥ 15 mm (i.e., by T-size), 37.6% of BCs in the screen-detected cohort were considered advanced (Table 2, $p < 0.001$). The percentages of advanced BCs in the interval (69.1%) and non-screened (58.2%) cohorts were also significantly higher ($p < 0.001$). Compared with the screen-detected cohorts, the ORs for advanced BC based on T-size were 3.68 (95% CI, 3.54–3.82) for the interval cohort and 2.29 (95% CI, 2.21–2.37) for the non-screened cohort (Figure 3). Compared with TNM staging, the percentage of advanced BC identified by T-size staging was higher for all detection modes, and the ORs for advanced T-size BC were lower in the interval and non-screened cohort.

The impact of different rates of cancer overdiagnosis

The effect of overdiagnosis was further explored by assuming either no overdiagnosis (0%) or higher overdiagnosis estimates (30%). However, regardless of the estimate used, the percentages of advanced cancers remained significantly higher in the interval and non-screened BC cohorts (Figure 2).

When assuming no overdiagnosis, the percentages of advanced disease decreased in all instances: for TNM staging, it changed from 4.9 to 4.4% (Figure 2, Supplementary Table 2), for NM staging, it changed from 21.2 to 19.0% and for T-size staging, it changed from 37.6 to 33.7%. Compared with screen-detected BC, the ORs for advanced stage were also significantly higher for interval and non-screened BCs when using all definitions (Supplementary Figure 3). Overdiagnosis only affected the percentage of screen-detected BC, and the percentages of advanced-stage BC remained similar in the interval and non-screened cohorts.

In contrast to the 0% estimate, defining 30% of all screen-detected BCs as overdiagnosed resulted in an increase in the percentages of advanced screen-detected BC compared with the 10% assumption. However, for all three definitions of advanced stage, the percentage of advanced BCs in the screen-detected cohort remained significantly lower than in the interval and non-screened cohorts. The ORs for advance stage remained significantly higher for interval and non-screened BCs when using all definitions (Supplementary Figure 4).

DISCUSSION

Screen-detected cancers were less often diagnosed at an advanced stage compared with interval and non-screened cancers, regardless of the definition used for advanced BC. Indeed, compared with the screen-detected cohort, the interval and non-screened cohorts were 2–3 times and 2–5 times more likely to be advanced BC, respectively. When exploring the impact of overdiagnosis, even with the assumption of a 30% overdiagnosis estimate, there remained significantly higher percentages of advanced BCs in the interval and non-screened cohorts.

Several studies have been performed to identify the percentages or incidence rates of early and advanced BC identified by screening, based on individual data [5,8,9,11,14,32–34]. Using different definitions of advanced stage, each of these studies has shown lower percentages of advanced BC in screen-detected cohorts. Furthermore, studies that have

used TNM staging [11,33,34] have showed larger differences in advanced BC than those that have used NM staging [8,9,14], which is consistent with our results. One study of advanced BC reported comparable differences when using definitions comparable to those in the current research [32]. Comparing ever-screened women to non-screened women aged 50–64 years, they reported an OR of 0.41 when defining advanced BC as stage IIB or higher, and 0.67 when using the NM-stage definition. The current study shows a direct comparison of the effect of breast screening on the percentage of advanced stage for each definition. Our results indicate that the larger differences found in other studies using TNM stage are indeed partly attributable to the definition used.

Overdiagnosis results in an artificial decrease in the percentage of advanced cancers. Such a decrease can result from an actual reduction in the number of advanced tumour stages or from an increase in the number of early tumour stages, which itself may be due to overdiagnosis. Most likely, both factors contributed to the reduction in advanced BC seen in our study. In previous research, we showed that there was a substantially lower incidence rate of advanced cancers among screened compared with non-screened women, and this difference in incidence rate was unaffected by overdiagnosis [7]. However, most studies that published percentages to date have concluded that overdiagnosis does play a role. In the present study, we assumed a 10% rate of overdiagnosis among screen-detected cancers to study the percentage of women with advanced BC accurately in the Dutch population.

A potential limitation of this study is that we had no information about women with a higher-than-average risk for BC (e.g., those with BRCA1/2 mutations or a high familial risk), so we cannot confirm if these women attended screening. However, because women younger than 49 years were not included, we doubt that this will have affected our conclusions. A second limitation is that participation in the screening programme is voluntary, meaning that certain factors may have influenced attendance. Although women with a low SES have lower attendance rates [35], we identified that this subgroup was more likely to be diagnosed with advanced cancer and corrected for SES in the multivariable analysis. In addition, the overall influence of bias due to self-selection, on the effectiveness of the Dutch screening programme, has been shown to be minor [36]. Finally, we obtained no structural information about breast density, which is known to reduce mammographic detectability, and to increase the risk of BC [37,38]. Unfortunately, the extent of this effect on our results is unknown.

The major strengths of this study are the population-based design covering the entire country, and the fact that we were able to link data from the cancer registry to those from the screening registry at the individual level. The same study population was also used for all definitions, enabling a direct comparison of the effect of breast screening on the percentage of advanced stage for each definition. Furthermore, BC cohorts were classified as screen-detected, interval and non-screened based on actual data for screening attendance. To minimise interference with hospital check-ups, we only included first and second cancers diagnosed at least 5 years after the first BC, we only studied the effects of BC stage in a steady-state situation and we excluded women diagnosed after their prevalent screen. Although the exact magnitude of overdiagnosis cannot be known for certain, we were able to show a consistent effect of screening on advanced BC for a wide range of overdiagnosis rates.

CONCLUSION

Irrespective of the definition used for advanced BC, screen-detected cohorts show lower rates of advanced BC than interval and non-screened cohorts. Our results support the hypothesis that mammographic screening causes a stage shift towards the diagnosis of early breast cancer stages, giving it the potential to reduce BC-related mortality and treatment-related burdens.

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AUTHOR CONTRIBUTIONS

L.M. contributed to the study design, data preparation, analysis and interpretation, prepared the first draft of the report, subsequent versions and the final report. S.S. and G.B. contributed to study design, data analysis and interpretation, prepared the first draft of the report, subsequent versions and the final report. J.F. contributed to data analysis and interpretation, reviewed the first draft of the report, subsequent versions and the final report. G.H. and M.B contributed to study design, data interpretation, reviewed the first draft of the report, subsequent versions and the final report.

ADDITIONAL INFORMATION

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki. The Central Committee on Research involving Human Subjects determined that this study did not require approval from an ethics committee. The study was approved by the Privacy Review Board of the NCR.

Data availability

The data used in this study are available with permission of the Netherlands Cancer Registry.

Competing interests

G.J. den Heeten is the founder of a spin-off company of the Academic Medical Centre Amsterdam (Sigmascreening, a medical device company), and is a member of the medical advisory board of Volpara Solutions (software, New Zealand). All other authors declare that they have no competing interests.

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SUPPLEMENTARY DATA

Supplementary Table 1. Breast cancer characteristics within the screen-detected cancers after excluding the percentage of assumed overdiagnosis.

	Screen-detected cancers		Screen-detected cancers	
	10% overdiagnosis	0% overdiagnosis*	30% overdiagnosis	
	N (%)	N (%)	N (%)	
Age				
- mean (IQR)	63 (58-68)	63 (58-68)	63 (57-68)	
49-59	15,610 (33.4)	17,351 (33.4)	12,294 (33.8)	
60-69	22,194 (47.5)	24,695 (47.6)	17,176 (47.3)	
70-74	8,932 (19.1)	9,881 (19.0)	6,879 (18.9)	
Year				
2006	3,631 (7.8)	4,036 (7.8)	2,820 (7.8)	
2007	3,976 (8.5)	4,444 (8.6)	3,151 (8.7)	
2008	4,051 (8.7)	4,467 (8.6)	3,140 (8.6)	
2009	4,127 (8.8)	4,577 (8.8)	3,282 (9.0)	
2010	4,526 (9.7)	4,999 (9.6)	3,487 (9.6)	
2011	4,850 (10.4)	5,369 (10.3)	3,707 (10.3)	
2012	5,241 (11.2)	5,807 (11.2)	4,083 (11.2)	
2013	5,490 (11.7)	6,141 (11.8)	4,262 (11.7)	
2014	5,349 (11.4)	5,967 (11.5)	4,169 (11.5)	
2015	5,493 (11.8)	6,120 (11.8)	4,248 (11.7)	
SES				
High (8-9-10)	14,486 (31.0)	16,105 (31.0)	11,268 (31.0)	
Medium (4-5-6-7)	18,681 (40.0)	20,800 (40.1)	14,521 (33.9)	
Low (1-2-3)	13,567 (29.0)	15,022 (28.9)	10,560 (29.1)	
Total	46,734 (100)	51,927 (100)	36,349 (100)	

Abbreviations: IQR: interquartile range; SES: socioeconomic status

* 0% overdiagnosis means that all patients are included in the analysis

Supplementary Table 2. Percentage early and advanced stage disease of the remaining selection of screen-detected cancers after excluding the percentage of assumed overdiagnosis.

	Screen-detected cancers		Screen-detected cancers
	10% overdiagnosis	0% overdiagnosis*	30% overdiagnosis
	N (%)	N (%)	N (%)
TNM-Stage			
Early stage (St 0-I-II)	44,368 (95.1)	49,561 (95.6)	33,983 (93.7)
Advanced stage (St III- IV)	2,272 (4.9)	2,272 (4.4)	2,272 (6.3)
Unknown	94	94	94
NM-Stage			
Early stage (N0M0)	35,391 (78.8)	40,584 (81.0)	25,006 (72.4)
Advanced stage (N+ and/or M+)	9,514 (21.2)	9,514 (19.0)	9,514 (27.6)
Unknown	1,829	1,829	1,829
T-size			
Early stage (<15mm)	28,467 (62.4)	33,660 (66.3)	18,082 (51.3)
Advanced stage (≥15mm)	17,133 (37.6)	17,133 (33.7)	17,133 (48.7)
Unknown	1,134	1,134	1,134
Total	46,734 (100)	51,927 (100)	36,349 (100)

* 0% overdiagnosis means that all patients are included

Supplementary Figure 1. Percentages of advanced breast cancers over time for two other definitions of advanced TNM-stage, compared to the main definition.

The solid line indicates the screen-detected cancers assuming 10% overdiagnosis. The shaded area then indicates the percentage assuming 0% overdiagnosis (lower limit) to 30% overdiagnosis (upper limit).

Supplementary Figure 2. Odds ratios for advanced breast cancer for two other definitions of advanced TNM-stage, compared to the main definition.

* Multivariable analyses corrected for age, year of diagnosis, socioeconomic status.

Abbreviations: 95%CI: 95% Confidence interval

Supplementary Figure 3. Odds ratios for advanced breast cancer between different cohorts by three definitions of advanced stage, assuming 0% no overdiagnosis.

* Multivariable analyses corrected for age, year of diagnosis, socioeconomic status.

Abbreviations: 95%CI: 95% Confidence interval

Supplementary Figure 4. Odds ratios for advanced breast cancer between different cohorts by three definitions of advanced stage, assuming 30% overdiagnosis[#]

[#] 30% of all screen-detected cancers (n=51,927) were assumed to be overdiagnosed (n=15,578). As overdiagnosis occurs in the early screen-detected cancers by definition, we randomly excluded 15,578 cancers from the early screen-detected cancers as an attempt to correct for overdiagnosis.

* Multivariable analyses corrected for age, year of diagnosis, socioeconomic status.

Abbreviations: 95%CI: 95% Confidence interval

3

Is the incidence of advanced-stage breast cancer affected by whether women attend a steady-state screening programme?

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ABSTRACT

In this cross-sectional population-based study, we assessed the incidence of advanced breast cancer based on screening attendance. Women from the Netherlands Cancer Registry were included if aged ≥ 49 years and diagnosed with breast cancer between 2006 and 2011, and data were linked with the screening programme. Cancers were defined as screen-related (diagnosed < 24 months after screening) or non-screened (all other breast cancers). Two cut-offs were used to define advanced breast cancer: TNM-stage (III–IV vs 0–I–II) and T-stage alone (≥ 15 mm vs < 15 mm or DCIS). The incidence rates were adjusted for age and logistic regression was used to compare groups. Of the 72,612 included women diagnosed with breast cancer, 44,246 (61%) had screen-related breast cancer. By TNM stage, advanced cancer was almost three times as likely to be at an advanced TNM stage in the non-screened group compared with the screen-related group (38 and 94 per 100,000, respectively; OR: 2.86, 95%CI: 2.72–3.00). By T-stage, the incidence of advanced cancer was higher overall, and in non-screened women was significantly higher than in screened women (210 and 169 per 100,000; OR: 1.85, 95%CI: 1.78–1.93). Data on actual screening attendance showed that the incidence of advanced breast cancer was significantly higher in non-screened women than in screened women, supporting the expectation that screening would cause a stage shift to early detection. Despite critical evaluations of breast cancer screening programmes, our data show that breast cancer screening is a valuable tool that can reduce the disease burden in women.

INTRODUCTION

Breast cancer screening aims to reduce breast cancer morbidity and mortality by detecting disease at earlier and more treatable stages. Indeed, trials of breast cancer screening have shown that it can reduce the rate of advanced stage cancer, and ultimately, reduce the associated mortality [1-5]. In a meta-analysis of these randomized trials, the associated relative risk reduction was 20% [6]. The strength of these data meant that population-based screening programmes were introduced, and subsequent observational studies have confirmed the ability of such programmes to reduce mortality [7-10]. Despite this evidence, however, the contribution of mammographic screening to a reduced rate of advanced stage breast cancer is still questioned [11-14].

When introduced, screening should cause a shift in the stage-specific breast cancer incidence [15], and this should stabilize when screening is fully implemented. Early detection is essential because tumour stage at diagnosis remains important to overall survival [16,17]. Although lower overall rates of advanced breast cancer in a screened population can indicate the effectiveness of screening, any meaningful study into this association requires that we know whether cancer was diagnosed in a screened or a non-screened population. To date, however, most observational studies have only reported the incidence of early and advanced breast cancer in all women, without differentiating by screening status [12,13,18-23].

Some recent studies have tried to remedy the failings of existing data by comparing regions with and without screening programmes [24] or by classifying women as participants or nonparticipants based on attendance at the first two rounds of screening [25]. However, these approaches use some approximations of screening status, and there is still some uncertainty whether cancer was diagnosed in the screened or the non-screened women. To the best of our knowledge, only one study has used information about screening attendance at an individual patient level, and this showed a lower rate of advanced disease among screened women [26].

It is important to consider the background incidence of breast cancer when evaluating stage-specific incidence in relation to screening [27]. If the background incidence was increasing, the rate of advanced cancer would also be expected to increase; therefore, if the incidence of advanced cancer was stable in the context of a screening programme, one could conclude that a relative reduction in the incidence of advanced cancer existed.

To evaluate the effect of a screening programme on the incidence of advanced breast cancer, it is necessary to link data on tumour stage with individual data on screening programme attendance. In this study, we compared the age-specific incidence rates of early and advanced breast cancer among attenders and nonattenders of a fully implemented, steady-state, breast cancer screening programme. We expected the incidence of advanced breast cancer to remain stable over calendar time in attenders and nonattenders due to the steady-state situation, but to be higher in the nonattenders.

METHODS

Study design

This was a cross-sectional population-based study of women aged 49 years or older diagnosed with breast cancer (invasive and ductal carcinoma in situ) between January 1, 2006, and December 31, 2011. Our focus was on comparing the incidence between women with screen-related breast cancer (screen-detected or interval) and those with non-screened breast cancer. We used data from the Netherlands Cancer Registry (NCR) that were linked to the Netherlands breast cancer screening programme. The Central Committee on Research involving Human Subjects determined that this study did not require approval from an ethics committee. The study was approved by the Privacy Review Board of the NCR.

The Netherlands Cancer Registry

In the Netherlands, all new cases of cancer are registered in the population-based NCR [28], which has contained data on patient, tumour and treatment characteristics for all in situ and invasive malignancies since 1989. The main source of notification for the NCR is the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). After the NCR is notified, registration clerks attend hospitals to collect information on patient and tumour characteristics directly from patient records. Coding in the NCR is based on international rules (i.e., the International Association of Cancer Registries), with TNM staging classified according to the sixth edition until 2009 and according to the seventh edition thereafter [29,30].

The Netherlands Breast Cancer Screening Programme

The population-based Netherlands Breast Cancer Screening Programme has invited women aged 49–69 years for biennial screening examination since 1990 [31], with women aged 70–74 years included since 1999. All mammographic examinations are performed by specialist radiographers and the results are read blindly by two certified radiologists.

Recall for further diagnostic assessment is indicated if examination is incomplete (Breast Imaging – Reporting And Data System [BI-RADS] 0) or if there are suspicious or malignant findings (BI-RADS 4 or 5) [32]. Between 2003 and 2010, screen-film mammography was gradually replaced by full-field digital mammography [33].

Study population

Permission for linkage to the NCR was requested for all women when they attended screening, and covered 99.98% of those screened during the study period [33]. We selected women aged ≥ 49 years and diagnosed with breast cancer (invasive and ductal carcinoma in situ, morphology 8010–8575) from the NCR and linked the data with that from the Netherlands Breast Cancer Screening Programme. The linkage data included women screened between January 1, 2004, and December 31, 2011, covering a period of at least 24 months before breast cancer diagnosis. Given that women were invited biennially, the 24-month threshold before diagnosis was considered important when investigating the association between the screening programme and diagnosis of cancer. Women can be diagnosed with breast cancer in the 24 months before their next invitation. Women who were diagnosed with breast cancer in the 5 years before the current diagnosis were excluded to minimize interference from hospital check-ups, as were women who had lobular carcinoma in situ. For women with synchronous breast cancer, only the most advanced cancer was included. In total 72,612 breast cancers were selected.

Definitions

For simplicity, we defined a screen-related group (screen-detected or interval cases) and a non-screened group (never or irregular attenders). Screen-detected and interval cancers included cases diagnosed within 24 months after positive and negative screening results, respectively. All other breast cancers were defined as non-screened, including those diagnosed in women who never attended screening and in women who were considered to have attended irregularly. The irregular attendance group comprised women who missed an opportunity for screening examination, so had an interval beyond the planned 2 years. When interpreting our results, it should be noted that the terms “screen-related” and “non-screened” only applied to the 2 years before the date of diagnosis.

Age at time of diagnosis was categorized as 49–59, 60–69, 70–74, 75–79, or ≥ 80 years, based on an age of 49 years as the official lower limit for screening used by Statistics Netherlands. Age 74 years was the upper age limit for screening, so we included cases of

breast cancer diagnosed up to 24 months after screening examination to cover outcomes in this age group. The screened population therefore included women aged 49–76 years. To provide insight in the upper age limit of the screening programme, we included patients aged 75–79 years as an extra cut-off point.

Two definitions were used to distinguish advanced from early breast cancer: 1) the TNM classification, with stages III–IV defined as advanced cancer and stages 0–I–II defined as early cancer; [29,30] and 2) the T-stage alone, with invasive tumour size ≥ 15 mm defined as advanced cancer and tumour size < 15 mm or ductal carcinoma in situ (regardless of size) defined as early cancer [34]. Breast cancers with an unknown T-stage were excluded from this latter analysis.

Incidence calculations

Breast cancer incidence rates per 100,000 women were calculated separately for the screen-related and non-screened cancers. To determine the screened population, the number of screened women was obtained directly from data held for the screening programme. For each year of diagnosis and age, the number of screened women was calculated by adding the sum of women of a specific age who were screened in a specific calendar year to the number of women 1-year younger and screened in the preceding calendar year. This sum included all women screened in the preceding 24-month period who had the same age in a specific calendar year. Incidence rates per 100,000 screened women were calculated by dividing the total number of screen-related cancers in a specific calendar year by the total number of women screened in that year, before multiplying by 100,000.

When calculating breast cancer incidence in the non-screened population, the denominator was obtained from data published by Statistics Netherlands [35]. To assess each year of diagnosis, we calculated the total number of women per calendar year as the average of the female population in a given calendar year plus the female population in the year before. To assess specific age ranges, we selected all women of a specific age per calendar year, plus women 1-year younger in the year before. The non-screened population was then calculated by subtracting the screened population from the total population per year and age. Finally, the non-screened population was divided into three age groups (49–74, 75–79 and ≥ 80 years) and the incidence was calculated per group. We calculated age-specific incidence rates per 100,000 non-screened women by dividing the total number of non-screened cancers in a specific calendar year by the population of non-screened women in that year, before multiplying by 100,000. All rates were reported

as age-adjusted European Standardized Rates, with direct standardization based on the 2013 European Standard Population [36].

Statistical analyses

The incidence rates of advanced-stage cancer in the screened and non-screened populations were compared by incidence rate ratios (IRR) with 95% confidence intervals (95%CI). Univariable and multivariable logistic regression analyses were used to estimate differences in advanced stage in cancers diagnosed in women in the screened and non-screened populations, controlling for age category, year of diagnosis and socioeconomic status (SES). SES was determined based on education, household income and labour market status (based on postal code). Odds ratios (ORs) and 95%CI were reported. The age category 60–69 years was defined as the reference group to handle the effect of prevalence screening. Breast cancer incidence rates were calculated separately for early and advanced cancer in both classifications (i.e., TNM and T-stage). Sensitivity analyses were performed by 1) excluding women attending the prevalence screening, 2) using a cut-off point of ≥ 20 mm for advanced T-stage and 3) including women with previous breast cancer in the 5-year period before diagnosis. Statistical significance was set at a p-value of < 0.05 , and all tests were two-sided. Analyses were performed using the STATA Software Package, Version 14.1 for Windows (Stata Corporation LP, College Station, TX).

RESULTS

The final study cohort included 72,612 women with breast cancer, after excluding women diagnosed with breast cancer in the 5 years before the current diagnosis ($N = 1,757$) and women with lobular carcinomas *in situ* ($N = 478$). The screen-related group included 44,246 cancers (61%), of which 32,158 (73%) were considered screen-detected (Table 1).

Advanced TNM stage (stages III and IV)

Based on TNM staging, breast cancer was considered advanced in 9.5% and 23% of the screen-related and non-screened cancers, respectively ($p < 0.001$) (Table 1, Supplementary Table 1). Cancers diagnosed in the screened population were more often TNM stage I, IA, or IB, whereas cancers diagnosed in the non-screened population were more often stage IIA or higher. Due to an increase in the detection of early stage TNM cancers, the overall incidence of breast cancer increased nonsignificantly from 369 to 408 per 100,000 women between 2006 and 2011 (IRR: 1.11; 95%CI: 0.95–1.27; Figure 1,

Table 1. Breast cancer characteristics within the screened and non-screened populations

	Screened group		Non-screened group		Total	p-value*
	N	%	N	%	N	
Age						<0.001
mean (IQR)	60.9 (55–67)		71.2 (60–82)			<0.001
49–59	19,531	44.1	7,036	24.8	26,567	
60–69	17,599	39.8	5,048	17.8	22,647	
70–74	6,675	15.1	2,152	7.6	8,827	
75–79	441	1.0	4,299	15.2	4,740	
≥80	0	0.0	9,831	34.7	9,831	
Year						<0.001
2006	6,549	14.8	4,448	15.7	10,997	
2007	7,015	15.9	4,567	16.1	11,582	
2008	7,151	16.2	4,827	17.0	11,978	
2009	7,247	16.4	4,852	17.1	12,099	
2010	7,909	17.9	4,732	16.7	12,641	
2011	8,375	18.9	4,940	17.4	13,315	
Socioeconomic status						<0.001
High	12,073	27.3	7,299	25.7	19,372	
Intermediate	19,039	43.0	11,634	41.0	30,673	
Low	13,134	29.7	9,433	33.3	22,567	
Relation						
Screen-detected	32,158	72.7	0	0.0	32,158	
Interval	12,088	27.3	0	0.0	12,088	
Non-screened	0	0.0	28,366	100.0	28,366	
Screening examination round						
Initial	5,744	13.0	0		5,744	
Subsequent	38,502	87.0	0		38,502	
Not applicable	0		28,366	100.0	28,366	
TNM stage						<0.001
Early (stage 0–I–II)	39,862	90.1	21,514	75.8	61,376	
Advanced (stage III–IV)	4,208	9.5	6,580	23.2	10,788	
Unknown	176	0.4	272	1.0	448	
T-stage						<0.001
Early (<15mm)	23,612	53.4	7,759	27.4	31,371	
Advanced (≥15mm)	19,062	43.1	14,899	52.5	33,961	
Unknown	1,572	3.6	5,708	20.1	7,280	
Total	44,246		28,366		72,612	

Additional characteristics are provided in Supplementary Table 1. The screened population included women aged 49–76 and the non-screened population included women aged 49 years and older.

* Chi-squared analysis. Abbreviations: IQR, interquartile range.

Supplementary Table 2). In the screened population, the age-adjusted overall incidence for 2006–2011 was 389/100,000, and the incidence of advanced cancer was 38/100,000 women based on TNM staging (Figure 2, Supplementary Table 3). In eligible non-screened women (aged 49–74), the overall incidence was similar to that in the screened population (403/100,000; $p = 0.619$; Table 2). By TNM staging, the incidence of advanced cancer in non-screened women aged 49–74 (94/100,000) was more than double that in screened women ($p < 0.001$). For non-screened women just over the age limit for the screening programme (aged 75–79), the overall incidence of breast cancer was 287/100,000, consistent with the expected compensatory drop after screening. Beyond age 80 years, the incidence increased again to 390/100,000.

Figure 1. Age-adjusted incidence rates for early and advanced breast cancer per 100,000 women per year of diagnosis. The incidence rates are reported as European Standardized Rates for advanced TNM stage (stages III–IV; left panel) and advanced T-stage (invasive tumor size ≥ 15 mm; right panel), using data for the total female population of the Netherlands aged 49 years and older.

In the multivariable analysis, non-screened cancers were almost three times more likely than screen-related cancers to be of an advanced TNM-stage, with an OR of 2.86 (95%CI: 2.72–3.00; Supplementary Table 4). By TNM-stage, advanced cancer was diagnosed more often in women aged 49–59 years compared with women aged 60–69 years (OR: 1.07, 95%CI: 1.02–1.13), but less often in women aged 70–74 years (OR: 0.92, 95%CI: 0.85–0.99). Women aged 75–79 and 2:80 years were not different from the reference category.

Also, the chance of being diagnosed with advanced TNM-stage cancer was lower with a more recent year of diagnosis (OR: 0.98, 95%CI: 0.97–0.99), but was higher with an intermediate SES (OR: 1.05, 95%CI: 1.00–1.11) and a low SES (OR: 1.05, 95%CI: 1.02–1.14). The sensitivity analysis, which excluded women attending the prevalence screening, showed similar results (Supplementary Tables 5 and 6).

Table 2. Incidence rates per 100,000 screened and non-screened women

	Incidence rate per 100 000 women		IRR (95%CI)	p-value
	Screened (age 49–76 years)	Non-screened (age 49–74 years)		
Overall incidence	389	403	1.04 (0.90–1.19)	0.619
Advanced TNM stage	38	94	2.47 (1.68–3.71)	<0.001
Advanced T-stage	169	210	1.24 (1.01–1.53)	0.035

The sample was taken from among those eligible for screening over the study period. Advanced TNM stage refers to stage III–IV cancer; Advanced T-stage refers to invasive disease ≥ 15 mm. Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

Figure 2. Age-adjusted incidence rates for early and advanced breast cancer based on TNM staging. The incidence rates are reported as European Standardized Rates, and data are shown per year of diagnosis in relation to screening and age. The screened population included women 49–76 years to allow for a 2-year follow-up period after the last screening examination at age 74 years.

Advanced T-stage (invasive tumours ≥ 15 mm)

Among the 72,612 cases, we excluded 7,280 breast cancers with an unknown T-stage (10%), leaving 65,332 cases for the T-stage analysis. Advanced T-stage was diagnosed in 43% of the screened population, compared with 53% in the non-screened population ($p < 0.001$; Table 1). In screened women, advanced T-stage cancer had an age-adjusted incidence of 169/100,000 (Figure 3, Supplementary Table 7), which was significantly lower than the incidence of 210/100,000 in non-screened women ($p = 0.035$, Table 2). Also, non-screened women just older than the screening programme's age limit (i.e., aged 75–79 years) had a lower overall incidence, but included more than half of all advanced breast cancers (165/100,000 of 287/100,000).

Figure 3. Age-adjusted incidence rates for early and advanced breast cancer based on T-stage alone. The incidence rates are reported as European Standardized Rates, and data are shown per year of diagnosis in relation to screening and age. The screened population included women 49–76 years to allow for a 2-year follow-up period after the last screening examination at age 74 years.

Multivariable analysis demonstrated that advanced T-stage cancers were more likely to be diagnosed in the non-screened group than in the screen-related group (OR: 1.85, 95%CI: 1.78–1.93; Supplementary Table 8). Compared with women aged 60–69 years, those aged 49–59 years were more likely to be diagnosed with advanced T-stage cancer (OR: 1.11, 95%CI: 1.07–1.15), as were women aged 75–79 years (OR: 1.84, CI: 1.70–1.99) and 2:80 years (OR: 1.93, 95%CI: 1.83–2.07). Women aged 70–74 years had results that were comparable to the reference category. Also, the chance of being diagnosed with advanced T-stage cancer was lower with a more recent year of diagnosis (OR: 0.93, 95%CI: 0.92–0.94), but was higher with an intermediate SES (OR: 1.10, 95%CI: 1.06–1.14) and

a low SES (OR: 1.08, 95%CI: 1.03–1.12). The sensitivity analysis, which excluded data for women attending the prevalence screening, showed similar results (Supplementary Tables 9 and 10).

DISCUSSION

Based on TNM-stage, the incidence of advanced cancer in women who did not attend breast cancer screening was more than double that in women who did attend (94 vs 38 per 100,000; OR: 2.86, 95%CI: 2.72–3.00). Although less prominent, this pattern was still present when using the T-stage classification (OR: 1.85, 95%CI: 1.78–1.93). Moreover, the incidence of advanced stage breast cancer was stable over calendar time. This was expected given that we studied the incidence in an established screening programme that was in a steady-state phase. These findings are consistent with the screening programme's goal to decrease breast cancer morbidity and mortality by detecting the disease earlier.

In this study, the non-screened cancers included cancers diagnosed in women who were never screened or who attended screening irregularly in the 24 months before diagnosis. This might have caused a lower rate of advanced cancers in the screened population, because these might have been diagnosed in women who attended irregularly and were screened >24 months before (i.e., bias overestimating the effect of screening). However, it is equally possible that early stage cancers were diagnosed shortly after 24 months, which would have underestimated the effect of screening with the rate of early stage cancer increasing in the non-screened population. Unfortunately, the extent of each bias is unknown in this study.

When studying the effect of screening attendance on cancer stage, it is essential to know whether cancers are diagnosed in screened or non-screened women. This observational study is among the first to have used actual screening attendance to compare the incidence of advanced breast cancer based on actual screening status. Our results corroborate the results of most randomized trials, which have shown that screening results in a decrease in the rate of advanced stage cancer [1-5]. Observational studies have also looked for possible changes in the incidence of advanced stage cancer after introducing a screening programme; although early stage disease tends to have increased in these studies, advanced stage disease has variously been shown to decrease significantly [20-22,37], slightly [12,18], or not at all [23,24,38]. However, none of these studies has been able to link tumour stage to actual attendance at the individual patient

level, and have instead relied on approximations. This lack of information on actual attendance means that tumours could have been detected in eligible nonattenders outside the screening programme.

In an observational study, Puliti *et al.* tried to allocate tumours by screening attendance (i.e., as screened and non-screened women) based on attendance at the first two screening rounds. Consistent with our results and those of their previous study [20], they described a higher incidence of advanced stage cancers in non-screened women [24]. Our review of the literature only revealed one study that used information about individual screening attendance, and this showed a lower incidence of advanced-stage disease among screened women [26]. It is difficult to compare our results with those of previous studies because we allocated tumours based on the actual attendance of each woman, which is a unique strength of our study.

Moreover, none of these studies corrected for a possible annual increase in the background incidence. Several reports have shown that the background incidence of breast cancer increased for several decades before the introduction of screening, with evidence showing that it was expected to increase further [27,39]. This increase might have resulted from an aging population, increased exposure to risk factors, or both [27]. Earlier studies, which showed that screening only reduced the rate of advanced stage disease slightly, were premised on the potentially erroneous basis that there would be no increase in background incidence [13,18,22]. Given the preceding epidemiological trends, and assuming an increase in the underlying incidence of breast cancer, a stable incidence of advanced cancer could be interpreted as a relative reduction. We contend that failing to take this into consideration could underestimate the effect of screening. In the present study, we reported data for a period in which the screening programme was well established, reflecting a steady-state situation, so we did not expect to observe the changes in incidence that would normally be expected to accompany the implementation of a screening programme. Nevertheless, we did find a slight but nonsignificant increase in the incidence of early stage cancer, possibly due to an increase in the background incidence.

It is likely that screening resulted in overdiagnosis by detecting cases of breast cancer (ductal carcinoma in situ or invasive carcinoma) that may not have presented clinically during a woman's lifetime [27]. The likely extent of overdiagnosis is unclear, but previous studies have given estimates that range from 0% to 52% [12,40-42]. The increase in early stage breast cancer might also be caused by the higher detection ability of digital

mammography during the latter study period. If present, one would expect overdiagnosis to cause a higher overall incidence in screened women compared with non-screened women, yet rates were similar throughout the study period (389 and 403 per 100,000, respectively; $p = 0.619$).

Among those aged 75–79 years, the incidence was low compared with younger age groups. This can be explained by the so-called compensatory drop: for example, due to the lead-time, an initial increase in incidence among screened women is followed by a decrease among older women who are no longer offered screening [43]. Compared with the reference category, the youngest age category (i.e., 49–59 years) had a higher incidence of advanced-stage disease in the multivariable analysis, possibly because of cancers diagnosed in the prevalence screening. However, similar results were shown in a sensitivity analysis that excluded women who underwent an initial screening examination. Despite the higher incidence in the youngest age category, the incidence of advanced breast cancer remained stable over time.

The steady-state of the screening programme meant that not only the number but also the age distribution of women invited and screened for the first time was relatively stable. The incidence of advanced cancer was also stable. An earlier study showed a significant decrease in advanced breast cancer in the former target age group (i.e., 50–69 years) after the Dutch screening programme was introduced, with a concomitant increase in these tumours among women in younger and older age categories [22]. At that time, however, it was not possible to determine the participation status at an individual level. The steady state of the screening programme and lack of major changes to screening policy after 2001 meant that we did not expect a further decrease in the incidence of advanced breast cancer during our study.

A major strength of this study is that we classified breast cancers as screen-related (screen-detected or interval) and non-screened (never or irregular attenders). We also calculated the incidence rates for early and advanced breast cancer based on staging by both the TNM classification and tumour size alone. The finding that rates of advanced cancer were lower by TNM-stage (including information on lymph node and distant metastasis) compared with T-stage alone is important because the TNM-stage determines clinical treatment, with less advanced TNM-stages associated with less treatment burden. However, knowing that the relationship was still valid for advanced cancers based on tumour size alone is relevant because screening relies on the detection of lesions that are visible on mammography. Our cut-off point of 15 mm for advanced T-stage disease

was based on previous research [34,44], and produced results that were similar to those obtained with a cut-off point of 20 mm (Supplementary Tables 11 and 12). To ensure that we used a clean definition for the relation to screening, without interference from hospital check-ups, we included all first cancers and any second cancers diagnosed at least 5 years after a first breast cancer. This will have led to a slightly lower overall incidence of breast cancer compared with the actual incidence which includes second breast cancers as well. However, sensitivity analyses produced similar results when including all breast cancers (Supplementary Tables 13 and 14).

A limitation of this study is that we had no information about women with a higher than average risk for breast cancer (e.g., those with a *BRCA1/2* mutation or a high familial risk), so we cannot exclude the possibility that these women did not attend screening. However, to reduce the potential influence of this group, women younger than 49 years were excluded. A systematic review has also shown that there is no difference in the proportions of advanced stage cancers between carriers and noncarriers of the *BRCA1/2* mutation [45]. Another issue is that participation in the screening programme was voluntary, which meant that several factors may have influenced attendance; in particular, it is known that women with a low SES have lower attendance rates [46]. Given that women with a low SES were more likely to be diagnosed with advanced cancer in this study, we corrected for SES in the multivariable analysis. Furthermore, another study has shown that the overall influence of bias due to self-selection was minor on the effectiveness of the Netherlands screening programme [47].

The exact tumour size was unknown in 10% of cases, with the highest unknown proportion in women aged ≥ 80 years. From 2010 onwards, this proportion decreased rapidly, with a shift toward early T-stage disease, probably reflecting the fact that older women now receive more specific diagnostic work-ups. There was also no information about breast density, which is important because a dense breast increases the risk of breast cancer and reduces mammographic detectability [48,49]. However, the inclusion of mostly postmenopausal women meant that breast density was probably not a major confounder for the differences in stage [50]. Finally, it should be noted that we estimated the non-screened population based on the screened and overall populations, which may have led to a small margin of error.

In conclusion, data based on actual screening attendance showed that the incidence of advanced breast cancer was significantly higher in non-screened women compared with screened women. Our results support the expectation that screening would cause a stage

shift to the detection of breast cancer at an earlier stage, making it possible to reduce morbidity and mortality associated with breast cancer. Despite critical evaluations of breast cancer screening programmes in other studies, our data show that breast cancer screening is a valuable tool that can reduce the disease burden in women.

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CONFLICT OF INTEREST

G.J. den Heeten is the founder of a spin-off company of the Academic Medical Centre Amsterdam (Sigmascreening, a medical device company) and has worked at any time during the last 2 years for Sectra Medical Systems (Sweden), and is a member of the medical advisory board of Volpara Solutions (software; New Zealand). All other authors declare that they have no conflicts of interest.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Breast cancer characteristics for the screened and non-screened populations

		Tumors within screened population		Tumors within non-screened population		Total N	p-value*
		N	%	N	%		
TNM-stage	0	6,167	13.9	1,770	6.2	7,937	<0.001
	I	13,176	29.8	5,340	18.8	18,516	
	IA	7,548	17.1	2,755	9.7	10,303	
	IB	613	1.4	202	0.7	815	
	IIA	9,017	20.4	7,815	27.6	16,832	
	IIB	3,341	7.6	3,632	12.8	6,973	
	III	3,485	7.9	4,248	15.0	7,733	
	IV	723	1.6	2,332	8.2	3,055	
	Unknown	176	0.4	272	1.0	448	
pT	Tis	6,070	13.7	1,733	6.1	7,803	<0.001
	T0	315	0.7	211	0.7	526	
	T1mic-T1b	9,911	22.4	3,874	13.7	13,785	
	T1c	17,153	38.8	8,171	28.8	25,324	
	T2	9,321	21.1	10,855	38.3	20,176	
	T3-T4	913	2.1	2,893	10.2	3,806	
	Unknown	563	1.3	629	2.2	1,192	
pN (only invasive)	N0	25,729	67.4	15,182	57.0	40,911	<0.001
	N1	9,230	24.2	7,667	28.8	16,897	
	N2	1,764	4.6	1,533	5.8	3,297	
	N3	1,213	3.2	1,331	5.0	2,544	
	Unknown	143	0.4	883	3.3	1,026	
Total		44,246		28,366		72,612	

* Chi-squared analyses. Data shown for screened (aged 49–76 years, initial and subsequent examinations) and non-screened (aged 49 years and older) populations.

Supplementary Table 2. Number of early and advanced stage breast cancers in the total population

	2006			2007			2008			2009			2010			2011			Total	
	N	N/100,000	A	N	N/100,000	A	N	N/100,000	A	N	N/100,000	A	N	N/100,000	A	N	N/100,000	A	N	N
	C	A	C	C	A	C	C	A	C	C	A	C	C	A	C	C	A	C	A	A
TNM-Stage																				
Early (St 0-I-II)	9,094	303	306	9,779	321	324	10,163	328	330	10,208	324	326	10,749	335	336	11,383	348	349	61,376	61,376
Advanced (St III-IV)	1,822	61	60	1,713	56	56	1,722	56	55	1,803	57	57	1,837	57	57	1,891	58	58	10,788	10,788
Unknown	81	3	3	90	3	3	93	3	3	88	3	3	55	2	2	41	1	1	448	448
T-stage																				
Early (<15mm)	4,260	142	144	4,650	153	155	4,906	158	160	5,075	161	163	5,789	180	181	6,691	205	205	31,371	31,371
Advanced (≥15mm)	5,450	182	182	5,605	184	184	5,731	185	185	5,646	179	179	5,717	178	178	5,812	178	178	33,961	33,961
Unknown	1,287	43	43	1,327	44	43	1,341	43	43	1,378	44	43	1,135	35	35	812	25	25	7,280	7,280
Total	10,997	367	369	11,582	380	383	11,978	386	388	12,099	384	385	12,641	394	394	13,315	407	408	72,612	72,612

Data are shown for the Dutch female population aged 49 years and older. A = age-adjusted rate; C, crude rate; N, number

Supplementary Table 3. Incidence rates for early and advanced TNM-stage breast cancer (Stages III and IV)

	2006	2007	2008	2009	2010	2011
Screen-related age 49–76 years						
Early stage	319	340	340	345	373	381
Advanced stage	38	37	38	36	38	39
Unknown	2	2	2	2	1	1
Total	359	379	380	383	412	421
Non-screened 49–74 years						
Early stage	307	331	356	337	299	317
Advanced stage	114	101	95	97	93	100
Unknown	3	4	6	4	2	2
Total	424	435	456	438	393	418
Non-screened age 75–79 years						
Early stage	217	216	219	212	207	229
Advanced stage	59	60	72	63	68	62
Unknown	2	2	2	2	2	0
Total	278	278	293	278	277	291
Non-screened age 80+ years						
Early stage	292	298	310	280	290	304
Advanced stage	98	88	87	95	89	90
Unknown	8	7	5	4	7	4
Total	398	393	401	379	386	399

Incidence rates shown as the European Standardized Rates per 100,000 women

Supplementary Table 4. Logistic regression analysis for advanced TNM-stage breast cancer (Stages III and IV)

	Univariable				Multivariable			
	OR	95%CI		p-value	OR	95%CI		p-value
Relation to screening								
Screen-related	Ref.				Ref.			
Non-screened	2.90	2.78	3.02	<0.001	2.86	2.72	3.00	<0.001
Age, years								
49–59	1.13	1.07	1.19	<0.001	1.07	1.02	1.13	0.010
60–69	Ref.				Ref.			
70–74	0.95	0.88	1.02	0.171	0.92	0.85	0.99	0.031
75–79	2.03	1.88	2.20	<0.001	1.04	0.96	1.13	0.362
80+	2.19	2.06	2.33	<0.001	1.04	0.97	1.12	0.252
Year (per 1 year)	0.97	0.96	0.98	<0.001	0.98	0.97	0.99	0.001

Supplementary Table 4. (continued)

	Univariable				Multivariable			
	OR	95%CI		p-value	OR	95%CI		p-value
Socioeconomic status								
High	Ref.				Ref.			
Intermediate	1.06	1.00	1.11	0.033	1.05	1.00	1.11	0.048
Low	1.12	1.06	1.18	<0.001	1.08	1.02	1.14	0.006

Abbreviations: 95%CI = 95% Confidence Interval

Supplementary Table 5. Incidence rates for women for early and advanced TNM-stage breast cancer (Stages III and IV), excluding tumors diagnosed after prevalence round

	2006	2007	2008	2009	2010	2011
Screen-related age 49–76 years (excluding women screened in the prevalence round)						
Early stage	309	326	328	334	360	367
Advanced stage	36	35	35	34	36	37
Unknown	2	2	2	2	1	1
Total	346	364	365	370	396	405

Incidence rates shown as the European Standardized Rates per 100,000 women

Supplementary Table 6. Logistic regression analysis for advanced TNM-stage breast cancer (Stages III and IV), excluding tumors diagnosed after prevalence round

	Univariable				Multivariable			
	OR	95%CI		P-value	OR	95%CI		P-value
Relation to screening								
Screen-related	Ref.				Ref.			
Non-screened	2.98	2.85	3.11	<0.001	2.92	2.77	3.08	<0.001
Age, years								
49–59	1.19	1.13	1.26	<0.001	1.05	0.99	1.11	0.116
60–69	Ref.				Ref.			
70–74	0.95	0.88	1.03	0.199	0.92	0.85	1.00	0.039
75–79	2.03	1.88	2.20	<0.001	1.03	0.94	1.12	0.510
80+	2.19	2.06	2.33	<0.001	1.03	0.96	1.10	0.424
Year (per 1 year)	0.97	0.96	0.99	<0.001	0.98	0.97	0.99	0.002
Socioeconomic status								
High	Ref.				Ref.			
Intermediate	1.04	0.99	1.10	0.123	1.04	0.99	1.10	0.133
Low	1.11	1.05	1.18	<0.001	1.08	1.02	1.14	0.009

Abbreviations: 95%CI = 95% Confidence Interval

Supplementary Table 7. Incidence rates for women with early and advanced T-stage breast cancer (invasiveness $\geq 15\text{mm}$)

	2006	2007	2008	2009	2010	2011
Screen-related age 49–76 years						
Early stage	180	193	196	206	227	232
Advanced stage	164	170	169	164	170	176
Unknown	15	15	16	13	14	13
Total	359	379	380	383	412	421
Non-screened 49–74 years						
Early stage	129	142	160	150	141	173
Advanced stage	229	230	237	226	209	205
Unknown	67	64	60	62	44	40
Total	424	435	456	438	393	418
Non-screened age 75–79 years						
Early stage	55	53	63	58	72	100
Advanced stage	179	177	172	168	173	168
Unknown	44	48	57	52	32	24
Total	278	278	293	278	277	291
Non-screened age 80+						
Early stage	44	41	42	33	84	169
Advanced stage	201	196	204	187	177	168
Unknown	153	156	155	159	125	62
Total	398	393	401	379	386	399

Incidence rates shown as the European Standardized Rates per 100,000 women

Supplementary Table 8. Logistic regression analysis for advanced T-stage breast cancer (invasive $\geq 15\text{mm}$)

	Univariable				Multivariable			
	OR	95%CI		p-value	OR	95%CI		p-value
Relation to screening								
Screen-related	Ref.	.			Ref.			
Non-screened	2.38	2.30	2.46	<0.001	1.85	1.78	1.93	<0.001
Age, years								
49–59	1.15	1.10	1.19	<0.001	1.11	1.07	1.15	<0.001
60–69	Ref.				Ref.			
70–74	1.01	0.96	1.06	0.783	0.99	0.94	1.04	0.612
75–79	2.82	2.62	3.03	<0.001	1.84	1.70	1.99	<0.001
80+	3.15	2.96	3.34	<0.001	1.93	1.83	2.07	<0.001
Year (per 1 year)	0.93	0.92	0.94	<0.001	0.93	0.92	0.93	<0.001

Supplementary Table 8. (continued)

	Univariable				Multivariable			
	OR	95%CI		p-value	OR	95%CI		p-value
Socioeconomic status								
High	Ref.				Ref.			
Intermediate	1.11	1.07	1.16	<0.001	1.10	1.06	1.14	<0.001
Low	1.10	1.05	1.14	<0.001	1.08	1.03	1.12	0.001

Abbreviations: 95%CI = 95% Confidence Interval

Supplementary Table 9. Incidence rates for women with early and advanced T-stage breast cancer (invasive ≥ 15 mm), excluding tumors diagnosed after the prevalence round

	2006	2007	2008	2009	2010	2011
Screen-related age 49–76 years (excluding women screened in the prevalence round)						
Early stage	175	188	188	198	220	224
Advanced stage	156	160	162	160	163	169
Unknown	14	15	15	12	13	13
Total	346	364	365	370	396	405

Incidence rates shown as the European Standardized Rates per 100,000 women

Supplementary Table 10. Logistic regression analysis for advanced T-stage breast cancer (invasive ≥ 15 mm), excluding tumors diagnosed after the prevalence round

	Univariable				Multivariable			
	OR	95%CI		p-value	OR	95%CI		p-value
Relation to screening								
Screen-related	Ref.				Ref.			
Non-screened	2.42	2.33	2.50	<0.001	1.87	1.80	1.95	<0.001
Age, years								
49–59	1.19	1.14	1.23	<0.001	1.10	1.06	1.15	<0.001
60–69	Ref.				Ref.			
70–74	1.01	0.96	1.06	0.674	0.99	0.94	1.04	0.739
75–79	2.83	2.63	3.04	<0.001	1.84	1.70	1.99	<0.001
80+	3.15	2.96	3.34	<0.001	1.92	1.79	2.06	<0.001
Year (per 1 year)	0.93	0.92	0.94	<0.001	0.93	0.92	0.93	<0.001
Socioeconomic status								
High	Ref.				Ref.			
Intermediate	1.11	1.07	1.16	<0.001	1.10	1.06	1.15	<0.001
Low	1.09	1.04	1.14	<0.001	1.07	1.02	1.12	0.003

Abbreviations: 95%CI = 95% Confidence Interval

Supplementary Table 11. Incidence rates for women with early and advanced T-stage breast cancer (invasive $\geq 20\text{mm}$)

	2006	2007	2008	2009	2010	2011
Screen-related age 49–76 years						
Early stage	254	269	268	276	298	308
Advanced stage	92	97	99	96	101	105
Unknown	13	12	13	12	12	9
Total	359	379	380	383	412	421
Non-screened 49–74 years						
Early stage	197	216	232	223	204	237
Advanced stage	163	160	167	156	149	148
Unknown	64	59	58	59	40	33
Total	424	435	456	438	393	418
Non-screened age 75–79 years						
Early stage	97	103	105	102	119	144
Advanced stage	138	128	133	124	127	126
Unknown	43	46	55	51	31	21
Total	278	278	293	278	277	291
Non-screened age 80+ years						
Early stage	90	84	81	79	121	206
Advanced stage	156	155	167	142	142	133
Unknown	152	154	153	157	124	60
Total	398	393	401	379	386	399

Incidence rates shown as the European Standardized Rates per 100,000 women

Supplementary Table 12. Logistic regression analysis for advanced T-stage breast cancer (invasive $\geq 20\text{mm}$)

	Univariable				Multivariable			
	OR	95%CI		p-value	OR	95%CI		p-value
Relation to screening								
Screen-related	Ref.				Ref.			
Non-screened	2.68	2.59	2.77	<0.001	2.07	1.98	2.15	<0.001
Age, years								
49–59	1.19	1.15	1.24	<0.001	1.15	1.10	1.20	<0.001
60–69	Ref.				Ref.			
70–74	0.99	0.94	1.05	0.823	0.97	0.92	1.03	0.362
75–79	2.03	1.88	2.20	<0.001	1.72	1.60	1.85	<0.001
80+	3.51	3.31	3.71	<0.001	2.01	1.88	2.14	<0.001

Supplementary Table 12. (continued)

	Univariable				Multivariable			
	OR	95%CI		p-value	OR	95%CI		p-value
Year (per 1 year)	0.95	0.94	0.96	<0.001	0.95	0.94	0.96	<0.001
Socioeconomic status								
High	Ref.				Ref.			
Intermediate	1.09	1.05	1.13	<0.001	1.08	1.04	1.13	<0.001
Low	1.10	1.06	1.15	<0.001	1.07	1.03	1.12	0.002

Abbreviations: 95%CI = 95% Confidence Interval

Supplementary Table 13. Incidence rates for women with early and advanced TNM-stage breast cancer (Stages III and IV), including women with a previous breast cancer diagnosis in the last 5-years

	2006	2007	2008	2009	2010	2011
Screen-related age 49–76 years						
Early stage	322	342	342	348	375	383
Advanced stage	38	37	38	36	38	39
Unknown	2	2	2	2	1	1
Total	362	381	383	386	414	423
Non-screened age 49–74 years						
Early stage	316	337	362	347	312	330
Advanced stage	112	97	92	96	93	98
Unknown	3	4	6	5	2	2
Total	432	438	459	448	406	429
Non-screened age 75–79 years						
Early stage	220	222	223	219	216	237
Advanced stage	58	60	72	64	68	62
Unknown	2	3	2	2	2	0
Total	280	285	297	285	286	300
Non-screened age 80+ years						
Early stage	298	303	317	284	296	308
Advanced stage	99	89	88	96	91	91
Unknown	8	7	5	4	7	4
Total	405	399	410	385	393	404

Incidence rates shown as the European Standardized Rates per 100,000 women

Supplementary Table 14. Logistic regression analysis for advanced TNM-stage breast cancer (Stages III and IV), including women with a previous breast cancer diagnosis in the last 5-years

	Univariable				Multivariable			
	OR	95%CI		p-value	OR	95%CI		p-value
Relation to screening								
Screen-related ¹	Ref.				Ref.			
Non-screened	2.82	2.70	2.94	<0.001	2.74	2.60	2.87	<0.001
Age, years								
49–59	1.13	1.07	1.19	<0.001	1.08	1.02	1.14	0.005
60–69	Ref.				Ref.			
70–74	0.95	0.88	1.02	0.145	0.92	0.85	0.99	0.024
75–79	1.99	1.84	2.15	<0.001	1.06	0.97	1.15	0.174
80+	2.19	2.06	2.32	<0.001	1.09	1.01	1.16	0.019
Year (per 1 year)	0.97	0.96	0.99	<0.001	0.98	0.97	0.99	0.001
Socioeconomic status								
High	Ref.				Ref.			
Intermediate	1.05	1.00	1.11	0.043	1.05	1.00	1.11	0.066
Low	1.12	1.06	1.18	<0.001	1.08	1.02	1.14	0.004

¹Screen-related: screen-detected + interval cancers

Abbreviations: 95%CI = 95% Confidence Interval

4

Digital vs screen-film mammography in population-based breast cancer screening: performance indicators and tumour characteristics of screen-detected and interval cancers

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ABSTRACT

Background

Full-field digital mammography (FFDM) has replaced screen-film mammography (SFM) in most breast cancer screening programmes due to technological advantages such as possibilities to adjust contrast, better image quality and transfer capabilities. This study describes the performance indicators during the transition from SFM to FFDM and the characteristics of screen-detected and interval cancers.

Methods

Data of the Netherlands Breast Cancer Screening Programme, region North from 2004 to 2010 were linked to The Netherlands Cancer Registry (N = 902,868). Performance indicators and tumour characteristics of screen-detected and interval cancers were compared between FFDM and SFM.

Results

After initial screens, recall rates were 2.1% (SFM) and 3.0% (FFDM; $p < 0.001$). The positive predictive values (PPV) were 25.6% (SFM) and 19.9% (FFDM; $p = 0.002$). Detection rates were similar, as were all performance indicators after subsequent screens. Similar percentages of low-grade ductal carcinoma in situ (DCIS) were found for SFM and FFDM. Invasive cancers diagnosed after subsequent screens with FFDM were more often of high-grade ($p = 0.024$) and ductal type ($p = 0.030$). The incidence rates of interval cancers were similar for SFM and FFDM after initial (2.69/1000 vs 2.51/1000; $p = 0.787$) and subsequent screens (2.30 vs 2.41; $p = 0.652$), with similar tumour characteristics.

Conclusions

FFDM resulted in similar rates of screen-detected and interval cancers, indicating that FFDM performs as well as SFM in a breast cancer screening programme. No signs of an increase in low-grade DCIS (which might connote possible overdiagnosis) were seen. Nonetheless, after initial screening, which accounts for 12% of all screens, FFDM resulted in higher recall rate and lower PPV that requires attention.

INTRODUCTION

In recent years, screen-film mammography (SFM) has been replaced by full-field digital mammography (FFDM) in most Western breast cancer screening programmes. The main reasons are a better image quality and dose optimisation, and easier and more efficient archiving and image transfer capabilities [1,2].

Studies have shown that FFDM does not result in differences in cancer detection rate [3-5] or higher overall breast cancer detection compared with SFM in the clinical as well as in a population-based setting [6-9]. However, others have shown a higher detection rate only for ductal carcinoma in situ (DCIS) [10,11]. Furthermore, FFDM results in a higher recall rate, in combination with higher detection rates and decreased positive predictive values (PPV) of recall [12,13]. Nevertheless, the opposite effect on recall rate and PPV has also been described [14]. The recall and detection rates for SFM vary between different screening programmes. These differences in 'baseline' measurements might partly explain the different outcomes for the introduction of FFDM when comparing with SFM.

FFDM seems associated with an increase in smaller cancers and DCIS [8,10,13,15]. It remains uncertain to which extent this might be associated with overdiagnosis and a wide range of overdiagnosis estimates exist [16]. Furthermore, some studies comparing FFDM with SFM have analysed tumour characteristics other than DCIS and report no differences in tumour characteristics such as T- or N-stage [4,5,10,13]. However, one study found that FFDM detected more lymph node-negative and hormone receptor positive cancers [17]. Studies about the incidence of interval cancers so far report no differences in interval cancer rates between SFM and FFDM [4,14]. As the recall rate in The Netherlands is lower than in other countries with population-based screening programmes, the transition from SFM to FFDM might lead to different conclusions regarding interval cancer rates. However, data regarding interval cancers in the Dutch situation, with a national screening programme, is still scarce [18].

The objective of this study was to evaluate whether the transition from SFM to FFDM resulted in changes in the recall rate, PPV, the detection rate of DCIS and invasive cancers and tumour characteristics of screen-detected cancers in the Dutch screening programme. Moreover, the rate and tumour characteristics of interval cancers were compared, as were programme sensitivity and specificity.

METHODS

Setting

In The Netherlands, a national population-based screening programme is operational since 1990, inviting women 50–69 years of age for a biennial screening examination [19]. Women 70–75 years of age are included from 1999 onwards. All mammographic examinations are performed by specialised radiographers. Recall for further diagnostic work-up was indicated in case of incomplete examination (BI-RADS 0) or suspicious or malignant findings (BI-RADS 4 or 5) [20,21]. The screening programme started in 1990 using screen-film mammography. In 2003 the first digital mammography unit was introduced and in 2010 all screening examinations were performed using digital mammography. By participating in the screening programme, women consent to the use of their data to evaluate the programme. Information about the use of their data is provided in a flyer accompanying the letter of invitation. If a woman does not want her data being used for this purpose, she can return a signed form to the screening organisation. Only a minor fraction of screened women (0.01%) uses this option [22]. Data on cancer is registered in The Netherlands Cancer Registry (NCR). The NCR is a population-based database, which contains data on patient, tumour and treatment characteristics of all in situ and invasive malignancies diagnosed in The Netherlands. This study was approved by the Committee of Privacy of The Netherlands Comprehensive Cancer Organisation (IKNL), which hosts the NCR.

Women and data

All women (50–75 years) who underwent a screening examination between 2004 and 2010 in the Netherlands Breast Cancer Screening Programme, region North-Netherlands were included. The target population of this area comprised ~300,000 women, of whom about 150,000 were invited each year. The region North-Netherlands followed the national programme. It started in 1991 with SFM and implemented the first digital mammography in 2003. During 2009, the remaining seven screen-film mammography units were replaced by digital mammography units. The screening data included all dates and results of the screening examinations. These screening data were linked to data of the NCR. The main source of notification for the NCR is PALGA, the nationwide Dutch network and registry of histo and cytological pathology. After notification to the NCR, specially trained registration clerks visit the hospitals to collect information on patient and tumour characteristics, stage and treatment from patient files. Coding of the items is based on international coding rules. For the staging of cancers, TNM classification is used [23].

Image acquisition and interpretation

SFM images were acquired with two types of systems (GE 600/800T, GE Healthcare, Buc, France). Digital mammograms were acquired by using Embrace DR (Agfa-Gevaert, Mortsel, Belgium) or Lorad Selenia FFDM systems (Hologic, Danbury, CT, USA). Initial screening examinations performed with SFM or FFDM always included two standard views, craniocaudal and mediolateral oblique. At subsequent screening examinations, mediolateral oblique views were routinely acquired, craniocaudal views were acquired if indicated by criteria based on, among others, breast density and visible abnormality. Radiologists interpreted mammograms made by SFM as well as FFDM. Mammograms were interpreted in batch mode and were independently read by two radiologists. Differences in opinion were resolved by consensus. In subsequent screens with SFM as well as FFDM, prior mammograms were available for comparison. To facilitate soft-copy reading of subsequent screening examinations with FFDM, the most recent screen-film mediolateral oblique and craniocaudal views were digitised by using film scanners and archiver designed for mammography (IMPAX TS5 transmit scanner, Agfa-Gevaert; DigitalNow, Hologic).

Definitions

Women with a 'screen-detected cancer' were defined as women having a positive screening examination at the breast cancer screening programme, which was subsequently followed by a diagnosis of breast cancer within 12 months. The second group comprised women with an 'interval cancer', that is, women who, despite a negative examination at the breast cancer screening, were diagnosed with breast cancer within 24 months. In the analysis, women with screen-detected breast cancer and women with interval cancer were considered separately. Recall rate was defined as the proportion of women with a positive screening examination out of all screened women. Detection rate was defined as the proportion of women diagnosed with breast cancer out of all screened women and PPV was calculated as the percentage of women with screen-detected breast cancer out of all recalled women. All screening examinations from 2004 to 2010 were considered for the calculation of recall rate, detection rate and PPV (N = 902,868). Programme sensitivity was defined as the proportion of screen-detected breast cancers out of all breast cancers (interval cancers plus screen-detected cancers). Programme specificity was defined as the proportion of women without breast cancer with a negative examination (true negatives) out of all women without breast cancer (true negatives plus false positives). Programme sensitivity, programme specificity and the incidence of interval cancers were calculated for women screened from 2004 to 2008. As follow up was complete until 2010, the complete number of breast cancer cases, including

interval cancers can be diagnosed up to 24 months after the last screening examination ($N = 638,663$). For women with bilateral disease, the tumour with the highest stage was selected. Tumour stage was defined according to the greatest dimension of the largest tumour size (T1a: ≤ 0.5 cm, T1b: >0.5 cm and ≤ 1 cm, T1c: >1 cm and ≤ 2 cm, T2+: <2 cm).

Statistical analysis

SFM and FFDM were compared regarding the performance indicators (recall rate, detection rate and PPV), tumour characteristics of screen-detected cancers, incidence rate and tumour characteristics of interval cancers, programme sensitivity and programme specificity. The comparison was stratified by initial and subsequent screening examinations. Pearson Chi2-tests or Fisher exact tests were applied. Missing values in tumour characteristics were excluded in the statistical comparison. Variation in recall and detection rate per year was graphically visualised for SFM and FFDM, stratified by initial and subsequent screening examinations. The statistical significance level was set at a p -value <0.05 . Analyses were performed using the STATA software package, version 13.1 for Windows (Stata Corporation LP, College Station, TX, USA).

RESULTS

In the period 2004–2010 in total 902,868 screening examinations were performed by Netherlands Breast Cancer Screening Programme, region North-Netherlands, of which 255,633 (28%) by FFDM. Twelve percent of the 647,235 examinations by SFM were initial examinations; for FFDM, this was 11% (Table 1).

Table 1. Performance indicators of women (50-75 years) screened, recalled and positive predictive value for SFM and FFDM (2004-2010).

2004-2010	SFM			FFDM			p-value	
	N		%	N		%		
Screened women	647,235			255,633				
Initial screens	76,642		11.8%	27,947		10.9%		
Subsequent screens	570,593		88.2%	227,686		89.1%		
Recalled women	8,174		1.26%	3,436		1.34%		.002
Initial screens	1,584		2.07%	844		3.02%		<0.001
Subsequent screens	6,590		1.15%	2,592		1.14%		.532
Screen-detected	N	Rate^a	PPV	N	Rate^a	PPV	p-value^b	p-value^c
Breast cancers	3,418	5.28	41.8%	1,339	5.24	39.0%	.800	.004
Initial screens	405	5.28	25.6%	168	6.01	19.9%	.159	.002
Subsequent screens	3,013	5.28	45.7%	1,171	5.14	45.2%	.445	.638

Table 1. (continued)

2004-2010		SFM		FFDM		p-value ^b	p-value ^c
Screen-detected	N	Rate ^a	PPV	N	Rate ^a	PPV	
DCIS	489	0.76	6.0%	218	0.85	6.3%	.137
Initial screens	66	0.86	4.2%	33	1.18	3.9%	.137
Subsequent screens	423	0.74	6.4%	185	0.81	7.1%	.298
Invasive cancers	2,929	4.53	35.8%	1,121	4.39	32.6%	.369
Initial screens	339	4.42	21.4%	135	4.83	16.0%	.385
Subsequent screens	2,590	4.54	39.3%	986	4.33	38.0%	.208

Abbreviations: DCIS = ductal carcinoma in situ; FFDM = full field digital mammography; PPV = positive predictive values; SFM = screen-film mammography

^a Detection rates per 1000 women screened;

^b Estimated p-values are based on comparison between Rate;

^c Estimated p-values are based on comparison between positive predictive value (PPV)

Recall rate, detection rate and positive predictive value

The recall rate after initial examination of 2.1% for SFM remained stable during the study period (Table 1). For FFDM the recall rate of 3.0% proved to be significantly higher than for SFM ($p < 0.001$). After the complete introduction of FFDM, the recall rate decreased to 2.8% in 2010 and was still significantly higher than the recall rate of 2.1% for SFM ($p < 0.001$; Figure 1A).

After initial examination, the detection rate for DCIS was 0.86 per 1000 women for SFM compared with 1.18 per 1000 women for FFDM ($p = 0.137$). For invasive cancers, detection rates were 4.42 per 1000 women for SFM and 4.83 per 1000 women for FFDM ($p = 0.338$). During the total period, the overall detection rate for SFM remained fairly constant. For FFDM the detection rate fluctuated markedly, due to small numbers (Figure 1B). The PPV after initial examination was 25.6% for SFM and 19.9% for FFDM ($p = 0.002$).

After subsequent examinations, the overall recall rate for SFM was 1.2% and for FFDM, after an initially high rate, 1.1% ($p = 0.532$; Table 1; Figure 1C.) The overall detection rates were 5.28 per 1000 women for SFM and 5.14 per 1000 women for FFDM ($p = 0.638$; Table 1). No differences were found in detection rates for DCIS (0.74 per 1000 women for SFM vs 0.81 per 1000 women for FFDM; $p = 0.298$), nor for invasive cancers (4.54 per 1000 women for SFM vs 4.33 per 1000 women for FFDM; $p = 0.210$). The detection rate remained stable over the years for SFM as well as FFDM (Figure 1D). Positive predictive values were 45.7% and 45.2% for SFM and FFDM, respectively ($p = 0.638$).

Figure 1. Recall and detection rates.

(A) Percentage of women recalled after initial screens.

(B) Detection rate per 1000 screened women after initial screens.

(C) The percentage of women recalled after subsequent screens.

(D) Detection rate per 1000 screened women after subsequent screens.

Of the women with SFM as initial examination, 92% were aged 50–54 years, compared with 95% of women with FFDM as initial examination. For subsequent examinations, 18 and 17% were aged 50–54 years for SFM and FFDM, respectively; 16% were aged 70–75 years for SFM as well as FFDM.

Tumour characteristics of screen-detected cancers

After initial examinations, no differences were found in tumour characteristics (Table 2), but a non-significant trend towards more T1a cancers was seen (4.7% for SFM and 10.6% after FFDM, $p = 0.138$). In 16.3% of all cancers a DCIS was diagnosed after SFM, compared with 19.6% after FFDM ($p = 0.335$). After subsequent examinations, DCIS was diagnosed in 14.0% of all cancers after SFM, 15.8% after FFDM ($p = 0.139$). After FFDM a significantly larger part of invasive cancers were ductal cancers (SFM: 81.6%, FFDM: 85.1%; $p = 0.030$) and the cancers were more often high-grade (SFM: 9.0%, FFDM: 23.4%; $p = 0.024$).

Table 2. Tumour characteristics of **screen-detected** cancers in women 50-75 years of age for SFM and FFDM (2004-2010)

	<i>Initial screen</i>					<i>Subsequent screen</i>				
	SFM		FFDM		p-value	SFM		FFDM		p-value
	N	%	N	%		N	%	N	%	
DCIS										
Grade										
Low	11	17.5	4	13.8	0.860	47	11.7	15	8.6	0.524
Intermediate	25	39.7	13	44.8		132	32.9	61	34.9	
High	27	42.9	12	41.4		222	55.4	99	56.6	
Unknown	3		4			22		10		
DCIS, total	66		33			423		185		
Invasive cancers										
Tumour size										
T1a	16	4.7	14	10.6	0.138	137	6.1	72	7.4	0.126
T1b	57	16.9	22	16.7		645	28.5	237	24.3	
T1c	171	50.7	63	47.7		1,296	57.3	476	48.9	
T2+	93	27.6	33	25		183	8.1	189	19.4	
Unknown	2		3			29		12		
Morphology										0.030
Ductal	293	86.4	115	85.2	0.089	2,114	81.6	839	85.1	
Lobular	37	10.9	11	8.1		345	13.3	113	11.5	
Other	9	2.7	9	6.7		131	5.1	34	3.4	
Grade										
Low	105	32.3	46	37.7	0.469	813	37	268	28.5	0.024
Intermediate	151	46.5	55	45.1		1,188	54	451	48	
High	69	21.2	21	17.2		498	9	220	23.4	
Unknown	14		13			91		47		
Lymph node status										
Negative	208	62.7	84	62.7	0.994	1,859	73.1	717	73.5	0.794
Positive	124	37.3	50	37.3		684	26.9	258	26.5	
Unknown	7		1			47		11		
Invasive cancers, total	339		135			2,597		986		

Abbreviations: DCIS = ductal carcinoma in situ; FFDM = full field digital mammography; SFM = screen-film mammography

Incidence rate of interval cancers, programme sensitivity and specificity

Overall incidence rates of interval cancers were similar with 2.35 per 1000 women for SFM and 2.42 per 1000 women for FFDM ($p = 0.748$). After initial screens, no difference was found in the incidence of interval cancers with 2.69 per 1000 women for SFM and 2.51 per

1000 women for FFDM ($p = 0.787$, Table 3). The sensitivity after initial examinations was 66.1% for SFM and 69.1% for FFDM ($p = 0.657$), specificity was 98.5% and 96.9% for SFM and FFDM, respectively ($p < 0.001$). After subsequent examinations, the overall incidence rate of all interval cancers was 2.30 per 1000 women for SFM and 2.41 per 1000 women for FFDM ($p = 0.652$), the sensitivity was 69.7% for SFM and 66.7% for FFDM ($p = 0.232$). Specificity was 99.4% SFM and 99.2% for FFDM ($p < 0.001$).

Table 3. Women (50-75 years) screened, recalled and the number of women with screen-detected or interval cancers (2004-2008).

2004-2008	SFM		FFDM		p-value
	N	%	N	%	
Screened women	582,869		55,794		
Initial screens	69,529	11.9%	6,768	12.1%	
Subsequent screens	51,334	88.1%	49,026	87.9%	
Screen-detected	N	Rate^a	N	Rate^a	
Breast cancers	3,089	5.30	274	4.91	0.226
Initial screens	365	5.25	38	5.61	0.692
Subsequent screens	2,724	5.31	236	4.81	0.150
Interval	N	Rate^a	N	Rate^a	
Breast cancers	1,370	2.35	135	2.42	0.748
Initial screens	187	2.69	17	2.51	0.787
Subsequent screens	1,183	2.30	118	2.41	0.652
DCIS	67	0.11	4	0.07	0.525
Initial screens	8	0.12	1	0.15	0.567
Subsequent screens	59	0.11	3	0.06	0.370
Invasive cancers	1,303	2.24	131	2.35	0.592
Initial screens	179	2.57	16	2.36	0.743
Subsequent screens	1,124	2.19	115	2.35	0.481

Abbreviations: DCIS = ductal carcinoma in situ; FFDM = full field digital mammography; SFM = screen-film mammography

^a Rates per 1000 women screened

Tumour characteristics of interval cancers

No differences were found in the tumour characteristics of interval cancers diagnosed after FFDM compared with SFM after initial or after subsequent examinations (Table 4).

Table 4. Tumour characteristics of **interval** cancers in women 50-75 years of age for SFM and FFDM (2004-2008)

	Initial screen					Subsequent screen				
	SFM		FFDM		p-value	SFM		FFDM		p-value
	N	%	N	%		N	%	N	%	
DCIS										
Grade										
Low	1	12.5	0	0		11	22.4	1	33.3	
Intermediate	2	25	1	100		11	22.4	0	0	
High	5	62.5	0	0		27	55.1	2	66.7	
Unknown						10		0		
DCIS, total	8		1			59		3		
Invasive cancers										
Tumour size										
T1a	3	1.7	0	0	0.288	27	2.5	2	1.8	0.457
T1b	13	7.3	2	12.5		80	7.4	13	11.7	
T1c	67	37.9	9	56.3		419	38.7	41	36.9	
T2+	94	53.1	5	31.3		557	51.4	55	49.5	
Unknown	2		0			41		4		
Morphology										
Ductal	143	79.9	11	68.8	0.325	850	75.6	85	73.9	0.868
Lobular	31	17.3	5	31.3		196	17.4	22	19.1	
Other	5	2.8	0	0		78	6.9	8	7	
Grade										
Low	34	20.2	1	7.1	0.384	178	18.1	14	13.6	0.523
Intermediate	67	39.9	5	35.7		417	42.4	46	44.7	
High	67	39.9	8	57.1		389	39.5	43	41.7	
Unknown	11		2			140		12		
Lymph node status										
Negative	94	52.8	9	56.3	0.792	575	52.6	66	58.4	0.240
Positive	84	46.9	7	43.8		518	47.4	47	41.6	
Unknown	1		0			31		2		
Invasive, cancers total	179		16			1,124		115		

Abbreviations: DCIS = ductal carcinoma in situ; FFDM = full field digital mammography; SFM = screen-film mammography

DISCUSSION

After initial screens with FFDM, we found a higher recall rate and a lower PPV. No difference was found in the proportion and malignancy grade of DCIS. Tumour characteristics of invasive cancers and the incidence rate and tumour characteristics of interval cancers were similar. After subsequent screens the proportion of DCIS was similar for SFM and FFDM. After FFDM, a significantly larger part of invasive cancers were ductal cancers and high-grade. No differences were found in the incidence of interval cancers or their tumour characteristics between SFM and FFDM.

In our study a higher recall rate and lower PPV were found after initial screens with FFDM, which accounts for 12% of all screens, but no differences were found after subsequent screens. A systematic review by Vinnicombe et al [3] showed that recall rates varied greatly with some studies showing lower and others showing higher recall rates for FFDM. We did not find a higher detection rate, which is in line with some other studies [3-5,8]. In contrast, other studies reported higher detection rates for FFDM [9,15], including a Dutch study. The latter study also describes some variation in detection rates between regions within The Netherlands. As our study only included data from one region and the study could not interfere with the ongoing screening programme, existing variation between regions and countries before the introduction of FFDM might explain the different results and might have an effect on the generalisability of our results. In the first years using FFDM, recall and detection rates fluctuated. This might be due to a learning curve, which has been described before [24], in combination with the relative low number of FFDM screens performed in comparison with SFM. As SFM was already in use since the start of the programme, recall and detection rates remained stable during this study period as expected. The overall increase in recall rate after FFDM is probably due to a higher resolution and the possibilities to adjust contrast. After FFDM, women are more often recalled due to microcalcifications, which might be the result of this contrast adjustment [17,24]. Unfortunately, we did not have any information if the higher recall rate after initial screens with FFDM lead to an increased number of biopsies performed in patients with a false-positive result.

After initial screens, no differences in tumour characteristics between SFM and FFDM were found, which might indicate that FFDM performs similar for the entire spectrum of breast cancer. However, a non-significant trend towards more T1a cancers was seen after initial screens with FFDM. To further analyse this, the percentages of T1a cancers of all invasive cancers diagnosed after initial FFDM (10.6%) and SFM (4.7%) in this regional

study were compared with the percentage of T1a cancers in initially screened women in the total Dutch population. For the period 1990–2007 (when most women were screened with SFM) this percentage was around 4% [25]. As we found a similar rate for SFM, this indicates that our data can be representative of the Dutch data and the trend towards more T1a cancers might be of interest. In literature a non-significant increase in T1a-cancers was described, but the T1a cancers were not studied separately [17].

After subsequent screens with FFDM, more ductal and high-grade invasive cancers were found, whereas other characteristics were similar. Another Dutch, multicentre study found no differences in grade in invasive cancers after subsequent screens [13]. Our findings also differ from two Norwegian studies reporting no differences in tumour characteristics in the total screened population [14]. These differences are interesting as they may reflect possible underlying differences in screening education or performance.

Overdiagnosis will always remain an issue in screening programmes. It is accepted as an inevitable side effect of the screening programme, but the debate to which extent overdiagnosis is acceptable still continues [26,27]. Overdiagnosis can be defined as a malignancy that, if left undetected and untreated, never would have surfaced in a person's lifetime. An increase in low-grade DCIS might connote possible overdiagnosis. However, in our study we did not find a higher incidence of DCIS nor did we find more low-grade DCIS after FFDM compared with SFM. Another study did report a higher incidence of DCIS, but no differences in the distribution of grade [13]. In contrast to our study, others did report that FFDM resulted in differences in grade. However, these studies reported opposite effects either towards more high-grade DCIS [10] or towards more low-grade DCIS [17]. Furthermore, any effect on breast cancer mortality is still unknown.

We found no decrease in the incidence rate of interval cancers after FFDM. The incidence of interval cancers for SFM and FFDM was similar, which is in concordance with a randomised trial comparing SFM and FFDM [12]. The rates of interval cancers in the Norwegian population-based screening programme were also similar to our study [14]. In addition, tumour characteristics did not differ between interval cancers diagnosed after SFM and FFDM, which is in concordance with other studies [14,18].

The programme sensitivity of SFM and FFDM found in the present study were both lower than in the study by Nederend et al [18], performed in another Dutch region. A Norwegian study found a slightly higher sensitivity for FFDM and lower for SFM than in our study [12]. Both studies did not discriminate between initial and subsequent screens, which

might explain the differences. Compared with the programme sensitivity of the complete Dutch programme of 70% after initial screens and 71% after subsequent screens [22], our study found a slightly lower sensitivity. The programme sensitivity has been stable at this level since at least 2004 and the Health Council of The Netherlands advised to continue the organised screening programme [28].

Our study has several strengths and limitations. In the current study, initial and subsequent screening examinations were analysed separately, increasing the insight of the effects of FFDM. Furthermore, this is a large population-based study using standardised collected data from the NCR, including tumour characteristics on tumour size, morphology, grade and lymph node status. Data on oestrogen or progesterone receptor or HER2neu status were not available for this cohort. A limitation in comparing results with other studies might lie in the fact that the Dutch screening programme invites women 50–75 years of age, which differs from other screening programmes mostly offering screening to women 50–69 years old. This might limit the generalisability of our results. Second, in The Netherlands, screening examinations are independently read by two radiologists and – particularly in the Northern region – recall rates are relatively low. Comparing FFDM with SFM might therefore lead to different conclusions in comparison with other studies. Furthermore, a Dutch study found variation in recall rate, with less variation in detection rate, between regions in The Netherlands [15]. Finally, during this study period a policy change towards making standard craniocaudal views at subsequent screening examinations started in The Netherlands. Also, during this period some radiologists synchronous read mammograms made using FFDM and SFM. Both effects could have influenced recall or detection rate for both SFM and FFDM. However, in our data we did not find an increased recall or detection rate for SFM after subsequent screening examination, indicating that these effects were negligible.

These data show that FFDM can be safely used for screening purposes. The easier image transfer capabilities of FFDM may prevent repeating the mammography during diagnostic work-up in the hospital. Further research on possible effects of the higher recall rate on the number of biopsies performed in patients with a false positive result might add to the comparison of FFDM and SFM, as can future research of the proportion of T1a tumours, hormone receptor and HER2 status.

In conclusion, FFDM resulted in similar rates of screen-detected and interval cancers compared with SFM. This indicates that FFDM performs as well as SFM in a breast cancer screening programme, with more ductal and high-grade invasive cancers found

after subsequent screens. No signs of an increase in low-grade DCIS (which might connote possible overdiagnosis) were seen. Nonetheless, after initial screening, which accounts for 12% of all screens, FFDM resulted in higher recall rate and lower PPV that requires attention.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Part **II**

**Outcome and follow-up up to
10 years after diagnosis**

5

Do screen-detected breast cancers have positive margins less often than clinically detected breast cancers?

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ABSTRACT

Positive tumour margins after breast-conserving surgery (BCS) have been selected as one of the major quality criteria for the surgical treatment of localized primary breast cancer. The national guideline states that the rate of positive margins should not exceed 30% in ductal carcinoma in situ and 20% in invasive cancers. We aimed to determine whether BCS in women with screen-detected breast cancer (SDBC) will have positive margins less often compared with women with clinically detected breast cancer (CDBC). Furthermore, the choice of subsequent therapy is studied when margins were positive after initial BCS. Women 50–75 years of age who underwent BCS for invasive breast cancer between July 2008 and December 2009 were selected from the Netherlands Cancer Registry. Data were merged with the Netherlands Breast Cancer Screening Programme, regions North and East, to identify women with SDBC. The relation to screening history, clinical and pathological factors was evaluated for correlation with margin status using multilevel analysis. Of 1,537 women with an invasive breast cancer, 873 (57%) were diagnosed through the screening programme. SDBC were significantly smaller (87 vs. 69% T1 tumours, i.e. ≤ 2 cm), more often well differentiated (33 vs. 26%), preoperatively confirmed (98 vs. 96%), diagnosed in a non-teaching hospital (60 vs. 66%) and more often had negative lymph nodes (LNs) (80 vs. 68%). In 170 out of 1,537 women, the resection margins were positive. Multivariable analysis showed that hospital, tumour size, multifocality, positive LNs and absent preoperative confirmation were predictors of positive margins. No difference was found between women with SDBC and CDBC. Of women with positive margins, 90% underwent additional surgery. Women diagnosed with SDBC do not have a lower risk of having positive margins after BCS than women with CDBC. Although positive margins may occur in 11% of women with invasive tumours, well below the percentage recommended by the national guideline, the presence of encouraging factors by SDBC such as a smaller tumour size, unifocality, negative LNs and the presence of preoperative confirmation should not lead to performing a more sparing excision than is considered usual for comparable CDBC.

INTRODUCTION

Breast cancer is the most common type of cancer in women, with 13,257 new cases in the Netherlands in 2010, and breast-conserving surgery (BCS), followed by radiotherapy, has been accepted as the standard treatment for patients with early-stage breast cancer [1-3]. In the Netherlands, a population-based screening programme has been implemented since 1991, inviting women 50–75 years of age for biennial mammography. Patients diagnosed with breast cancer through this programme are more often diagnosed with early-stage breast cancer, and are therefore more often suited for BCS [4,5]. Although successful BCS leads to better cosmetic results, less psychological burden and a better quality of life compared with mastectomy [6,7], the disadvantage is the risk of local recurrence (LR), which influences the prognosis. To minimize the risk of an LR, BCS requires clear histological margins. However, clear margins are not always obtained during initial surgery and 20–30% of women undergo further surgery after initial BCS [8-10]. Information on the factors associated with positive margins is likely to allow clinicians to identify subgroups of women at risk for an irradical resection. In patients with factors indicating a higher risk for positive margins, more extensive surgery can be performed at the initial operation, thus reducing the risk of positive margins and preventing further surgery.

Studies have identified factors associated with positive margins, including tumour characteristics (tumour size, multifocality and positive lymph nodes [LNs]), surgical factors (presence of confirmed preoperative diagnosis) as well as differences between hospitals or pathology laboratories [10-15]. However, little is known about the relation between the method of detection and margin status. One could hypothesize that screen-detected breast cancers (SDBC) are smaller and better differentiated than clinically detected breast cancers (CDBC); therefore, they should be less prone to positive margins. Only a few studies comment on the relation of tumours diagnosed through the screening programme and clear surgical margins, compared with tumours diagnosed through other ways. One of these studies found less positive margins after referral through the screening programme and another found no relation [9,16].

The aim of this population-based study is to determine whether women with SDBC have positive margins less often after initial BCS, compared with women diagnosed with CDBC, and to identify other clinical and pathological factors associated with margin status after BCS. Furthermore, the choice of subsequent therapy is studied when margins were positive after initial BCS.

PATIENTS AND METHODS

Patients

Patients were selected from the population-based Netherlands Cancer Registry (NCR). The main source of notification for the NCR is PALGA, the nationwide Dutch network and registry of histological and cytological pathology, through which all newly diagnosed malignancies are reported to the cancer registry. Case ascertainment is completed using the national hospital discharge database, which receives diagnoses of admitted patients from all hospitals. After notification to the NCR, specially trained registry clerks of the Netherlands Comprehensive Cancer Organisation visit the hospitals to collect information on patient and tumour characteristics from patient files. Coding of the items is based on international coding rules (IACR); the TNM classification is used for the staging of tumours [17]. For women for whom the date of pathological confirmation of the tumour and surgery was the same, diagnosis was confirmed during surgery. Therefore, a preoperative diagnosis was defined as 'no' when the date of incidence was the same as the date of surgery.

Women 50–75 years of age diagnosed in the North Eastern region of the Netherlands who underwent initial BCS for invasive breast cancer (IBC) between 1 July 2008 and 31 December 2009 were selected from the NCR (N = 1,565). Women who received neoadjuvant treatment (N = 9) and women whose margin status of initial BCS was unknown (N = 19) were excluded. A total of 1,537 women were included in the analysis.

Relation to screening

Data were merged with the data of the Netherlands Breast Cancer Screening Programme, region North, and the Netherlands Breast Cancer Screening Programme, region East, together covering the North Eastern region of the Netherlands with 3.3 million inhabitants (20% of all Dutch inhabitants). Two subgroups were defined: women with breast cancer following an abnormal mammogram by screening were defined as SDBC and all other women were defined as CDBC.

Margin status

Margin status was defined according to the Dutch guideline for the pathology laboratories [2]. According to this guideline, surgical margins of the excised lump can be divided into three subgroups: clear margins (tumour not touching the inked surface of the specimen), focally positive margins (tumour in a limited area of the inked surface; i.e. two low-power fields, magnification x100, equalling 4–5mm) and more than focally positive margins

(Figure. 1). Margin status determines which additional treatment is provided to the patient. Patients with invasive tumours undergo re-excision in case of more than focally positive margins. Therefore, clear and focally positive margins were defined as clear margins. More than focally positive margins were defined as positive margins (invasive and/or ductal carcinoma in situ [DCIS] component). Margin status was unknown in 1.2% of cases and ranged from 1 to 4% in 11 hospitals (0% in 12 hospitals). Cases with unknown margin status were excluded from analysis (N = 19).

Figure 1. Margin status (invasive or ductal carcinoma in situ component) (Source: oncoline.nl)

Hospitals and pathology laboratories

The type of hospital was based on the hospital where the surgery was performed. A teaching hospital was defined as a hospital that provides medical training to surgical residents. A teaching pathology laboratory was a laboratory that provides medical training to pathology residents. Surgery was performed in 23 hospitals and evaluation of surgical margins was carried out in nine pathology laboratories. Most pathology laboratories will serve more than one hospital.

Statistical analysis

Chi2-Analysis was used to compare categorical variables. Multilevel logistic regression was performed to study differences in margin status and the relation to screening. Multilevel analysis takes into account a hierarchical structure. Our data had a two-level data structure: tumours were clustered within hospitals of surgery. The magnitude of the variance of a level in combination with its standard error can be used as a rough test for judging significance of the variance. The dependency of observations within a certain level was estimated by the intraclass correlation coefficient. In a logistic multilevel analysis, the intraclass correlation coefficient can be estimated by between-group variance/between-group variance+ $(\pi^2/3)$ [18]. First, a null model without any variables was estimated. In our data, hospital was a significant factor; adding pathology laboratory as the next level did not result in a better model. Therefore, multilevel analysis was carried out taking hospital level into account. Second, tumour characteristics (tumour size, histological grade,

number of breast cancer foci and nodal status), preoperative cytological/histological confirmation and type of pathology laboratory were included as covariates. Tumours coded pT1mic were included in the pT1a (N = 5). Variables with a significance level of less than 0.10 by univariable analysis were included in the multivariable analysis. The statistical significance level was set at a p-value less than 0.05. Analyses were carried out using the STATA software package, version 10.1 for Windows (Stata Corporation LP, College Station, Texas, USA).

RESULTS

Study population and relation to the screening programme

A total of 1,537 women were diagnosed with an invasive breast tumour. Of these 1,537 women, 873 (57%) were diagnosed with SDBC and 664 (43%) were diagnosed with CDBC (Table 1). SDBCs were significantly smaller (87 vs. 69% T1 tumours, i.e. <2cm; $p < 0.001$), more often well differentiated (33 vs. 26%; $p < 0.001$) and more often had negative LNs (80 vs. 68%; $p < 0.001$). Furthermore, they were more often preoperatively confirmed (98 vs. 96%; $p = 0.031$) and more often treated in a non-teaching hospital (60 vs. 66%; $p = 0.012$) or diagnosed in a non-teaching pathology laboratory (49 vs. 42%; $p = 0.012$).

Table 1. Characteristics of the study population of patients with invasive tumours (+/- DCIS component)

	SDBC		CDBC		Total	
	N	%	N	%	N	%
Tumour size [†]						
1A	62	7	27	4	89	6
1B	257	29	108	16	365	24
1C	439	50	323	49	762	50
2+	111	13	205	31	316	21
Unknown	4	1	1	0	5	0
Histological grade [‡]						
Well differentiated	289	33	170	26	459	30
Moderately differentiated.	398	46	263	40	661	43
Poorly differentiated	147	17	195	29	342	22
Unknown	39	5	36	5	75	5
Number of breast cancer foci						
Unifocal	826	95	622	94	1,448	94
Multifocal	47	5	42	6	89	6

Table 1. (continued)

	SDBC		CDBC		Total	
	N	%	N	%	N	%
Nodal status [‡]						
Negative	702	80	454	68	1,156	75
Positive	171	20	210	32	381	25
Preoperative cytol/histol confirmation *						
Yes	855	98	638	96	1,493	97
No	18	2	26	4	44	3
Type of hospital *						
Teaching	525	60	441	66	966	63
Non-teaching	348	40	223	34	571	37
PA laboratory *						
Teaching	450	52	385	58	835	54
Non-teaching	423	49	279	42	702	46
Total	873	100	664	100	1,537	100

CDBC, clinical detected breast cancer; cytol, cytological; histol, histological; PA, pathology; SDBC, Screen-detected breast cancer

*: $p < 0.05$

‡: $p < 0.001$

Predictors of positive margins

In 170 of the 1,537 (11%) women, the resection margin was positive (Table 2). There was no difference between the women with SDBC compared with the women with CDBC. Table 2 shows the percentages of positive margins for invasive tumours. The percentage of positive margins is divided into positive margins for the invasive tumour or just the DCIS component. A large range of percentages in positive margins was found between hospitals (range 2–29%). In a multilevel analysis taking into account hospital, there was no difference between women with SDBC compared with women with CDBC (Table 3). Nevertheless, margin status was affected by other factors. Larger tumour size, multifocality, positive LNs and the absence of preoperative confirmation were all predictors of positive margins. In univariable analysis, the localization of the tumour and histological grade were related to positive margins as well.

Table 2. Percentage of invasive tumours with positive margins, by detection method

	SDBC			CDBC		
	Total N	INV positive %	DCIS positive %	Total N	INV positive %	DCIS positive %
Tumour size						
1A	62	5	23	27	4	19
1B	257	3	2	108	10	4
1C	439	8	3	323	5	2
2+	111	14	4	205	12	3
Unknown	4	0	50	1	0	0
Histological grade						
Well differentiated	289	5	2	170	8	2
Moderately differentiated	398	9	4	263	7	4
Poorly differentiated	147	6	6	195	9	4
Unknown	39	5	13	36	8	3
Number of breast cancer foci						
Unifocal	826	6	4	622	7	3
Multifocal	47	17	11	42	26	5
Nodal status						
Negative	702	6	5	454	5	3
Positive	171	12	4	210	13	3
Preoperative cytol/histol confirmation						
Yes	855	7	4	638	7	3
No	18	11	11	26	27	12
Type of hospital						
Teaching	525	7	4	441	7	3
Non-teaching	348	7	5	223	10	4
PA laboratory						
Teaching	450	5	4	385	6	4
Non-teaching	423	9	4	279	10	3
Total	873	7 (N = 59)	4 (N = 38)	664	8 (N = 52)	3 (N = 21)

The number of patients are followed by the percentage with positive margins of the invasive component (INV pos) and the percentage with positive margins of the DCIS component in an invasive tumour (DCIS pos).

Abbreviations: CDBC, clinical detected breast cancer; cytol, cytological; histol, histological; PA, pathology; SDBC, Screen-detected breast cancer

Table 3. Multilevel analysis on positive margin status in all invasive tumours taking hospital level into account (N = 1,537)

	Univariable analysis				Multivariable analysis		
	OR	95%CI			OR	95%CI	
Relation to screening program							
SDBC	Reference				Reference		
CDBC	1.04	0.74	1.46		0.80	0.55	1.16
Tumour size							
1A	3.53	2.02	6.18	‡	4.72	2.56	8.72 ‡
1B	0.86	0.54	1.37		1.02	0.63	1.66
1C	Reference				Reference		
2+	2.08	1.39	3.12	‡	1.68	1.08	2.60 *
Unknown	7.30	1.11	48.22	*	6.18	0.79	48.48
Histological grade							
Well differentiated	Reference				Reference		
Moderately differentiated	1.70	1.12	2.59	*	1.68	1.08	2.62 *
Poorly differentiated	1.89	1.17	3.07	*	1.76	1.03	3.01 *
Unknown	2.29	1.08	4.82	*	1.32	0.59	2.94
Number of breast cancer foci							
Unifocal	Reference				Reference		
Multifocal	4.04	2.43	6.72	‡	4.00	2.36	6.79 ‡
Nodal status							
Negative	Reference				Reference		
Positive	1.87	1.32	2.65	‡	1.94	1.32	2.87 ‡
Preoperative cytol/histol confirmation							
Yes	Reference				Reference		
No	3.17	1.60	6.29	†	3.43	1.64	7.19 †
Type of hospital							
Teaching	Reference				-		
Non-teaching	1.28	0.77	2.13		-	-	-
PA laboratory							
Teaching	Reference				-		
Non-teaching	1.48	0.86	2.53		-	-	-

Abbreviations: CDBC, clinical detected breast cancer; CI, confidence interval; cytol, cytological; histol, histological; OR, odds ratio; PA, pathology; SDBC, Screen-detected breast cancer

*: $p < 0.05$

†: $p < 0.01$

‡: $p < 0.001$

Subsequent treatment for positive margins after breast-conserving surgery

A total of 170 women (11%) with an invasive tumour had positive margins after BCS, of whom 111 women (65%) had a positive invasive component. Most women (90%) were treated with a subsequent re-excision or mastectomy, 5% received radiotherapy and 5% received no additional treatment specific for positive margins (Table 4). Of women with an invasive tumour in whom the invasive component had free margins, but the DCIS component was more than focally positive (N = 59, 35%), additional re-excision or mastectomy was performed in 83%, 12% received radiotherapy and 5% received no treatment specific for positive margins. No differences in subsequent treatment were found between women with SDBC and CDBC. The differences in subsequent treatment between positive invasive components and positive DCIS components were not significant ($p = 0.053$ and 0.619 for the SDBCs and CDBCs, respectively).

Table 4. Subsequent treatment for positive margins after breast-conserving surgery

	SDBC		CDBC		Total		p-value
	N	%	N	%	N	%	
Invasive component							0.248
Re-excision + RT ^a	27	46	19	37	46	41	
Mastectomy	29	49	25	48	54	49	
RT only	1	2	5	10	6	5	
No further treatment	2	3	3	6	5	5	
Total	59	100	52	100	111	100	
DCIS component							0.239
Re-excision + RT ^b	11	29	11	52	22	37	
Mastectomy	19	50	8	38	27	46	
RT only	5	13	2	10	7	12	
No further treatment	3	8	0	0	3	5	
Total	38	100	21	100	59	100	

Abbreviations: CDBC, clinical detected breast cancer; DCIS, ductal carcinoma in situ; RT, radiotherapy; SDBC, Screen-detected breast cancer

^a Two patients had re-excision without RT

^b Four patients had re-excision without RT

DISCUSSION

In 170 out of 1,537 (11%) women with IBC, the resection margins were positive. No difference in the risk of positive margins was found between women with SDBC compared with women with CDBC. The Dutch guideline states that the upper limit of positive margins is 20% for invasive cancer [19]. Our results show that the percentage of positive margins for invasive tumours is well within the upper limit according to the guidelines. Van der Heiden-van der Loo et al. presented results on positive margins after BCS on a national level, and found a percentage of 9% positive margins for IBC [15].

The clinical relevance of positive margins still remains controversial. Most evidence supports the view that positive margins herald LR. The most plausible explanation is that for a high volume of residual tumour, radiotherapy alone is not sufficient to eliminate all tumour cells. However, the question of whether and how close margins affect LR is still unresolved. This lack of consistency in the definition of free margins contributes towards the lack of consensus on end results. In the literature, various definitions are used [20,21]. In our study, positive margins were defined specifically for invasive tumours. Patients with invasive tumours with more than focally positive margins should undergo a re-excision as LR rates are high even after radiotherapy with a booster dose. Patients with an invasive tumour with focally positive margins always receive a radiotherapy booster dose. Looking at the three subgroups (clear, focally positive, more than focally positive) of margin status separately resulted in similar results and no difference was found between SDBC and invasive CDBC ($p = 0.389$, results not shown). Furthermore, we excluded women with an unknown margin status, which might be a reason for bias. We do not have any information on why margin status is unknown, but it ranged from 1 to 4% in 11 hospitals (0% in 12 hospitals) and it is unlikely that it is unknown for a specific subgroup of patients or hospitals.

We have found just a few papers evaluating data from a breast screening programme. Dillon et al. found less involved margins in screen-detected invasive cancers [9]. In their study, they defined involved margins as foci of DCIS or invasive carcinoma within 5 mm from the resection margin. In our study, we did not collect data on the precise margin distance, but we used the presence of a tumour within the resection surface as the definition for positive margins. Furthermore, in contrast to Dillon et al, we did carry out a multivariable analysis to take other patient-related and tumour-related factors into account, which might be the reason for a different outcome. Kurniawan et al. included only patients diagnosed through a breast screening programme [11]. Therefore, they

could not compare the relation of positive margins between women with screen-detected and other tumours, but they did find that tumour size and multifocality are risk factors for positive margins, as well as the presence of calcifications on mammography. These results are in agreement with those of our study. Lovrics et al. found that tumour size, positive LNs and multifocality were risk factors for positive margins, next to other tumour characteristics [13]. Dillon et al. found that tumour size, multifocality and absence of preoperative confirmation were risk factors [9]. The absence of preoperative confirmation can serve as a proxy for the use of a needle plus ultrasound localization technique. Failure of this method is associated with compromised margins, and our result supports this association. All three studies mentioned above found a significant risk of tumour size: larger tumours have an increased risk of positive margins. In our study, however, we found that T1A tumours were also at high risk. Most of the T1A cases had an extensive DCIS component (microinvasive cancers). Because a characteristic of DCIS is its extensive and discontinuous spread throughout a single duct system, this may explain the fact that even these small SDBC carry the same risk of positive margins as the CDBC.

Chiarelli et al. found that clinically detected tumours are more often undifferentiated and have a high mitotic index [22]. This might be another reason for a more wispy growth type, with its inherent higher chance of irradical resection. It has also been argued that tumours detected by the initial or prevalent screening round would have more favourable characteristics than subsequent SDBCs. Therefore, inclusion of all SDBCs in our study may not provide the right comparison. We have focused on margin status and we found positive margins in 7% for invasive components and 4% for DCIS components in all (prevalent and subsequent) SDBCs. Analysis of subsequent SDBCs only yielded the same results, with 7 and 4%, respectively (results not shown), and so the screening round did not have an influence on margin status.

Of the women with positive margins after initial BCS, 90% underwent a re-excision. This is in accordance with the breast cancer guideline and in agreement with other studies reporting re-excision rates from 70 to 93% [11,23].

CONCLUSION

Women diagnosed with SDBC do not have a lower risk of having positive margins after BCS than women with CDBC. Although positive margins may occur in 11% of women with invasive tumours, well below the percentage recommended by the national guideline, the presence of encouraging factors by SDBC such as a smaller tumour size,

unifocality, negative LNs and the presence of preoperative confirmation should not lead to performing a more sparing excision than is considered usual for comparable CDDB.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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6

10-year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study

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SUMMARY

Background

Investigators of registry-based studies report improved survival for breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer. As these studies did not present long-term overall and breast cancer-specific survival, the effect of breast-conserving surgery plus radiotherapy might be overestimated. In this study, we aimed to evaluate 10-year overall and breast cancer-specific survival after breast-conserving surgery plus radiotherapy compared with mastectomy in Dutch women with early breast cancer.

Methods

In this population-based study, we selected all women from the Netherlands Cancer Registry diagnosed with primary, invasive, stage T1–2, N0–1, M0 breast cancer between January 1, 2000, and December 31, 2004, given either breast-conserving surgery plus radiotherapy or mastectomy, irrespective of axillary staging or dissection or use of adjuvant systemic therapy. Primary outcomes were 10-year overall survival in the entire cohort and breast cancer-specific survival in a representative subcohort of patients diagnosed in 2003 with characteristics similar to the entire cohort. We estimated breast cancer-specific survival by calculating distant metastasis-free and relative survival for every tumour and nodal category. We did multivariable Cox proportional hazard analysis to estimate hazard ratios (HRs) for overall and distant metastasis-free survival. We estimated relative survival by calculating excess mortality ratios using life Tables of the general population. We did multiple imputation to account for missing data.

Findings

Of the 37,207 patients included in this study, 21,734 (58%) received breast-conserving surgery plus radiotherapy and 15,473 (42%) received mastectomy. The 2003 representative subcohort consisted of 7,552 (20%) patients, of whom 4,647 (62%) received breast-conserving surgery plus radiotherapy and 2,905 (38%) received mastectomy. For both unadjusted and adjusted analysis accounting for various confounding factors, breast-conserving surgery plus radiotherapy was significantly associated with improved 10-year overall survival in the whole cohort overall compared with mastectomy (HR: 0.51 [95%CI: 0.49–0.53]; $p < 0.0001$; adjusted HR: 0.81 [0.78–0.85]; $p < 0.0001$), and this improvement remained significant for all subgroups of different T and N stages of breast cancer. After adjustment for confounding variables, breast-conserving surgery plus radiotherapy did not significantly improve 10-year distant metastasis-free survival in the 2003 cohort

overall compared with mastectomy (adjusted HR: 0.88 [0.77–1.01]; $p = 0.07$), but did in the T1N0 subgroup (adjusted HR: 0.74 [0.58–0.94]; $p = 0.014$). Breast-conserving surgery plus radiotherapy did significantly improve 10-year relative survival in the 2003 cohort overall (adjusted HR: 0.76 [0.64–0.91]; $p = 0.003$) and in the T1N0 subgroup (adjusted HR: 0.60 [0.42–0.85]; $p = 0.004$) compared with mastectomy.

Interpretation

Adjusting for confounding variables, breast-conserving surgery plus radiotherapy showed improved 10-year overall and relative survival compared with mastectomy in early breast cancer, but 10-year distant metastasis-free survival was improved with breast-conserving surgery plus radiotherapy compared with mastectomy in the T1N0 subgroup only, indicating a possible role of confounding by severity. These results suggest that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy with respect to overall survival and may influence treatment decision making for patients with early breast cancer.

INTRODUCTION

In the 1980s, findings from randomised controlled trials [1-3] of local treatment of early breast cancer showed that breast-conserving surgery plus radiotherapy resulted in equal survival compared with mastectomy without radiotherapy. Randomised controlled trials are well described to provide high-quality evidence of treatment effects [4]. However, they are often done on highly selected patient populations, excluding, for example, older patients, thereby limiting generalisability of the results [5]. Properly done observational studies, taking confounding variables into account, can produce valid results to assess treatment effects in representative real-world populations [6]. Several subsequent observational studies [7-13] have challenged the equivalence of breast-conserving surgery plus radiotherapy and mastectomy seen in the early randomised controlled trials, showing that breast-conserving surgery plus radiotherapy might be associated with improved survival in early breast cancer compared with mastectomy. However, none of these registry-based studies have reported data for 10-year overall and breast cancer-specific survival. Hence, the influence of confounding by severity and, consequently, non-breast cancer deaths is difficult to identify. Additionally, these studies are limited by correction for a small number of variables and short follow-up.

The aim of this study was to compare long-term survival of breast-conserving surgery plus radiotherapy with mastectomy in women with early breast cancer in a large population-based cohort.

To overcome the possible bias of the absence of information about non-breast cancer death, we estimated 10-year overall and breast cancer-specific survival (distant metastasis-free survival and relative survival) in Dutch women with early breast cancer, treated with either breast-conserving surgery plus radiotherapy or mastectomy. We analysed overall survival in the entire cohort and in subgroups by cancer stage (tumour [T] and node [N] category), as well as breast cancer-specific survival in a subcohort.

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for scientific literature written in all languages including the terms “breast conserving surgery”, “mastectomy”, and “survival”, from March 30, 1989, until November 24, 2015. We included synonyms. We reviewed 94 papers, of which we considered 40 to be relevant. Of these, 23 studied a similar population to ours. Ten were observational studies (eight historic cohort studies and two prospective cohort studies), ten were randomised controlled trials, one was a review, and two were meta-analyses of randomised controlled trials. Randomised controlled trials are considered to be very relevant in understanding of survival after breast-conserving surgery plus radiotherapy and mastectomy. However, observational studies might better reflect the real-world population than do randomised controlled trials. All ten randomised controlled trials showed no differences in survival outcomes when breast-conserving surgery plus radiotherapy was compared with mastectomy. Taking into account the fact that these trials include a selected patient population and were all done in the 1980s and that surgical treatments have been improved in the last few decades, these survival estimates might have changed. The observational studies that we found in our search all show that survival after breast-conserving surgery plus radiotherapy is equal to or improved compared with mastectomy. We found ten observational studies that were done using registry-based data; however, only one was a nationwide population-based study.

Added value of this study

To our knowledge, this study is the first population-based study that combines 10-year overall and breast cancer-specific survival (estimated by distant metastasis-free and relative survival) in early breast cancer, stratified for T and N category. We used a large study population with long follow-up and were able to correct for more confounding variables than were other registry-based studies. Our results suggest that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy with respect to long-term survival in early breast cancer.

Implications of all the available evidence

Our results agreed with those from previous studies that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy. Although the choice of mastectomy is increasing, primarily due to fear of recurrent cancer, use of MRI, and access to immediate reconstruction, our study might influence this choice by reducing patients' fears of recurrent cancer after breast-conserving surgery plus radiotherapy.

METHODS

Study design and patients

In this population-based study, we selected patients from the Netherlands Cancer Registry. This registry covers the whole Dutch population, recording data for all newly diagnosed malignancies since 1989. We included all female patients diagnosed with primary invasive, pathologically staged T1–2, N0–1, M0 breast cancer (morphology codes 8500–8575, excluding Paget’s disease of the nipple) between January 1, 2000, and December 31, 2004, excluding those with primary carcinoma in situ. We allocated cases to groups according to the most extensive surgery of the primary tumour that the patient had. We excluded patients from the breast-conserving surgery plus radiotherapy group who did not receive radiotherapy after breast-conserving surgery. We excluded patients from the mastectomy group who received radiotherapy after mastectomy. Type of surgery was irrespective of axillary staging or dissection or use of adjuvant systemic therapy. We excluded women who had primary systemic therapy, were treated in foreign or unknown hospitals, or had undifferentiated tumours or macroscopic residual tumour.

Procedures

We obtained patient-related, tumour-related, and treatment-related characteristics from the Netherlands Cancer Registry. The Netherlands Cancer Registry has specialised trained and dedicated registrars who derive these data from hospital records of all patients with a diagnosis of cancer. We coded tumour topography and morphology according to the International Classification of Diseases for Oncology [14] using the tumour, node, and metastasis classification system (International Union Against Cancer 5th edition (2000–02) [15] or 6th edition (2003–04) [16]). We derived additional data for vital status and date of death from the Municipal Personal Records Database up to December 31, 2014.

Primary invasive breast cancer represents patients diagnosed with cancer for the first time. Since the definition of the N1 category in the tumour, node, and metastasis classification system changed between the 5th and 6th editions of the International Classification of Diseases for Oncology, we used the number of positive lymph nodes to classify patients into N categories. We classified patients without involved lymph nodes as N0 and those with one to three positive nodes as N1. We defined axillary dissection as a standardised surgical en-bloc removal of level I and II axillary lymph nodes. Data regarding where patients were treated (by the nine regions in the Netherlands) were also collected and used in the analysis as this may have had an influence on survival. We calculated follow-up from date of diagnosis (overall and relative survival) or last known date of surgery of the primary tumour

(distant metastasis-free survival) to date of event. We calculated follow-up for distant metastasis-free survival from date of last surgery of the primary tumour, since this date was the date by which the patient was expected to be tumour free and at risk of recurrent disease. We censored patients at date of event or last date of observation. We defined distant metastases according to Moossdorff and colleagues [17] consensus- based event definitions for recurrence classification and Definition for the Assessment of Time-to-Event Endpoints in Cancer Trials guidelines [18]. In the distant metastasis- free survival analysis, we did not count deaths as events. To account for the diagnostic period, we considered events that occurred within 3 months of the date of primary diagnosis synchronous with the primary tumour and did not count them as events.

Outcomes

The main outcomes were 10-year overall survival (cumulative probability of being alive 10-years after diagnosis) in the entire 2000–04 cohort, distant metastasis-free survival (free from distant metastases after 10-year follow-up) in the 2003 cohort (all patients diagnosed from January 1, 2003, to December 31, 2003), and relative survival (ratio of observed survival of patients to the expected survival of the nationwide population) in the 2003 cohort. Distant metastasis-free and relative survival are both indicators for breast cancer-specific survival. For the whole 2000–04 cohort, cause of death was not available in the Netherlands Cancer Registry. To estimate distant metastasis-free survival, data for all recurrences (including distant metastases) within 10-years of diagnosis were gathered directly from patient files. Since this data gathering was only done for the 2003 cohort (because of time and resource constraints), we calculated distant metastasis-free survival only for this 2003 cohort. Because of statistical complexity, we also estimated relative survival for the 2003 cohort only.

Statistical analysis

We summarised patient-related, tumour-related, and treatment-related characteristics, and compared treatment groups using the χ^2 test or Wilcoxon rank sum test, for the entire 2000–04 cohort as well as for the 2003 cohort. As not all items were routinely established or registered for the entire period, we did multiple imputation using the *mi impute chained* equation command in Stata. As missing values were related to coding rules that changed over time, we considered these values as missing at random. We repeated the imputation 20 times, followed by application of Rubin's rule to combine parameter estimates and standard errors (SEs) [19]. To establish the validity of the imputed data, we compared observed values of complete cases with imputed values. We then used the imputed data for analyses.

To estimate crude 10-year overall and distant metastasis-free survival, we applied the Kaplan-Meier method and compared breast-conserving surgery plus radiotherapy and mastectomy groups using the log-rank test, for every T and N category. We did multivariable Cox proportional hazard analysis to correct for confounding and estimate hazard ratios (HRs) with 95% CIs for 10-year overall and distant metastasis-free survival. We estimated 10-year relative survival by calculating excess mortality ratios using general linear models with Poisson distribution, with life Tables of the general population as a reference. We established excess mortality ratios with 95% CIs using the Ederer II method [20]. We analysed 10-year relative survival with imputed datasets using a modification of the Stata code described by Nur and colleagues [21]. We based expected survival of the nationwide population on life Tables and matched it by age and year of diagnosis. To compare excess mortality ratios with other populations with different age distributions, we did age standardisation as described in the International Cancer Survival Standard [22].

To adjust all analyses for confounders, we included potential confounding variables (ie, baseline characteristics) that differed between treatment groups and significantly contributed to the outcome in univariable analysis in the multivariable models. We manually removed variables that did not significantly contribute to the multivariable models using backward selection. We tested the proportional hazards assumption by plotting the scaled Schoenfeld residuals of all coefficients over time and inspecting these for consistency. We found no violations. Finally, we tested the goodness of fit of the model graphically by observation of Cox-Snell residuals. Statistical tests were two-sided and we considered a p-value of less than 0.05 significant, except for analysis of the 2003 cohort, where we used Bonferroni correction to adjust for multiple testing and used a p-value of 0.025. We did all statistical analyses in Stata version 13.1.

Role of the funding source

There was no funding for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

40,220 female patients diagnosed with primary invasive breast cancer between 2000 and 2004 from the Netherlands Cancer Registry were eligible. Of these, we excluded 627 (2%) who did not receive radiotherapy after breast-conserving surgery, 2,173 (5%) who received radiotherapy after mastectomy, 152 (<1%) who had primary systemic therapy, 28 (<1%) who were treated in foreign or unknown hospitals, ten (<1%) who had undifferentiated tumours, and 23 (<1%) who had macroscopic residual tumour left.

The final study population of the 2000–04 cohort therefore consisted of 37,207 (93%) patients with non-metastatic early breast cancer, of whom 21,734 (58%) received breast-conserving surgery plus radiotherapy and 15,473 (42%) received mastectomy (Figure 1).

Figure 1. Flow diagram of included patients. (A) The two cohorts with percentages of patients who are still alive and who died, specified for primary surgery. (B) Presence or absence of distant metastases in the 2003 cohort, specified for primary surgery.

Abbreviations: BCS+RT: breast-conserving surgery followed by radiotherapy; DM: distant metastasis; MAST: mastectomy

For patients diagnosed in 2003 (7,783 [21%] patients), data for recurrences were complete for 7,552 (97%) patients. Of this final 2003 cohort, 4,647 (62%) received breast-conserving surgery plus radiotherapy and 2,905 (38%) received mastectomy. To establish the validity of imputed data, we compared observed values of complete cases with imputed values, which showed similar distributions (Supplementary Table 1). All analyses based on imputed datasets were similar to complete case analyses, and the estimates were more precise than were complete case analyses (data not shown).

Patient-related, tumour-related, and treatment-related characteristics of the entire 2000–04 cohort according to type of surgery are presented in Table 1 and Supplementary Table 2. Patients who had mastectomies were generally older and had less favourable tumour characteristics than those who had breast-conserving surgery plus radiotherapy. Additionally, patients who had mastectomy more often received axillary lymph node dissection and adjuvant hormonal therapy than did patients given breast-conserving surgery plus radiotherapy. Stratification for cancer stage (T and N category) showed that node-positive patients (T1N1 and T2N1) received axillary lymph node dissection and adjuvant hormonal therapy more frequently than did node-negative patients (T1N0 and T2N0; Supplementary Table 2). Use of adjuvant chemotherapy was higher in the T1N1 group than in the T1N0 group, but was almost equal for T2N0 and T2N1 (Supplementary Table 2). 4,853 (80%) of 6,092 patients with T1N0 stage cancer in the mastectomy group had not received adjuvant systemic therapy in the 2000–04 cohort compared with 10,128 (79%) of 12,768 in the breast-conserving surgery plus radiotherapy group. For the 2003 cohort, 891 (79%) of 1,130 patients with T1N0 stage cancer in the mastectomy group did not receive adjuvant systemic therapy compared with 2,152 (78%) of 2,761 patients in the breast-conserving surgery group. The characteristics of the 2003 subcohort were similar to those of the 2000–04 cohort (Supplementary Table 3), indicating that it could serve as a representative cohort.

Table 1. Baseline characteristics

Characteristics	Mastectomy (N = 15,473)	BCT (N = 21,734)
Year of diagnosis*		
2000	3,113 (20.1)	3,909 (18.0)
2001	3,171 (20.5)	4,097 (18.9)
2002	3,128 (20.2)	4,248 (19.6)
2003	3,059 (19.8)	4,724 (21.7)
2004	3,002 (19.4)	4,756 (21.9)

Table 1. (continued)

Characteristics	Mastectomy (N = 15,473)	BCT (N = 21,734)
Age (years)*		
<40	929 (6.0)	1,232 (5.7)
40-49	2,618 (16.9)	4,264 (19.6)
50-59	3,465 (22.4)	7,222 (33.2)
60-69	2,989 (19.3)	5,479 (25.2)
70-79	3,346 (21.6)	3,098 (14.3)
>79	2,126 (13.7)	439 (2.0)
SES*		
Low	4,686 (30.3)	6,436 (29.6)
Medium	6,319 (40.8)	8,577 (39.5)
High	4,468 (28.9)	6,721 (30.9)
Hospital volume (patients per year)*		
0-49	3,123 (20.2)	4,654 (21.4)
50-99	7,004 (45.3)	9,085 (41.8)
100-149	3,359 (21.7)	4,924 (22.7)
>149	1,987 (12.8)	3,071 (14.1)
Region*		
A	2,087 (13.5)	3,084 (14.2)
B	1,558 (10.1)	1,606 (7.4)
C	1,100 (7.1)	1,772 (8.2)
D	2,346 (15.2)	4,375 (20.1)
E	1,595 (10.3)	2,192 (10.1)
F	3,031 (19.6)	2,484 (11.4)
G	1,848 (11.9)	3,427 (15.8)
H	832 (5.4)	1,335 (16.1)
I	1,076 (7.0)	1,459 (6.7)
Lateralisation†		
Left	8,131 (52.6)	11,244 (51.7)
Right	7,340 (47.4)	10,489 (48.3)
Unknown	2 (0.0)	1 (0.0)
Sublocalisation*		
Outer quadrants	7,037 (45.5)	11,574 (53.3)
Inner quadrants	2,780 (18.0)	4,711 (21.7)
Central portion	1,378 (8.9)	1,095 (5.0)
Overlapping lesions	3,918 (25.3)	4,036 (18.6)
Unknown	360 (2.3)	318 (1.5)
Histological tumour type*		
Ductal	11,987 (77.5)	17,876 (82.3)
Lobular	1,830 (11.8)	1,730 (8.0)
Mixed	874 (5.7)	798 (3.7)
Other	782 (5.1)	1,330 (6.1)

Table 1. (continued)

Characteristics	Mastectomy (N = 15,473)	BCT (N = 21,734)
Differentiation*		
Grade I	2,365 (15.3)	4,821 (22.2)
Grade II	6,275 (40.6)	8,681 (39.9)
Grade III	4,602 (29.7)	5,343 (24.6)
Unknown	2,231 (14.4)	2,889 (13.3)
Tumour size (mm)*		
Median (IQR)	20 (14-27)	15 (11-20)
Unknown	6,013 (38.9)	7,773 (35.8)
Number of positive nodes*		
Median (IQR)	0 (0-1)	0 (0-1)
Unknown	57 (0.4)	37 (0.2)
Multifocality*		
Yes	1,594 (10.3)	434 (2.0)
No	5,721 (37.0)	9,416 (43.3)
Unknown	8,158 (52.7)	11,884 (54.7)
Hormone receptor status*		
ER and PR +	3,946 (25.5)	6,464 (29.7)
ER or PR+	1,029 (6.7)	1,423 (6.6)
ER and PR –	1,127 (7.3)	1,561 (7.2)
Unknown	9,371 (60.6)	12,286 (56.5)
Adjuvant systemic therapy*		
No	7,505 (48.5)	12,145 (55.9)
Hormonal therapy	4,017 (26.0)	3,834 (17.6)
Chemotherapy	1,864 (12.1)	2,778 (12.8)
Both	2,087 (13.5)	2,977 (13.7)
Axillary lymph node dissection*		
Yes	10,987 (71.0)	9,852 (45.3)
No	4,486 (29.0)	11,882 (54.7)

Data are N (%) or median (IQR). $p < 0.1$ for comparison between treatment groups was considered significant. Abbreviations: BCT: breast-conserving surgery plus radiotherapy; SES: socioeconomic status; ER: oestrogen receptor; PR: progesterone receptor.

* $p < 0.0001$ for comparison between treatment groups.

† $p = 0.119$ for comparison between treatment groups.

In the 2000–04 cohort, 16,686 (77%) of 21,734 patients survived in the breast-conserving surgery plus radiotherapy group compared with 9,229 (60%) of 15,473 in the mastectomy group (Figure 1), after a median follow-up of 11.4 years (IQR: 10.0–13.0). Kaplan-Meier analysis and the log-rank test showed that breast-conserving surgery plus radiotherapy was significantly associated with improved overall survival compared with mastectomy in all T and N categories (Figure 2, Table 2). All subgroups of patients with different cancer stages had different overall survival irrespective of type of surgery, with the T1N0 subgroup

being the most favourable and T2N1 being the least (Figure 2, Table 2). After adjustment for confounders, the adjusted HR for 10-year overall survival was 0.81 (95%CI: 0.78–0.85) in the overall cohort, favouring breast-conserving surgery plus radiotherapy over mastectomy;

Figure 2. Unadjusted 10 year overall survival analysis in the 2000–04 cohort (N = 37,207). (A) Breast-conserving surgery plus radiotherapy compared with mastectomy in the whole cohort. (B) Patients with T1N0, T1N1, T2N0, and T2N1 stage cancer, irrespective of type of surgery. Breast-conserving surgery plus radiotherapy compared with mastectomy in patients with (C) T1N0, (D) T1N1, (E) T2N0, and (F) T2N1 stage cancer.

Table 2. 10-year overall survival

		2000-04 cohort (N = 37,207)				2003 cohort (N = 7,552)			
		Crude		Adjusted		Crude		Adjusted	
	N	HR	p-value	HR	p-value	N	HR	p-value	HR
Overall cohort									
Mastectomy	15,473	1		1		2,905	1		1
BCT	21,734	0.51 [0.49-0.53]	<0.0001	0.81 [0.78-0.85]*	<0.0001	4,647	0.50 [0.45-0.54]	<0.0001	0.81 [0.73-0.89]*†
									<0.0001
Subgroups									
T1N0									
Mastectomy	6,092	1		1		1,130	1		1
BCT	18,860	0.58 [0.55-0.62]	<0.0001	0.82 [0.77-0.87]†	<0.0001	2,761	0.55 [0.48-0.63]	<0.0001	0.79 [0.68-0.91]§
									0.002
T1N1									
Mastectomy	2,185	1		1		388	1		1
BCT	3,741	0.60 [0.54-0.66]	<0.0001	0.81 [0.73-0.90]*	<0.0001	738	0.62 [0.48-0.79]	<0.0001	0.79 [0.60-1.03]
									0.085
T2N0									
Mastectomy	4,174	1		1		772	1		1
BCT	3,165	0.52 [0.48-0.56]	<0.0001	0.82 [0.75-0.90]**	<0.0001	704	0.54 [0.45-0.64]	<0.0001	0.85 [0.69-1.04]††
									0.108
T2N1									
Mastectomy	3,022	1		1		615	1		1
BCT	2,060	0.56 [0.51-0.61]	<0.0001	0.80 [0.72-0.88]‡‡	<0.0001	444	0.59 [0.48-0.72]	<0.0001	0.85 [0.68-1.08]§§
									0.181

Data in parentheses are 95% CIs. HR: hazard ratio. Cancer stage is indicated by the T and N status. T: tumour. N: node. BCT: breast-conserving surgery plus radiotherapy.

*Corrected for age, socioeconomic status, hospital volume, region, sublocalisation of tumour, histological tumour type, differentiation grade, tumour size, number of positive lymph nodes, hormone receptor status, and adjuvant systemic therapy.

†Corrected for age, socioeconomic status, hospital volume, sublocalisation of tumour, histological tumour type, differentiation grade, tumour size, number of positive lymph nodes, hormone receptor status, and adjuvant systemic therapy.

‡Corrected for age, hospital volume, region, sublocalisation of tumour, differentiation grade, tumour size, and hormone receptor status. §Corrected for age, socioeconomic status, region, histological tumour type, differentiation grade, tumour size, hormone receptor status, and adjuvant systemic therapy.

¶Corrected for age, socioeconomic status, region, sublocalisation of tumour, differentiation grade, tumour size, number of positive lymph nodes, adjuvant systemic therapy, and axillary lymph node dissection.

||Corrected for age, region, sublocalisation of tumour, and tumour size.

**Corrected for age, socioeconomic status, region, sublocalisation of tumour, differentiation grade, hormone receptor status, tumour size, and adjuvant systemic therapy.

††Corrected for age, differentiation grade, tumour size, adjuvant systemic therapy, and axillary lymph node dissection.

‡‡Corrected for age, socioeconomic status, region, sublocalisation of tumour, histological tumour type, tumour size, number of positive lymph nodes, hormone receptor status, adjuvant systemic therapy, and axillary lymph node dissection.

§§Corrected for age, region, sublocalisation of tumour, tumour size, hormone receptor status, and axillary lymph node dissection.

Table 3. 10-year distant metastasis-free and relative survival in the 2003 cohort

	Distant metastasis-free survival				Relative survival			
	Crude analysis		Adjusted analysis		Crude analysis		Adjusted analysis	
	N	HR	p-value	HR	p-value	Excess mortality ratio	p-value	Excess mortality ratio
Overall cohort	2,905	1		1	0.070			
Mastectomy	4,647	0.66 [0.58-0.75]	<0.0001	0.88 [0.77-1.01]*		0.58 [0.49-0.69]	<0.0001	0.76 [0.64-0.91]*
BCT						1		1
0.003								0.003
Subgroups								
T1N0								
Mastectomy	1,130	1		1		1		1
BCT	2,761	0.64 [0.51-0.82]	<0.0001	0.74 [0.58-0.94]†	0.014	0.51 [0.36-0.73]	<0.0001	0.60 [0.42-0.85]§
0.004								0.004
T1N1								
Mastectomy	388	1		1		1		1
BCT	738	0.94 [0.67-1.33]	0.741	1.00 [0.71-1.23]¶	0.994	0.75 [0.48-1.18]	0.214	0.71 [0.45-1.13]
0.148								0.148
T2N0								
Mastectomy	772	1		1		1		1
BCT	704	0.98 [0.76-1.26]	0.855	0.94 [0.72-1.23]**	0.644	0.90 [0.65-1.25]	0.539	0.94 [0.66-1.33]††
0.720								0.720
T2N1								
Mastectomy	615	1		1		1		1
BCT	444	0.86 [0.67-1.10]	0.234	0.95 [0.73-1.24]††	0.718	0.79 [0.59-1.05]	0.121	0.81 [0.58-1.12]§§
0.202								0.202

Data in parentheses are 95% CIs. We used life tables of the general Dutch population, matched by age and year of diagnosis, as a reference. HR: hazard ratio; T: tumour; N: node.

*Corrected for region, sublocalisation of tumour, histological tumour type, differentiation grade, tumour size, number of positive lymph nodes, hormone receptor status, and adjuvant systemic therapy. †Corrected for age, socioeconomic status, hospital volume, sublocalisation of tumour, histological tumour type, differentiation grade, tumour size, number of positive lymph nodes, hormone receptor status, and adjuvant systemic therapy.

‡Corrected for age, sublocalisation of tumour, histological tumour type, differentiation grade, tumour size, hormone receptor status, and adjuvant systemic therapy. §Corrected for age, socioeconomic status, region, histological tumour type, differentiation grade, tumour size, hormone receptor status, and adjuvant systemic therapy.

¶Corrected for region, differentiation grade, and tumour size. ||Corrected for age, region, sublocalisation of tumour, and tumour size.

**Corrected for age, sublocalisation of tumour, histological tumour type, and differentiation grade. ††Corrected for age, differentiation grade, tumour size, adjuvant systemic therapy, and axillary lymph node dissection.

‡‡Corrected for sublocalisation of tumour, tumour size, and hormone receptor status. §§Corrected for age, region, sublocalisation of tumour, tumour size, hormone receptor status, and axillary lymph node dissection.

the HRs were similar in all T and N categories in this cohort (Table 2). In the 2003 subcohort, 3,686 (79%) of 4,647 patients survived in the breast-conserving surgery plus radiotherapy group compared with 1,840 (63%) of 2,905 in the mastectomy group (Figure 1). Median follow-up was 11.3 years (IQR 10.3–11.7). Kaplan-Meier curves (Supplementary Figure 1) and HRs (Table 2) were similar to those the entire 2000–04 cohort.

In the 2003 subcohort, 509 (11%) of 4,647 patients in the breast-conserving surgery plus radiotherapy group were diagnosed with distant metastases compared with 427 (15%) of 2,905 in the mastectomy group (Figure 1). Median follow-up was 9.8 years (IQR: 5.6–10.0). Kaplan-Meier analysis and the log-rank test showed that, overall, breast-conserving surgery plus radiotherapy was significantly associated with better 10-year distant metastasis-free survival than that for mastectomy (HR: 0.66 [95%CI 0.58–0.75]; $p < 0.0001$; Figure 3, Table 3). In patients with T1N0 stage cancer, breast-conserving surgery plus radiotherapy was associated with improved 10-year distant metastasis-free survival compared with mastectomy ($p < 0.0001$; Figure 3, Table 3). In patients with other stages of cancer (T1N1, T2N0, T2N1), we found no significant differences between treatments (Figure 3). After adjustment for confounders, the adjusted HR was 0.88 (95%CI: 0.77–1.01), indicating no significant difference between breast-conserving surgery plus radiotherapy and mastectomy (Table 3). However, after stratification by cancer stage, breast-conserving surgery plus radiotherapy was associated with improved 10-year distant metastasis-free survival in the T1N0 subgroup (adjusted HR: 0.74 [95%CI 0.58–0.94]). In patients with T1N1, T2N0, or T2N1 stage cancer, we noted no significant difference between treatments (Table 3). We repeated the analyses with follow-up calculated from date of diagnosis, which resulted in similar estimates (Supplementary Table 4).

Overall, crude 10-year relative survival in the 2003 cohort was significantly better for breast-conserving surgery plus radiotherapy than for mastectomy ($p < 0.0001$; Figure 4, Table 3). After stratification for cancer stage, we observed significantly different proportions of crude relative survival for all cancer stage subtypes, irrespective of the type of surgery given (Figure 4, Table 3). Breast-conserving surgery plus radiotherapy was only significantly related to improved 10-year relative survival in patients with T1N0 stage cancer (Figure 4, Table 3). After adjustment for confounding, the adjusted excess mortality ratio for 10-year relative survival was 0.76 (95%CI: 0.64–0.91; Table 3). After stratification for cancer stage, the favourable outcome of breast-conserving surgery plus radiotherapy compared with mastectomy remained in patients with T1N0 stage cancer only.

Figure 3. Unadjusted 10 year distant metastasis-free survival in the 2003 cohort. (A) Breast-conserving surgery plus radiotherapy compared with mastectomy in the whole cohort. (B) Patients with T1N0, T1N1, T2N0, and T2N1 stage cancer, irrespective of type of surgery. Breast-conserving surgery plus radiotherapy compared with mastectomy in patients with (C) T1N0, (D) T1N1, (E) T2N0, and (F) T2N1 stage cancer.

Figure 4. Unadjusted 10 year relative survival in the 2003 cohort. (A) Breast-conserving surgery plus radiotherapy compared with mastectomy in the whole cohort. (B) Patients with T1N0, T1N1, T2N0, and T2N1 stage cancer, independent of type of surgery. Breast-conserving surgery plus radiotherapy compared with mastectomy in patients with (C) T1N0, (D) T1N1, (E) T2N0, and (F) T2N1 stage cancer. We used life tables of the general Dutch population, matched by age and year of diagnosis, as a reference.

DISCUSSION

In this study, patients with early, non-metastatic breast cancer treated with breast-conserving surgery plus radiotherapy had improved 10-year overall survival compared with that in patients treated with mastectomy. In a subset of patients with T1N0 stage disease, unadjusted analysis showed that 10-year breast cancer-specific survival, including distant metastasis-free survival and relative survival, was improved in patients treated with breast-conserving surgery plus radiotherapy compared with patients treated with mastectomy; this difference was not observed between treatment groups in patients with other stages of disease. After adjusting for confounders, the difference in breast cancer-specific survival (distant metastasis-free and relative survival) remained significant in patients with T1N0 stage disease.

The difference in outcomes between 10-year overall and breast cancer-specific survival might need further clarification. Older patients with larger, more aggressive lobular or multifocal tumours are thought to more often receive mastectomy than breast-conserving surgery plus radiotherapy, which is also seen in our data. These patients have lower survival because of worse tumour characteristics, and age and confounding by severity are issues. For this reason, observational studies only reporting overall survival outcomes [12,13] might not adequately compare treatment effects. Breast cancer-specific survival might estimate real treatment effects more reliably than might overall survival by eliminating the large influence of age and comorbidities (leading to non-breast cancer deaths), which are expected to have a larger influence on overall survival in the mastectomy group than in the breast-conserving surgery group. However, Adkisson and colleagues [23] showed that absence of comorbidities was independently associated with patient's choice of mastectomy over breast-conserving surgery plus radiotherapy, and primary tumour characteristics were not associated with treatment choice, indicating that the above-mentioned argument does not always hold.

Our result that breast-conserving surgery plus radiotherapy was associated with improved overall survival in early breast cancer is substantiated by conclusions from other observational studies [7-13]. The only one of these studies that stratified the analysis for T and N cancer stage category [9] described 5-year overall and breast cancer-specific survival after breast-conserving surgery plus radiotherapy equal to or better than mastectomy, but did not report exact estimates by cancer stage. In our study, the breast-conserving surgery results are mainly determined by the T1N0 category, as this

group accounts for more than 50% of the entire cohort. Thus, studies that only report one outcome measure for the whole group should be interpreted with caution.

Our results are not consistent with outcomes of previous randomised controlled trials [1-3], which showed overall and distant metastasis-free survival to be equal for breast-conserving surgery plus radiotherapy and mastectomy in early breast cancer. This inconsistency can be explained by the different study designs (randomised controlled trials versus historic cohort design) and patient populations [5], and the fact that these randomised controlled trials were all done in the 1980s, when local recurrence was much higher after breast-conserving surgery plus radiotherapy than it is now [24] and when population-based screening programmes were non-existent. To establish if the starting point of follow-up in our study (last date of primary surgery) could partly explain the difference, we repeated the analyses with date of diagnosis as the starting point of follow-up and found similar results, indicating that this factor did not influence our results. Furthermore, diagnostic, surgical, and radiotherapy procedures have improved over the last 30 years, which might explain why we observed an improvement in patients treated with breast-conserving surgery plus radiotherapy compared with patients treated with mastectomy.

Onitilo and colleagues investigated overall survival after breast-conserving surgery with and without radiotherapy compared with mastectomy [12], and showed that overall survival for breast-conserving surgery without radiotherapy was equal to that for mastectomy, but overall survival was longer for breast-conserving surgery plus radiotherapy than for mastectomy. The authors suggest that the finding that breast-conserving surgery plus radiotherapy is better than mastectomy is more likely to be related to the addition of radiotherapy than to the surgery itself. The Early Breast Cancer Trialists' Collaborative Group showed that addition of radiotherapy after breast-conserving surgery for early-stage breast cancer avoided about one breast cancer death by year 15 for every four breast cancer recurrences avoided by year 10 [25]. As adjuvant systemic therapy is expected to have a similar effect to postoperative radiotherapy on recurrence risk [26], the effect of postoperative radiotherapy alone can only be studied in patients who did not receive adjuvant systemic therapy. In our study, a significant difference in 10-year distant metastasis-free survival in favour of breast-conserving surgery plus radiotherapy was only found in patients with T1N0 stage cancer. More than 75% of patients in this subgroup had not received adjuvant systemic therapy (compared with 7–48% of patients with other stages of cancer). Part of this effect could therefore be attributed to postoperative radiotherapy in the breast-conserving surgery

plus radiotherapy group. The interplay between risk factors and efficacy of systemic treatment and the influence of locoregional treatments on survival is complex [27]. The intuitive notion that the influence of radiotherapy might be most evident in patients with positive lymph nodes therefore might not hold in this study.

To our knowledge, this study is the first population-based study investigating overall and breast cancer-specific survival in subgroups of patients with T1N0, T1N1, T2N0, and T2N1 stage breast cancer, with 10-years of follow-up. An important strength of the study is use of data from the Netherlands Cancer Registry that includes all Dutch women diagnosed with breast cancer, which enhances the validity of the results and provides a good reflection of daily practice. Furthermore, the Netherlands Cancer Registry has detailed and thorough records, which allowed us to account for more confounding variables than other registry-based studies [7-13], and to provide valid adjusted survival estimates. In addition, besides stratification for breast cancer T and N stage, we used exact (up to 1 mm) tumour size and number of positive lymph nodes in the multivariable analyses. Importantly, a decline of 1 cm in tumour size has been associated with a reduction in 15-year mortality of about 10% [28]. Since the range in tumour size in every T category is up to a few cm and patients who have mastectomy more often have larger tumours than do those who have breast-conserving surgery plus radiotherapy, we accounted for exact size to eliminate this possibly large effect on the outcome. Additionally, an increasing number of positive lymph nodes is associated with worse overall survival [29].

As in all observational studies, our results could have been influenced by confounding by severity and residual unknown confounding, despite our extensive corrections. Since overall survival is not breast cancer specific, this outcome might be influenced by non-breast cancer deaths. This influence is largely overcome by use of distant metastasis-free and relative survival, which are an approximation for breast cancer-specific survival. Findings from the Early Breast Cancer Trialists' Collaborative Group overview [30] – looking at breast cancer-specific survival after mastectomy compared with mastectomy plus radiotherapy – showed that survival curves of patients who had mastectomy with and without radiotherapy do not separate until at least 5-years after treatment. In our study, survival curves separate earlier, which might reflect differences in baseline characteristics between treatment groups.

Some additional limitations of this study should be mentioned. After developments in diagnostic and therapeutic strategies, treatment guidelines for women with early breast cancer have changed and our study population may not reflect outcomes for women

currently being treated. For example, our study population might have an underuse of adjuvant systemic therapy compared with current treatment standards. However, according to the Dutch guidelines [31], low-risk early stage breast cancer patients still do not receive adjuvant systemic therapy. As this factor applies for both breast-conserving surgery plus radiotherapy and mastectomy, it is not expected to have biased the results. Unfortunately, in the period studied, information about HER2 status was very scarce, was not established or registered on a large scale, and was not part of decision making regarding targeted therapy. Since HER2 status has been shown to be a strong prognostic factor for relapse [32], any difference in HER2 status between treatment groups might have influenced survival outcomes. The absence of data for comorbidities and relevant contraindications to radiotherapy could also have influenced the results. The presence of missing data can be considered a weakness of this study. We did multiple imputation to achieve better and more reliable estimates of the differences than if imputation was not done when data were missing. Even with substantial amounts of missing data, this technique provides effect estimates similar to those obtained with complete case analysis. Additionally, a gain in precision has been achieved [33]. In this study, all analyses based on imputed datasets were similar to complete case analyses, and the estimates were more precise than were complete case analyses (data not shown).

Our results, along with previous studies, provide convincing evidence that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy with respect to long-term survival in early breast cancer. Although the choice of mastectomy is increasing, primarily due to fear of recurrent cancer, use of MRI, and access to immediate reconstruction [34], our study might influence this choice by reducing patients' fears of recurrent cancer after breast-conserving surgery plus radiotherapy. Shared decision making in treatment choices between physicians and patients is advisable, taking into account the associated psychological effect. In case both treatments are suitable, patients should be adequately informed regarding both treatments, discussing not only better cosmetic aspects of breast-conserving surgery plus radiotherapy compared with mastectomy, but also long-term overall and breast cancer-specific survival probabilities. Additionally, mastectomy can remain the first choice of treatment for specific groups of patients such as women with a known genetic alteration associated with a high risk of second primary breast cancer, those with contraindications for radiotherapy, such as patients with Li-Fraumeni syndrome, and for women with a large tumour-to-breast ratio [35,36]. Whether these results hold true for operative choices after primary systemic therapy is unclear. Since too few patients were given primary systemic therapy to draw meaningful conclusions, we excluded those receiving primary systemic therapy from

our study. Although 10-year breast cancer-specific survival was improved for breast-conserving surgery plus radiotherapy compared with mastectomy in T1N0 disease only, suggesting a possible role for confounding by severity (including presence of comorbidities) in overall survival, our study results emphasise that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy concerning survival and these results might form a basis for further analytical and predictive modelling in view of individual (stratified) prognosis and outcome of treatment in early breast cancer.

CONTRIBUTORS

MCvM, PP, and LJJAS did the literature search, designed the study, interpreted data, and discussed and wrote the manuscript. MCvM was also responsible for the statistical methods, data analysis, and figures and tables. LdM designed the study, interpreted data, reviewed the statistical methods, and discussed and wrote the manuscript. GHdB, JJJ, TvD, and SCL interpreted data and discussed and wrote the manuscript. SS designed the study, interpreted data, and discussed and wrote the manuscript.

DECLARATION OF INTERESTS

We declare no competing interests.

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SUPPLEMENTARY DATA

Supplementary Table 1. Distribution of key variables before and after multiple imputation

Variables	Cohort 2000-2004 (N = 37,207)		Cohort 2003 (N = 7,552)	
	Original	Average imputed	Original	Average imputed
Lateralisation				
Left	52.3	52.1	-	-
Right	47.7	47.9	-	-
Sublocalisation				
Outer quadrants	50.5	50.9	51.0	50.8
Inner quadrants	20.7	20.5	20.8	21.3
Central portion	7.1	6.8	7.2	7.0
Overlapping lesions	21.6	21.8	20.9	20.9
Differentiation grade				
Grade I	23.3	22.9	24.1	25.0
Grade II	45.5	46.8	44.5	44.7
Grade III	31.2	30.2	31.4	30.4
Multifocality				
Yes	10.9	11.5	8.6	8.9
No	89.1	88.5	91.4	91.1
Hormone receptor status				
ER and PR +	66.3	65.2	65.5	65.8
ER or PR +	15.6	16.0	16.3	16.5
ER and PR -	18.1	18.8	18.2	17.7
Tumour size (mm) (median [IQR])	17 [12-23]	17 [12-23]	17 [12-23]	17 [12-23]
Number of positive lymph nodes (median [IQR])	0 [0-1]	0 [0-1]	0 [0-1]	0 [0-1]

Numbers are % unless otherwise specified. The imputation was performed using the mi impute chained equation command in STATA®. Percentages and medians displayed are derived from imputed variables only. Abbreviations: ER: oestrogen receptor; PR: progesterone receptor; IQR: interquartile range.

Supplementary Table 2. Baseline characteristics of T1-T2N0-1 staged breast cancer patients in the according to type of surgery in the 2000-2004 cohort (N = 37,207)

Characteristics	Mastectomy			Breast-conserving surgery plus radiotherapy						
	Overall (N = 15,473)	T1N0 (N = 6,092)	T1N1 (N = 2,185)	T2N0 (N = 4,174)	T2N1 (N = 3,022)	Overall (N = 21,734)	T1N0 (N = 12,768)	T1N1 (N = 3,741)	T2N0 (N = 3,165)	T2N1 (N = 2,060)
Year of diagnosis ¹²⁴										
2000	3,113 (20.1)	1,301 (21.4)	420 (19.2)	842 (20.2)	550 (18.2)	3,909 (18.0)	2,313 (18.1)	685 (18.3)	557 (17.6)	354 (17.2)
2001	3,171 (20.5)	1,255 (20.6)	445 (20.4)	904 (21.7)	567 (18.8)	4,097 (18.9)	2,381 (18.7)	723 (19.3)	589 (18.6)	404 (19.6)
2002	3,128 (20.2)	1,236 (20.3)	471 (21.6)	809 (19.4)	612 (20.3)	4,248 (19.6)	2,448 (19.2)	773 (20.7)	608 (19.2)	419 (20.3)
2003	3,059 (19.8)	1,190 (19.5)	410 (18.8)	805 (19.3)	654 (21.6)	4,724 (21.7)	2,811 (22.0)	753 (20.1)	714 (22.6)	446 (21.7)
2004	3,002 (19.4)	1,110 (18.2)	439 (20.1)	814 (19.5)	639 (21.1)	4,756 (21.9)	2,815 (22.1)	807 (21.6)	697 (22.0)	437 (21.2)
Age ^{123,45}										
<40	929 (6.0)	296 (4.9)	150 (6.9)	248 (5.9)	235 (7.8)	1,232 (5.7)	554 (4.3)	244 (6.5)	248 (7.8)	186 (9.0)
40-49	2,618 (16.9)	854 (14.0)	457 (20.9)	634 (15.2)	673 (22.3)	4,264 (19.6)	2,085 (16.3)	863 (23.1)	758 (24.0)	558 (27.1)
50-59	3,465 (22.4)	1,463 (24.0)	573 (26.2)	776 (18.6)	653 (21.6)	7,222 (33.2)	4,253 (33.3)	1,307 (34.9)	944 (29.8)	718 (34.9)
60-69	2,989 (19.3)	1,451 (23.8)	404 (18.5)	674 (16.2)	460 (15.2)	5,479 (25.2)	3,544 (27.8)	898 (24.0)	684 (21.6)	353 (17.1)
70-79	3,346 (21.6)	1,449 (23.8)	386 (17.7)	999 (23.9)	512 (16.9)	3,098 (14.3)	2,119 (16.6)	377 (10.1)	409 (12.9)	193 (9.4)
>79	2,126 (13.7)	579 (9.5)	215 (9.8)	843 (20.2)	489 (16.2)	439 (2.0)	213 (1.7)	52 (1.4)	122 (3.9)	52 (2.5)
SES ^{13,45}										
Low	4,686 (30.3)	1,821 (29.9)	634 (29.0)	1,319 (31.6)	912 (30.2)	6,436 (29.6)	3,780 (29.6)	1,056 (28.2)	969 (30.6)	631 (30.6)
Medium	6,319 (40.8)	2,473 (40.6)	928 (42.5)	1,688 (40.4)	1,230 (40.7)	8,577 (39.5)	5,083 (39.8)	1,519 (40.6)	1,205 (38.1)	770 (37.4)
High	4,468 (28.9)	1,798 (29.5)	623 (28.5)	1,167 (28.0)	880 (29.1)	6,721 (30.9)	3,905 (30.6)	1,166 (31.2)	991 (31.3)	659 (32.0)
Hospital volume										
(patients per year) ^{123,45}										
0-49	3,123 (20.2)	1,253 (20.6)	443 (20.3)	841 (20.2)	586 (16.4)	4,654 (21.4)	2,784 (21.8)	824 (22.0)	619 (19.6)	427 (20.7)
50-99	7,004 (45.3)	2,693 (44.2)	972 (44.5)	1,919 (46.0)	1,420 (47.0)	9,085 (41.8)	5,366 (42.0)	1,530 (40.9)	1,369 (43.3)	820 (39.8)
100-149	3,359 (21.7)	1,316 (21.6)	458 (21.0)	902 (21.6)	683 (22.6)	4,924 (22.7)	2,841 (22.3)	844 (22.6)	747 (23.6)	492 (23.9)
>149	1,987 (12.8)	830 (13.6)	312 (14.3)	512 (12.3)	333 (11.0)	3,071 (14.1)	1,777 (13.9)	543 (14.5)	430 (13.6)	321 (15.6)

Supplementary Table 2. (continued)

	Mastectomy					Breast-conserving surgery plus radiotherapy				
Characteristics	Overall (N = 15,473)	T1N0 (N = 6,092)	T1N1 (N = 2,185)	T2N0 (N = 4,174)	T2N1 (N = 3,022)	Overall (N = 21,734)	T1N0 (N = 12,768)	T1N1 (N = 3,741)	T2N0 (N = 3,165)	T2N1 (N = 2,060)
Region ¹²³⁴⁵										
A	2,087 (13.5)	799 (13.1)	292 (13.4)	567 (13.6)	429 (14.2)	3,084 (14.2)	1,796 (14.1)	544 (14.5)	439 (13.9)	305 (14.8)
B	1,558 (10.1)	623 (10.2)	237 (10.9)	385 (9.2)	313 (10.4)	1,606 (7.4)	944 (7.4)	295 (7.9)	237 (7.5)	130 (6.3)
C	1,100 (7.1)	429 (7.0)	194 (8.9)	249 (6.0)	228 (7.5)	1,772 (8.2)	1,030 (8.1)	343 (9.2)	239 (7.6)	160 (7.8)
D	2,346 (15.2)	955 (15.7)	353 (16.2)	604 (14.5)	434 (14.4)	4,375 (20.1)	2,512 (19.7)	817 (21.8)	600 (19.0)	446 (21.7)
E	1,595 (10.3)	579 (9.5)	217 (9.9)	458 (11.0)	341 (11.3)	2,192 (10.1)	1,301 (10.2)	352 (9.4)	343 (10.8)	196 (9.5)
F	3,031 (19.6)	1,234 (20.3)	407 (18.6)	803 (19.2)	587 (19.4)	2,484 (11.4)	1,489 (11.7)	364 (9.7)	410 (13.0)	221 (10.7)
G	1,848 (11.9)	706 (11.6)	242 (11.1)	554 (13.3)	346 (11.5)	3,427 (15.8)	2,060 (16.1)	577 (15.4)	463 (14.6)	327 (15.9)
H	832 (5.4)	332 (5.5)	126 (5.8)	204 (4.9)	170 (5.6)	1,335 (16.1)	810 (6.3)	223 (6.0)	183 (5.8)	119 (5.8)
I	1,076 (7.0)	435 (7.1)	117 (5.4)	350 (8.4)	174 (5.8)	1,459 (6.7)	826 (6.5)	226 (6.0)	251 (7.9)	156 (7.6)
Lateralisation ⁴										
Left	8,131 (52.6)	3,218 (52.8)	1,154 (52.8)	2,220 (53.2)	1,539 (51.0)	11,244 (51.7)	6,603 (51.7)	1,946 (52.0)	1,601 (50.6)	1,094 (53.1)
Right	7,340 (47.4)	2,874 (47.2)	1,031 (47.2)	1,954 (46.8)	1,481 (49.0)	10,489 (48.3)	6,164 (48.3)	1,795 (48.0)	1,564 (49.4)	966 (46.9)
Unknown	2 (0.0)				2 (0.1)	1 (0.0)	1 (0.0)			
Sublocalisation ¹²³⁴⁵										
Outer quadrants	7,037 (45.5)	2,715 (44.6)	1,039 (47.6)	1,811 (43.4)	1,472 (48.7)	11,574 (53.3)	6,613 (51.8)	2,080 (55.6)	1,699 (53.7)	1,182 (57.4)
Inner quadrants	2,780 (18.0)	1,223 (20.1)	340 (15.6)	798 (19.1)	419 (13.9)	4,711 (21.7)	3,003 (23.5)	669 (17.9)	680 (21.5)	359 (17.4)
Central portion	1,378 (8.9)	492 (8.1)	202 (9.2)	378 (9.1)	306 (10.1)	1,095 (5.0)	620 (4.9)	227 (6.1)	140 (4.4)	108 (5.2)
Overlapping lesions	3,918 (25.3)	1,490 (24.5)	548 (25.1)	1,105 (26.5)	775 (25.7)	4,036 (18.6)	2,319 (18.2)	723 (19.3)	614 (19.4)	380 (18.5)
Unknown	360 (2.3)	172 (2.8)	56 (2.6)	82 (2.0)	50 (1.7)	318 (1.5)	213 (1.7)	42 (1.1)	32 (1.0)	31 (1.5)
Histological tumour type ¹²³⁴⁵										
Ductal	11,987 (77.5)	4,804 (78.9)	1,777 (81.3)	3,061 (73.3)	2,345 (77.6)	17,876 (82.3)	10,388 (81.4)	3,199 (85.5)	2,533 (80.0)	1,756 (85.2)
Lobular	1,830 (11.8)	605 (9.9)	212 (9.7)	616 (14.8)	397 (13.1)	1,730 (8.0)	1,038 (8.1)	246 (6.6)	293 (9.3)	153 (7.4)
Mixed	874 (5.7)	347 (5.7)	140 (6.4)	195 (4.7)	192 (6.4)	798 (3.7)	423 (3.3)	177 (4.7)	111 (3.5)	87 (4.2)
Other	782 (5.1)	336 (5.5)	56 (2.6)	302 (7.2)	88 (2.9)	1,330 (6.1)	919 (7.2)	119 (3.2)	228 (7.2)	64 (3.1)

Supplementary Table 2. (continued)

Characteristics	Mastectomy		Breast-conserving surgery plus radiotherapy							
	Overall (N = 15,473)	T1N0 (N = 6,092)	T1N1 (N = 2,185)	T2N0 (N = 4,174)	T2N1 (N = 3,022)	Overall (N = 21,734)	T1N0 (N = 12,768)	T1N1 (N = 3,741)	T2N0 (N = 3,165)	T2N1 (N = 2,060)
Differentiation ¹²³⁴										
Grade I	2,365 (15.3)	1,270 (20.9)	384 (17.6)	440 (10.5)	271 (9.0)	4,821 (22.2)	3,479 (27.3)	787 (21.0)	337 (10.7)	218 (10.6)
Grade II	6,275 (40.6)	2,526 (41.5)	892 (40.8)	1,643 (39.4)	1,214 (40.2)	8,681 (39.9)	5,067 (39.7)	1,633 (43.7)	1,142 (36.1)	839 (40.7)
Grade III	4,602 (29.7)	1,327 (21.8)	615 (28.2)	1,527 (36.6)	1,133 (37.5)	5,343 (24.6)	2,424 (18.9)	860 (23.0)	1,297 (41.0)	762 (37.0)
Unknown	2,231 (14.4)	969 (15.9)	294 (13.5)	564 (13.5)	404 (13.4)	2,889 (13.3)	1,798 (14.1)	461 (12.3)	389 (12.3)	241 (11.7)
Tumour size (mm) ¹²³⁴⁵										
Median (IQR)	20 (14-27)	14 (10-17)	15 (12-18)	27 (24-32)	28 (25-35)	15 (11-20)	12 (9-15)	15 (12-17)	25 (22-29)	25 (22-29)
Unknown	6,013 (38.9)	2,489 (40.9)	835 (38.2)	1,614 (38.7)	1,075 (35.6)	7,773 (35.8)	4,630 (36.3)	1,310 (35.0)	1,137(35.9)	696 (33.8)
Number of positive nodes ¹³⁵										
Median (IQR)	0 (0-1)	0 (0-0)	1 (1-2)	0 (0-0)	1 (1-2)	0 (0-1)	0 (0-0)	1 (1-2)	0 (0-0)	1 (1-2)
Unknown	57 (0.4)		22 (1.0)		35 (1.2)	37 (0.2)		23 (0.6)		14 (0.7)
Multifocality ¹²³⁴⁵										
Yes	1,594 (10.3)	666 (10.9)	297 (13.6)	332 (8.0)	299 (9.9)	434 (2.0)	250 (2.0)	82 (2.2)	62 (2.0)	897 (43.5)
No	5,721 (37.0)	2,198 (36.1)	711 (32.5)	1,618 (38.8)	1,193 (39.5)	9,416 (43.3)	5,543 (43.4)	1,530 (40.9)	1,446 (45.7)	
Unknown	8,158 (52.7)	3,228 (53.0)	1,177 (53.9)	2,224 (53.3)	1,529 (50.6)	11,884 (54.7)	6,975 (54.6)	2,129 (56.9)	1,660 (52.4)	1,123 (54.5)
Hormone receptor status ¹²⁴⁵										
ER and PR +	3,946 (25.5)	1,522 (25.0)	627 (28.7)	957 (22.9)	840 (27.8)	6,464 (29.7)	3,855 (30.2)	1,200 (32.1)	786 (24.8)	623 (30.2)
ER or PR+	1,029 (6.7)	410 (6.7)	131 (6.0)	259 (6.2)	229 (7.6)	1,423 (6.6)	840 (6.6)	225 (6.0)	237 (7.5)	121 (5.9)
ER and PR -	1,127 (7.3)	345 (5.7)	124 (5.7)	402 (9.6)	256 (8.5)	1,561 (7.2)	772 (6.1)	199 (5.3)	411 (13.0)	179 (8.7)

Supplementary Table 2. (continued)

	Mastectomy		Breast-conserving surgery plus radiotherapy							
	Overall	T1N0	T1N1	T2N0	T2N1	Overall	T1N0	T1N1	T2N0	T2N1
Characteristics	(N = 15,473)	(N = 6,092)	(N = 2,185)	(N = 4,174)	(N = 3,022)	(N = 21,734)	(N = 12,768)	(N = 3,741)	(N = 3,165)	(N = 2,060)
Unknown	9,371 (60.6)	3,815 (62.6)	1,303 (59.6)	2,556 (61.2)	1,697 (56.2)	12,286 (56.5)	7,301 (57.2)	2,117 (56.6)	1,731 (54.7)	1,137 (55.2)
Adjuvant systemic therapy ¹²³⁴⁵										
No	7,505 (48.5)	4,853 (79.7)	330 (15.1)	1,984 (47.5)	338 (11.2)	12,145 (55.9)	10,128 (79.3)	472 (12.6)	1,407 (44.5)	138 (6.7)
Hormonal therapy	4,017 (26.0)	650 (10.7)	934 (42.8)	1,149 (27.5)	1,284 (42.5)	3,834 (17.6)	1,064 (8.3)	1,475 (39.5)	620 (19.6)	674 (32.7)
Chemotherapy	1,864 (12.1)	357 (5.9)	346 (15.8)	630 (15.1)	531 (17.6)	2,778 (12.8)	962 (7.5)	619 (16.6)	725 (22.9)	472 (22.9)
Both	2,087 (13.5)	232 (3.8)	575 (26.3)	411 (9.9)	869 (28.8)	2,977 (13.7)	614 (4.8)	1,174 (31.4)	413 (13.1)	776 (37.7)
Axillary lymph node dissection ¹²³⁴⁵										
Yes	10,987 (71.0)	3,348 (55.0)	2,082 (95.3)	2,647 (63.4)	2,910 (96.3)	9,852 (45.3)	3,734 (29.2)	3,321 (88.8)	921 (29.1)	1,876 (91.1)
No	4,486 (29.0)	2,744 (45.0)	103 (4.7)	1,527 (36.6)	112 (3.7)	11,882 (54.7)	9,034 (70.8)	420 (11.2)	2,244 (70.9)	184 (8.9)

Numbers are N (%) unless otherwise specified. Abbreviations: SES: social economic status; ER: oestrogen receptor; PR: progesterone receptor; IQR: interquartile range.

¹ = significant difference between treatment groups in overall analysis, $p < 0.1$;

² = significant difference between treatment groups in T1N0 analysis, $p < 0.1$;

³ = significant difference between treatment groups in T1N1 analysis, $p < 0.1$;

⁴ = significant difference between treatment groups in T2N0 analysis, $p < 0.1$;

⁵ = significant difference between treatment groups in T2N1 analysis, $p < 0.1$

Supplementary Table 3. Baseline characteristics of T1-2N0-1 staged breast cancer patients according to type of surgery in the 2003 cohort (N = 7,552)

Characteristics	Mastectomy					Breast-conserving surgery plus radiotherapy				
	Overall (N = 2,905)	T1N0 (N = 1,130)	T1N1 (N = 388)	T2N0 (N = 772)	T2N1 (N = 615)	Overall (N = 4,647)	T1N0 (N = 2,761)	T1N1 (N = 738)	T2N0 (N = 704)	T2N1 (N = 444)
Age ¹²³⁴⁵										
<40	189 (6.5)	59 (5.2)	34 (8.8)	49 (6.4)	47 (7.6)	236 (5.1)	105 (3.8)	39 (5.3)	52 (7.4)	40 (9.0)
40-49	528 (18.2)	170 (15.0)	94 (24.2)	120 (15.5)	144 (23.4)	916 (19.7)	462 (16.7)	167 (22.6)	171 (24.3)	116 (26.1)
50-59	630 (21.7)	267 (23.6)	99 (25.5)	138 (17.9)	126 (20.5)	1,641 (35.3)	971 (35.2)	265 (35.9)	226 (32.1)	179 (40.3)
60-69	559 (19.2)	282 (25.0)	58 (15.0)	128 (16.6)	91 (14.8)	1,144 (24.6)	729 (26.4)	199 (27.0)	155 (22.0)	61 (13.7)
70-79	593 (20.4)	247 (21.9)	68 (17.5)	175 (22.7)	103 (16.8)	621 (13.4)	449 (16.3)	59 (8.0)	74 (10.5)	39 (8.8)
>79	406 (14.0)	105 (9.3)	35 (9.0)	162 (21.0)	104 (16.9)	89 (1.9)	45 (1.6)	9 (1.2)	26 (3.7)	9 (2.0)
SES ¹³⁴⁵										
Low	920 (31.7)	351 (31.1)	116 (29.9)	260 (33.7)	193 (31.4)	1,347 (29.0)	793 (28.7)	202 (27.4)	226 (32.1)	126 (28.4)
Medium	1,165 (40.1)	470 (41.6)	156 (40.2)	277 (35.9)	262 (42.6)	1,849 (39.8)	1,113 (40.3)	302 (40.9)	254 (36.1)	180 (40.5)
High	820 (28.2)	309 (27.4)	116 (29.9)	235 (30.4)	160 (26.0)	1,451 (31.2)	855 (31.0)	234 (31.7)	224 (31.8)	138 (31.1)
Hospital volume (patients per year) ¹²³⁴⁵										
0-49	509 (17.5)	215 (19.0)	64 (16.5)	118 (15.3)	112 (18.2)	848 (18.3)	512 (18.5)	132 (17.9)	116 (16.5)	88 (19.8)
50-99	1,424 (49.0)	547 (48.4)	194 (50.0)	388 (50.3)	295 (48.0)	2,114 (45.5)	1,274 (46.1)	339 (45.9)	322 (45.7)	179 (40.3)
100-149	602 (20.7)	209 (18.5)	73 (18.8)	174 (22.5)	146 (23.7)	1,057 (22.8)	606 (22.0)	175 (23.7)	171 (24.3)	105 (23.7)
>149	370 (12.7)	159 (14.1)	57 (14.7)	92 (11.9)	62 (10.1)	628 (13.5)	369 (13.4)	92 (12.5)	95 (13.5)	72 (16.2)
Region ¹²³⁴⁵										
A	363 (12.5)	137 (12.1)	39 (10.1)	111 (14.4)	76 (12.4)	644 (13.9)	392 (14.2)	90 (12.2)	97 (13.8)	65 (14.6)
B	279 (9.6)	117 (10.4)	34 (8.8)	70 (9.1)	58 (9.4)	356 (7.7)	215 (7.8)	49 (6.6)	65 (9.2)	27 (6.1)
C	201 (6.9)	75 (6.6)	26 (6.7)	47 (6.1)	53 (8.6)	389 (8.4)	219 (7.9)	83 (11.3)	51 (7.2)	36 (8.1)
D	489 (16.8)	189 (16.7)	79 (20.4)	118 (15.3)	103 (16.8)	905 (19.5)	522 (18.9)	160 (21.7)	128 (18.2)	95 (21.4)
E	294 (10.1)	112 (9.9)	43 (11.1)	73 (9.5)	66 (10.7)	496 (10.7)	288 (10.4)	80 (10.8)	84 (11.9)	44 (9.9)
F	540 (18.6)	217 (19.2)	74 (19.1)	139 (18.0)	110 (17.9)	525 (11.3)	311 (11.3)	74 (10.0)	92 (13.1)	48 (10.8)
G	379 (13.1)	144 (12.7)	45 (11.6)	112 (14.5)	78 (12.7)	767 (16.5)	473 (17.1)	118 (16.0)	103 (14.6)	73 (16.4)
H	160 (5.5)	66 (5.8)	24 (6.2)	34 (4.4)	36 (5.9)	236 (5.1)	147 (5.3)	39 (5.3)	28 (4.0)	22 (5.0)
I	200 (6.9)	73 (6.5)	24 (6.2)	68 (8.8)	35 (5.7)	329 (7.1)	194 (7.0)	45 (6.1)	56 (8.0)	34 (7.7)

Supplementary Table 3. (continued)

Characteristics	Mastectomy		Breast-conserving surgery plus radiotherapy							
	Overall (N = 2,905)	T1N0 (N = 1,130)	T1N1 (N = 388)	T2N0 (N = 772)	T2N1 (N = 615)	Overall (N = 4,647)	T1N0 (N = 2,761)	T1N1 (N = 738)	T2N0 (N = 704)	T2N1 (N = 444)
Lateralisation ⁴										
Left	1,561 (53.7)	635 (56.2)	207 (53.4)	406 (52.6)	313 (50.9)	2,423 (52.1)	1,424 (51.6)	389 (52.7)	370 (52.6)	240 (54.1)
Right	1,344 (46.3)	495 (43.8)	181 (46.7)	366 (47.4)	302 (49.1)	2,224 (47.9)	1,337 (48.4)	349 (47.3)	334 (47.4)	204 (46.0)
Sublocalisation ¹²³⁴⁵										
Outer quadrants	1,344 (46.3)	510 (45.1)	201 (51.8)	332 (43.0)	301 (48.9)	2,447 (52.7)	1,422 (51.5)	396 (53.7)	366 (52.0)	263 (59.2)
Inner quadrants	546 (18.8)	254 (22.5)	53 (13.7)	152 (19.7)	87 (14.2)	1,042 (22.4)	672 (24.3)	146 (19.8)	164 (23.3)	60 (13.5)
Central portion	276 (9.5)	94 (8.3)	42 (10.8)	76 (9.8)	64 (10.4)	246 (5.3)	127 (4.6)	56 (7.6)	38 (5.4)	25 (5.6)
Overlapping lesions	697 (24.0)	254 (22.5)	84 (21.7)	200 (25.9)	159 (25.9)	859 (18.5)	507 (18.4)	130 (17.6)	132 (18.8)	90 (20.3)
Unknown	42 (1.5)	18 (1.6)	8 (2.1)	12 (1.6)	4 (0.7)	53 (1.1)	33 (1.2)	10 (1.4)	4 (0.6)	6 (1.4)
Histological tumour type ¹²³⁴⁵										
Ductal	2,267 (78.0)	883 (78.1)	331 (85.3)	553 (71.6)	500 (81.3)	3,809 (82.0)	2,233 (80.9)	633 (85.8)	565 (80.3)	378 (85.1)
Lobular	365 (12.6)	134 (11.8)	27 (7.0)	130 (16.8)	75 (12.2)	384 (8.3)	234 (8.5)	49 (6.6)	68 (9.7)	33 (7.4)
Mixed	123 (4.2)	45 (4.0)	22 (5.7)	28 (3.6)	28 (4.6)	170 (3.7)	88 (3.2)	38 (5.2)	26 (3.7)	18 (4.1)
Other	150 (5.2)	69 (6.1)	8 (2.1)	61 (7.9)	12 (2.0)	284 (6.1)	206 (7.5)	18 (2.4)	45 (6.4)	15 (3.4)
Differentiation ¹²³⁴										
Grade I	500 (17.2)	264 (23.4)	67 (17.3)	100 (13.0)	69 (11.2)	1,160 (25.0)	848 (30.7)	177 (24.0)	89 (12.6)	46 (10.4)
Grade II	1,230 (42.3)	487 (43.1)	174 (44.9)	321 (41.6)	248 (40.3)	1,839 (39.6)	1,084 (39.3)	319 (43.2)	246 (34.9)	190 (42.8)
Grade III	916 (31.5)	266 (23.5)	119 (30.7)	288 (37.3)	242 (39.5)	1,238 (26.6)	579 (21.0)	181 (24.5)	305 (43.3)	173 (39.0)
Unknown	259 (8.9)	113 (10.0)	28 (7.2)	63 (8.2)	55 (8.9)	410 (8.8)	250 (9.1)	61 (8.3)	64 (9.1)	35 (7.9)
Tumour size (mm) ¹²³⁴⁵										
Median (IQR)	20 (14-26)	14 (10-17)	15 (12-18)	26 (24-32)	28 (25-35)	11 (15-20)	12 (10-16)	15 (12-17)	25 (22-28)	25 (22-30)
Unknown	134 (4.6)	67 (5.9)	18 (4.6)	25 (3.2)	24 (3.9)	194 (4.2)	115 (4.2)	33 (4.5)	26 (3.7)	20 (4.5)
Number of positive nodes ¹³⁵										
Median (IQR)	0 (0-1)	0 (0-0)	1 (1-2)	0 (0-0)	1 (1-2)	0 (0-1)	0 (0-0)	1 (1-2)	0 (0-0)	1 (1-2)
Unknown	19 (0.7)	14 (1.2)	1 (0.3)	3 (0.4)	1 (0.2)	31 (0.7)	21 (0.8)	1 (0.1)	9 (1.3)	

Supplementary Table 3. (continued)

	Mastectomy					Breast-conserving surgery plus radiotherapy				
Characteristics	Overall (N = 2,905)	T1N0 (N = 1,130)	T1N1 (N = 388)	T2N0 (N = 772)	T2N1 (N = 615)	Overall (N = 4,647)	T1N0 (N = 2,761)	T1N1 (N = 738)	T2N0 (N = 704)	T2N1 (N = 444)
Multifocality ¹²³⁴⁵										
Yes	489 (16.8)	200 (17.7)	91 (23.5)	98 (12.7)	100 (16.3)	129 (2.8)	71 (2.6)	18 (2.4)	32 (4.6)	8 (1.8)
No	2,234 (76.9)	853 (75.5)	271 (69.9)	631 (81.7)	479 (77.9)	4,170 (89.7)	2,474 (89.6)	663 (89.8)	635 (90.2)	398 (89.6)
Unknown	182 (6.3)	77 (6.8)	26 (6.7)	43 (5.6)	36 (5.9)	348 (7.5)	216 (7.8)	57 (7.7)	37 (5.3)	38 (8.6)
Hormone receptor status ¹²⁴⁵										
ER and PR +	1,758 (60.5)	695 (61.5)	263 (67.8)	441 (57.1)	359 (58.4)	3,061 (65.9)	1,856 (67.2)	536 (72.6)	380 (54.0)	289 (65.1)
ER or PR+	509 (17.5)	201 (17.8)	69 (17.8)	128 (16.6)	111 (18.1)	701 (15.1)	411 (14.9)	112 (15.2)	122 (17.3)	56 (12.6)
ER and PR -	542 (18.7)	184 (16.3)	51 (13.1)	178 (23.1)	129 (21.0)	732 (15.8)	377 (13.7)	79 (10.7)	186 (26.4)	90 (20.3)
Unknown	96 (3.3)	50 (4.4)	5 (1.3)	25 (3.2)	16 (2.6)	153 (3.3)	117 (4.2)	11 (1.5)	16 (2.3)	9 (2.0)
Adjuvant systemic therapy ¹²³⁴⁵										
No	1,385 (47.7)	891 (78.9)	62 (16.0)	369 (47.8)	63 (10.2)	2,559 (55.1)	2,152 (77.9)	98 (13.3)	287 (40.8)	22 (5.0)
Hormonal therapy	676 (23.3)	112 (9.9)	126 (32.5)	194 (25.1)	244 (39.7)	707 (15.2)	218 (7.9)	250 (33.9)	130 (18.5)	109 (24.6)
Chemotherapy	315 (10.8)	75 (6.6)	41 (10.6)	103 (13.3)	96 (15.6)	507 (10.9)	200 (7.2)	72 (9.8)	150 (21.3)	85 (19.1)
Both	529 (18.2)	52 (4.6)	159 (41.0)	106 (13.7)	212 (34.5)	874 (18.8)	191 (6.9)	318 (43.1)	137 (19.5)	228 (51.4)
Axillary lymph node dissection ¹²³⁴⁵										
Yes	1,864 (64.2)	479 (42.4)	376 (96.9)	416 (53.9)	593 (96.4)	1,716 (36.9)	520 (18.8)	647 (87.7)	136 (19.3)	413 (93.0)
No	1,041 (35.8)	651 (57.6)	12 (3.1)	356 (46.1)	22 (3.6)	2,931 (63.1)	2,241 (81.2)	91 (12.3)	568 (80.7)	31 (7.0)

Numbers are N (%) unless otherwise specified. Abbreviations: SES: social economic status; ER: oestrogen receptor; PR: progesterone receptor; IQR: interquartile range.

¹ = significant difference between treatment groups in overall analysis, $p < 0.1$;

² = significant difference between treatment groups in T1N0 analysis, $p < 0.1$;

³ = significant difference between treatment groups in T1N1 analysis, $p < 0.1$;

⁴ = significant difference between treatment groups in T2N0 analysis, $p < 0.1$;

⁵ = significant difference between treatment groups in T2N1 analysis, $p < 0.1$

Supplementary Table 4. Hazard ratios of 10-year distant metastasis-free survival in the 2003 cohort (N = 7,552), with different starting points of follow-up.

	Follow-up calculated from last date of surgery		Follow-up calculated from date of diagnosis	
	Adjusted HR [95%CI]	p-value	Adjusted HR [95%CI]	p-value
Overall cohort				
Mastectomy	1		1	
Breast-conserving surgery plus radiotherapy	0.88 [0.77-1.01]	0.070	0.88 [0.77-1.02]	0.081
Subgroups				
T1N0				
Mastectomy	1		1	
Breast-conserving surgery plus radiotherapy	0.74 [0.58-0.94]	0.014	0.75 [0.59-0.96]	0.021
T1N1				
Mastectomy	1		1	
Breast-conserving surgery plus radiotherapy	1.00 [0.71-1.42]	0.994	1.00 [0.71-1.43]	0.965
T2N0				
Mastectomy	1		1	
Breast-conserving surgery plus radiotherapy	0.94 [0.72-1.23]	0.644	0.95 [0.72-1.25]	0.711
T2N1				
Mastectomy	1		1	
Breast-conserving surgery plus radiotherapy	0.95 [0.73-1.224]	0.718	0.95 [0.73-1.23]	0.694

p-values depicted in bold are considered significant ($p < 0.025$). ^a = corrected for region, sublocalisation, histological tumour type, differentiation grade, tumour size (mm), number of positive lymph nodes, hormone receptor status, adjuvant systemic therapy. ^b = corrected for age, sublocalisation, histological tumour type, differentiation grade, tumour size (mm), hormone receptor status, adjuvant systemic therapy. ^c = corrected for region, differentiation grade, tumour size (mm). ^d = corrected for age, sublocalisation, histological tumour type, differentiation grade. ^e = corrected for sublocalisation, tumour size (mm), hormone receptor status. Abbreviations: N = number of patients; HR: hazard ratio; CI: confidence interval; EMR: excess mortality ratio.

Supplementary Figure 1. Cumulative 10-year overall survival in T1-2N0-1 staged breast cancer patients in the 2003 cohort, in every T and N subgroup (N = 7,552). A = Cumulative 10-year overall survival for breast-conserving surgery plus radiotherapy compared to mastectomy in the whole cohort; B = Cumulative 10-year overall survival for T1N0, T1N1, T2N0, T2N1 subgroups separately, independent of type of surgery; C = Cumulative 10-year overall survival for breast-conserving surgery plus radiotherapy compared to mastectomy in the T1N0 subgroup, in the T1N1 subgroup (D), in the T2N0 subgroup (E), and in the T2N1 subgroup (F). Breast-conserving* = Breast-conserving surgery plus radiotherapy.

7

Attending the breast screening programme after breast cancer treatment: a population- based study

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ABSTRACT

Introduction

In the Netherlands, breast cancer patients are treated and followed at least 5 years after diagnosis. Furthermore, all women aged 50–74 are invited biennially for mammography by the nationwide screening programme. The relation between the outpatient follow-up (follow-up visits in the outpatient clinic for 5 years after treatment) and the screening programme is not well established and attending the screening programme as well as outpatient follow-up is considered undesirable. This study evaluates potential factors influencing women to attend the screening programme during their outpatient follow-up (overlap) and the (re-)attendance to the screening programme after 5 years of outpatient follow-up.

Methods

Data of breast cancer patients aged 50–74 years, treated for primary breast cancer between 1996 and 2007 were selected from the Netherlands Cancer Registry and linked to the Netherlands Breast Cancer Screening Programme in the Northern region. Cox regression analyses were used to study women (re-)attending the screening programme over time, possible overlap with the outpatient follow-up and factors influencing this.

Results

In total 11,227 breast cancer patients were included, of whom 19% attended the screening programme after breast cancer treatment, 4.4% within 5 years and 15.4% after more than 5 years. Factors that independently influenced attendance within 5 years as well as more than 5 years after treatment were: interval tumours (HR: 0.77; 95%CI: 0.61–0.97 and HR: 0.69; 95%CI: 0.53–0.88, Ref: screen-detected tumours), receiving adjuvant radiotherapy (HR: 0.65; 95%CI: 0.47–0.90 and HR: 0.66; 95%CI: 0.47–0.93; Ref: none) and diagnosis of in situ tumours (HR: 1.67; 95%CI: 1.25–2.23 and HR: 1.39; 95%CI: 1.05–1.85; Ref: stage I tumours). Non-screen related tumours (HR: 0.41; 95%CI: 0.29–0.58) and recent diagnosis (HR: 0.89 per year; 95%CI: 0.86–0.92) were only associated with attendance within 5 years after treatment.

Conclusion

The interrelation between outpatient follow-up and screening should be improved to avoid overlap and low attendance to the screening programme after outpatient follow-up. Breast cancer patients should be informed that attending the screening programme during the outpatient follow-up is not necessary.

INTRODUCTION

Breast cancer is the most common type of cancer in women in the Netherlands, with an incidence of 16,000 new cases in 2011 (www.cancerregistry.nl) [1]. In the Netherlands a population-based breast cancer screening programme has been fully implemented since 1996. Women aged 50–74 (70–74 since 1999) are invited biennially for mammography [2]. Due to the implementation of this screening programme, breast cancer is diagnosed at an earlier stage. Together with improved treatment options, this has led to an increasing number of women surviving 5 years and more after diagnosis. Although the optimal follow-up after breast cancer treatment is still unknown, women frequently attend scheduled outpatient follow-up visits (follow-up visits in the outpatient clinic for 5 years after treatment), including mammography [3–10].

Women attending outpatient follow-up after breast cancer diagnosis aged 50–74 can also attend the screening programme which is considered undesirable. In the guideline for breast cancer, recommendations are given about outpatient follow-up after treatment of breast cancer for the first 5 years [11]. These visits focus on wound healing, adverse effects of the treatment, the need for psychosocial care and the early detection of second primary tumours. From the revision of 2008 onwards, the Dutch guideline for breast cancer states that breast cancer patients treated with mastectomy could, after 5 years of outpatient follow-up and then 60–74 years of age, be referred to the screening programme [12]. Nevertheless, little is known about the relation between the outpatient follow-up and the attendance to the screening programme after treatment for breast cancer, and which factors influence the screening participation.

The objective of this population-based study was to determine whether breast cancer patients attended the screening programme during their outpatient follow-up (overlap) and the (re-)attendance to the screening programme after more than 5 years of outpatient follow-up, and which factors (method of detection, tumour characteristics and primary and adjuvant treatment) influenced this attendance.

PATIENTS AND METHODS

Patients

Women with breast cancer were selected from the population-based Netherlands Cancer Registry (NCR) of the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR contains data on patient and tumour characteristics, stage and treatment of all newly

diagnosed malignancies [13]. The Netherlands Breast Cancer Screening Programme invites women 50–74 years of age (70–74 since 1999). All women aged 50–74 at the time of their first invasive or in situ breast cancer between 1996 and 2007 were selected (N = 12,010). Women with metastases at diagnosis (N = 497) and women without primary treatment (N = 46) were excluded, as well as women with bilateral mastectomy (N = 240). In total 11,227 women were included in this study. For the analyses of women attending the screening programme after more than 5 years of outpatient follow-up, women aged 50–69, diagnosed between 1996 and 2004, not attending screening within 5 years after treatment were included (N = 6,251).

Relation to screening

Data of the NCR were merged with the data of the Netherlands Breast Cancer Screening Programme, region North, covering an area of 3.3 million inhabitants comprising 1.6 million women. Thereafter only data from the NCR covering the same area as the screening programme were selected, to ensure that all breast cancer patients had the chance to be invited by the Netherlands Breast Cancer Screening Programme, region North. Dutch legislation states that the breast screening programme is obliged to invite all women aged 50–74 (70–74 since 1999), even after breast cancer treatment. Women do have the option to return a non-attender form on which they can state that they are in follow-up after breast cancer treatment in the hospital. The data of the screening programme include the date of attendance and the screening result. Three groups were defined: the first group comprised of women with a suspect mammography by breast cancer screening who were subsequent diagnosed with breast cancer within 12 months (“screen-detected tumour”). The second group comprised of women who developed breast cancer within 24 months after a normal mammogram by breast screening (“interval tumour”). The third group comprised of women with breast cancer without a relation to the screening programme (“non-screen related tumours”). This group included women who never attended the screening programme before their breast cancer diagnosis and women diagnosed with breast cancer more than 24 months after the last biennial screening mammography. Data until 31 December 2009 were available.

Statistical analysis

Chi-squared analysis was used to compare categorical variables. The time period between diagnosis and attendance to the screening programme was defined as the date of pathological confirmation and the first screen mammography afterwards. Patients were censored at the date of a new primary breast tumour, death, date when a woman reached the age of 75, or end of the study period (31 December 2009). The percentage of

women attending the screening programme was calculated using Kaplan Meijer analysis. Multivariable Cox regression analyses were used to identify independent prognostic factors for the chance of attending the screening programme. Factors considered were: age, year of diagnosis, stage, type of surgery and adjuvant therapy (radio-, chemo- and/or endocrine). Analyses were performed using the STATA software package, version 12.0 for Windows (Stata Corporation LP, College Station, TX, USA).

RESULTS

Attendance to the screening programme within 5 years after treatment

In total 11,227 breast cancer patients were included in the study and tumour and treatment characteristics are shown in Table 1. In total 19% attended the screening programme after breast cancer treatment. Of 11,227 breast cancer patients, 4.4% attended the screening programme within 5 years after treatment. Of the screen-detected cases, 5.2% attended the screening programme within 5 years. Furthermore, 4.0% of women with an interval tumour and 2.7% of women with a non-screen related tumour attended the screening programme within 5 years after treatment. Figure 1a shows the results of multivariable analysis for attending screening within 5 years after treatment. Breast cancer patients with interval and non-screen related cancer attended the screening programme after breast cancer treatment less often than breast cancer patients with screen-detected tumours (HR: 0.77; 95%CI: 0.61–0.97 and HR:0.41; 95%CI: 0.29–0.58 resp.; Table 2), as well as later year of diagnosis (HR: 0.89 per year; 95%CI: 0.86–0.92) and breast cancer patients who received adjuvant radiotherapy (HR: 0.65; 95%CI: 0.47–0.90 compared to patients without adjuvant radiotherapy). Breast cancer patients with in situ tumours (HR: 1.67; 95%CI: 1.25–2.23) were more likely to attend the screening programme than patients with stage I tumours.

Table 1. Characteristics of the total study population

	Total (N = 11,227)	
	N	(%)
Detection		
Screen-detected	6,002	53.5
Interval	3,328	29.6
Non-screen related ^a	1,897	16.9
Age at diagnosis		
50-54	2,595	23.1
55-59	2,310	20.6
60-64	2,222	19.8
65-69	2,117	18.9
70-74	1,983	17.7
Year of diagnosis		
1996-1998	1,757	15.6
1999-2001	2,831	25.2
2002-2004	2,926	26.1
2005-2007	3,213	28.6
Stage		
Stage I	4,772	42.5
Stage II	4,303	38.3
Stage III	969	8.6
In-Situ	1,183	10.5
Surgery		
BCS	6,315	56.2
Mastectomy	4,706	41.9
Other	206	1.8
Radiotherapy		
No	3,953	35.2
Yes	7,274	64.8
Chemotherapy		
No	8,922	79.5
Yes	2,305	20.5
Endocrine therapy		
No	7,630	68.0
Yes	3,597	32.0
Hospital type		
Non-teaching	5,282	47.0
Teaching	5,945	53.0

^a non-screen related tumours include women who never attended the screening programme, and women diagnosed with breast cancer more than 24 months after the last screen
Abbreviation: BCS: breast-conserving surgery

Table 2. Hazard ratios (HR) and associated 95% Confidence Intervals (CI) for attending screening within 5 years after breast cancer treatment and more than 5 years after treatment.

	attending screening <5 years					attending screening ≥ 5 years				
	N	HR	95%CI		p-value	N	HR	95%CI		p-value
Detection					<0.001					0.014
Screen-detected	6,002	Ref.				3,353	Ref.			
Interval	3,328	0.77	0.61	0.97	0.026	1,862	0.69	0.53	0.88	0.004
Non-screen related	1,897	0.41	0.29	0.58	<0.001	1,036	0.91	0.70	1.18	0.478
Age										
by year	11,227	0.99	0.97	1.00	0.133	6,251	1.01	0.99	1.03	0.227
Year of diagnosis										
by year	11,227	0.89	0.86	0.92	<0.001	6,251	1.00	0.95	1.05	0.882
Stage					0.002					0.015
Stage I	4,772	Ref.				2,584	Ref.			
Stage II	4,303	1.17	0.87	1.56	0.300	2,567	0.76	0.57	1.02	0.065
Stage III	969	1.69	1.01	2.82	0.044	480	0.82	0.40	1.67	0.582
In-Situ	1,183	1.67	1.25	2.23	0.001	620	1.39	1.05	1.85	0.021
Surgery					0.413					0.095
BCS	6,315	Ref.				3,400	Ref.			
Mastectomy	4,706	0.90	0.65	1.25	0.539	2,731	0.79	0.56	1.11	0.175
Other	206	1.37	0.68	2.78	0.381	120	0.15	0.02	1.12	0.065
Radiotherapy										
No	3,953	Ref.				2,248	Ref.			
Yes	7,274	0.65	0.47	0.90	0.009	4,003	0.66	0.47	0.93	0.017
Chemotherapy										
No	8,922	Ref.				4,959	Ref.			
Yes	2,305	0.96	0.69	1.34	0.798	1,292	0.72	0.49	1.07	0.107
Endocrine therapy										
No	7,630	Ref.				4,356	Ref.			
Yes	3,597	0.88	0.67	1.17	0.389	1,895	1.14	0.85	1.54	0.391

Abbreviation: BCS: breast-conserving surgery

Figure 1. Factors influencing the attendance to the screening programme for (a) attending screening < 5 year after treatment and (b) attending screening ≥ 5 year after treatment, multivariable Cox regression analyses.

Attendance to the screening programme after more than 5 years after treatment

Of 6,251 women, 15.4% attended the screening programme more than 5 years after treatment. Of women with screen-detected tumours 15.4% of patients attended the screening programme more than 5 years after treatment, compared to 13.0% and 18.3% women with an interval tumour and women with a non-screen related tumour, respectively. In multivariable analysis for attending screening more than 5 years after treatment, breast cancer patients with interval tumours attended the screening programme after breast cancer treatment less often than breast cancer patients with screen-detected tumours (HR: 0.69; 95%CI: 0.53–0.88; Table 2; Figure 1b). Furthermore, breast cancer patients who received adjuvant radiotherapy attended less often than patients without adjuvant radiotherapy (HR: 0.66; 95%CI: 0.47–0.93). Breast cancer patients with in situ tumours (HR: 1.39; 95%CI: 1.05–1.85) were more likely to attend the screening programme more than 5 years after treatment than patients with stage I tumours.

DISCUSSION

Of the breast cancer patients, 4.4% attended the breast screening programme within 5 years after breast cancer treatment, followed by another 15.4% of patients attending the programme more than 5 years after treatment. Factors associated with a lower attendance to the screening programme within 5 years after treatment were interval tumours and non-screen related tumours (compared to screen-detected tumours), higher age, later year of diagnosis, and receiving adjuvant radiotherapy (compared to none). Diagnosis with in situ tumours was related to a higher attendance to the screening programme compared to women with stage I tumours. Breast cancer patients with interval tumours and patients who received adjuvant radiotherapy were also less likely to attend the screening programme more than 5 years after treatment, patients with in situ tumours were more likely to attend.

Breast cancer patients with screen-detected tumours were more likely to return to the screening programme, which may be caused by more trust in the programme. Women with in situ tumours were also more likely to attend the screening programme. It is known that these women have a lower risk of local recurrence [14]. Due to this lower risk, specialists might be more willing to refer these patients to the screening programme. Breast cancer patients with an interval tumour, which either did not exist at the time of the screening or was undetected, may have been disappointed and therefore reluctant to re-enter the programme.

Breast cancer patients receiving adjuvant radiotherapy were less likely to attend the screening programme. A study by Grandjean et al. revealed that women who had received radiotherapy had follow-up by both the surgeon and the radiation oncologist and therefore received more outpatient follow-up than recommended by the guidelines [15]. This might reduce the urge for women to attend the regular screening programme.

Besides the specialists in the hospital, the patient's needs and preferences are important factors. These factors should be taken into account when discussing follow-up. De Bock et al. studied the needs of patients during follow-up and showed that patients have widely different needs and preferences [16]. Furthermore, there is an ongoing debate about the effectiveness of routine follow-up including an annual mammography. De Bock et al. showed that still 40% of recurrences were detected in an asymptomatic stage during routine follow-up visits or tests. A simulation study found that patients aged 50 years with standard follow-up examinations had only 2 months gain in life expectancy compared to patients without follow-up examinations. For older patients the benefit was even less [17]. On the other hand, several studies reported that most patients prefer frequent follow-up visits for a long, even a life-long period [3,6,10]. Patients indicated that the main benefit attending follow-up visits was the perceived reassurance they gained [18,19]. This might be an important reason why women will attend the screening programme when invited, while still attending outpatient follow-up.

After breast cancer diagnosis and treatment, women frequently attend scheduled outpatient follow-up visits [11]. According to guidelines, in the first year the breast cancer patients are seen four times, in the second year twice, and thereafter once a year. During these visits women receive a physical examination, and annually a mammography. Until 2008, after a follow-up of 5 years, annual or biennial mammography was recommended, and the optimal length of follow-up given was to be decided individually by the specialist and the breast cancer patient. In specific situations, depending on age and treatment, the option was to be referred to the screening programme after 10 years of follow-up [20,21]. As no explicit recommendations were made about referral to the screening programme, this might result in the low percentage of breast cancer patients attending the screening programme after treatment. In 2008 the Dutch guideline for breast cancer was revised and since then a clear recommendation is given about referral to the screening programme after curative treatment: after 5 years outpatient follow-up, female patients over 60 years of age and treated with mastectomy should be referred to the screening programme [11,12,22]. This might result in more women attending the screening programme after treatment. However, surgeons and radiologists might not be willing to refer a patient to the screening programme for many different reasons.

Furthermore, screen radiologists are probably not so eager to include breast cancer patients who underwent BCS in the screening programme, as these mammographies are more difficult to analyse. After surgery and/or radiotherapy the women's breast will change in appearance and density. On mammography scar tissue from the operation and radiotherapy may have an appearance similar to a second breast tumour [23]. For the screen radiologist a comparison is difficult, as he has only the screen mammographies made before diagnosis or none at all. Therefore, screen radiologists are more likely to refer the women for further diagnostics. In the future it may become more feasible to exchange digital images from hospitals to the screening programme, enabling screen radiologists in interpreting mammographies over time.

To reduce overlap, breast cancer patients should be informed by their specialist that attending the screening programme in the first 5 years of follow-up is unnecessary and the interrelation between the outpatient follow-up and the screening programme should be improved. The recommendation in the national guideline that breast cancer patients can be referred to the screening programme 5 years after mastectomy is the first step in creating a more efficient follow-up. The effect of this recommendation should be seen in the forthcoming years.

In conclusion, 4.4% of the breast cancer patients attended the breast screening programme within 5 years after breast cancer treatment, followed by another 15.4% of patients attending the programme after 5 years after treatment. Women with screen-detected breast cancer, in situ tumours, and women treated without adjuvant radiotherapy were more likely to return to the screening programme. In the future, improving the interrelation between the outpatient follow-up and the screening programme is desirable to avoid overlap and low attendance to the screening programme after outpatient follow-up. Breast cancer patients should be informed by their specialist that attending the screening programme during the outpatient follow-up is not necessary.

CONFLICT OF INTEREST STATEMENT

None declared.

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8

Evaluating the age-based recommendations for long-term follow-up in breast cancer

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ABSTRACT

Background

After 5 years of annual follow-up following breast cancer, Dutch guidelines are age based: annual follow-up for women <60 years, 60–75 years biennial, and none for >75 years. We determined how the risk of recurrence corresponds to these consensus-based recommendations and to the risk of primary breast cancer in the general screening population.

Subjects, Materials, and Methods

Women with early-stage breast cancer in 2003/2005 were selected from the Netherlands Cancer Registry (N = 18,568). Cumulative incidence functions were estimated for follow-up years 5–10 for locoregional recurrences (LRRs) and second primary tumours (SPs). Risks were compared with the screening population without history of breast cancer. Alternative cut-offs for age were determined by log-rank tests.

Results

The cumulative risk for LRR/SP was lower in women <60 years (5.9%, 95% confidence interval [CI] 5.3–6.6) who are under annual follow-up than for women 60–75 (6.3%, 95%CI 5.6–7.1) receiving biennial visits. All risks were higher than the 5-year risk of a primary tumour in the screening population (ranging from 1.4% to 1.9%). Age cut-offs <50, 50–69, and > 69 revealed better risk differentiation and would provide more risk-based schedules. Still, other factors, including systemic treatments, had an even greater impact on recurrence risks.

Conclusion

The current consensus-based recommendations use suboptimal age cut-offs. The proposed alternative cut-offs will lead to a more balanced risk-based follow-up and thereby more efficient allocation of resources. However, more factors should be taken into account for truly individualizing follow-up based on risk for recurrence.

INTRODUCTION

Early detection and improved treatment have substantially decreased breast cancer–related mortality, yet the resulting increase in the need for follow-up care has an impact on health care resources [1]. In the first year of follow-up, the focus is on psychosocial complaints, monitoring quality of life and side effects [1]. After the first year, the main goal of follow-up is early detection of locoregional recurrences (LRRs) and second primary breast cancer (SP). Detection of asymptomatic distant metastasis (DM) is not part of routine follow-up [2,3], as early detection of DM currently has no proven impact on survival [4]. Despite the current intensive follow-up, its actual survival benefit is unclear, with only 34% of the LRRs being detected asymptotically during regular follow-up visits [5]. Approximately 40%–50% of the recurrences are detected by women themselves between regularly scheduled follow-up visits [4]. Follow-up visits are also a burden to patients, as they induce anxiety and stress [6,7]. Additionally, there is disutility linked to false-positive tests and subsequent invasive biopsies, as well as costs. Moreover, the current follow-up is uniform for all patients and not based on the individual risk of recurrence. Previous studies revealed that risk of recurrence within the 5-year follow-up period is dependent on patient-, tumour-, and treatment-related characteristics and changes over time [8]. One of these characteristics is age; especially young women are at increased risk of recurrence [8–10].

Implications for Practice

The current age-based recommendations for breast cancer follow-up after 5 years are suboptimal and do not reflect the actual risk of recurrent disease. This results in situations in which women with higher risks actually receive less follow-up than those with a lower risk of recurrence. Alternative cut-offs could be a start toward risk-based follow-up and thereby more efficient allocation of resources. However, age, or any single risk factor, is not able to capture the risk differences and therefore is not sufficient for determining follow-up. More risk factors should be taken into account for truly individualizing follow-up based on the risk for recurrence.

The current follow-up in The Netherlands consists of annual follow-up visits in the hospital for a minimum of 5 years, with clinical examination and mammography [3]. This is comparable to follow-up schedules in other countries, such as the U.K. [11], Australia [12] and the U.S. [13]. Dutch recommendations on the monitoring after 5 years of follow-up are based on consensus. The age after 5 years of follow-up determines the schedule: women <60 years will continue with annual visits and those between the ages of 60 and 75 biennial visits (in the population-based screening program), whereas for those >75 years, the

guideline suggests to consider stopping follow-up. With these age-based recommendations, implicit assumptions are made as to what level of risk is appropriate for which frequency of follow-up visits. It is uncertain whether the recommendations capture the differences of developing an LRR or SP between the age groups after 5 years. Ideally, risk groups should clearly differentiate in risk and the frequency of follow-up visits should match the risk of recurrence, with higher-risk patients receiving more follow-up visits, unless the abovementioned lack of value of follow-up becomes translated into practice.

Women without a history of breast cancer aged 50–74 years are invited by the national breast cancer screening program to undergo biennial screening. It is unclear how the risk for primary breast cancer in the healthy screening population and the corresponding recommendations relate to women with a history of breast cancer who are at risk for recurrence and are advised annual, biennial, or no hospital follow-up. When examining the patterns in the risk of recurrence, risk thresholds could be identified and support evidence-based follow-up decisions.

Therefore, the aims of this study were to analyse long term breast cancer recurrence patterns and determine how the current age-based recommendations on the follow-up schedules after 5 years correspond to the actual risk of LRR and SP. Moreover, alternative age cut-offs are proposed, and risk of LRR or SP was compared with the risk of breast cancer in the general screening population aged 50–74 years.

SUBJECTS, MATERIALS, AND METHODS

Data

Women were selected from the nationwide population-based database of the Netherlands Cancer Registry (NCR). Based on pathological notification through the Pathology Automated Archives system, trained registration clerks gathered data concerning patient, tumour, and treatment characteristics directly from patients' files. Information on 10 years of follow-up was gathered in retrospect from the patient files.

Women diagnosed with primary invasive breast cancer in 2003 or 2005 without DM or previous malignant, in situ, or synchronous tumours who were curatively treated by means of surgery and of whom complete 10-year follow-up was available were selected from the NCR. Women with macroscopic residue after surgery or microscopic residue without adjuvant treatment, those with tumour stage pT4, or those treated outside The Netherlands were excluded. This led to the inclusion of 18,568 women. Vital status was obtained through linkage

with the municipality registry and complete until February 2016. Missing data were multiple imputed based on the chained equation method [14,15]. The imputation model consisted of all variables used in the analysis. Thirty data sets were generated, and the estimates and standard errors were pooled using Rubin's rules [16]. For comparison, the analysis was performed using both the imputed data set and the data set that contained only the complete cases. Also, the convergence of the imputations was checked graphically.

The primary endpoint in this study was diagnosis of either LRR or SP during 10 years of follow-up, whichever came first. Recurrent disease in the ipsilateral breast, chest wall, ipsilateral axillary, or supraclavicular, infraclavicular, or internal mammary lymph nodes was registered as LRR in the NCR [17]. Any epithelial breast cancer with or without lymph node metastasis in the contralateral breast was registered as an SP [17]. The date of last surgery was considered the starting point of the follow-up.

Comparison of Risk in Current Age Groups, Screening Population, and Alternative Age Groups

With competing-risks regression, the cumulative incidence functions for the first LRR, SP, and LRR/SP together were estimated with maximum likelihood according to the method of Fine and Gray [18]. Patients developing synchronous (within 3 months) LRR and DM or SP and DM were registered as having DM. DM was used as competing event for the analyses with both LRR and SP as endpoint, both DM and SP for the analysis with LRR as endpoint, and both DM and LRR where SP was endpoint. Furthermore, DM served as a proxy for breast cancer-related death [19], as more than 80% of the patients with DM after the primary tumour died within 10 years. The selection of explaining variables besides age during 10 years of follow-up was based on literature [20–30] and consisted of characteristics of the primary tumour: histology (ductal, lobular, mixed, or other), primary tumour grade (Bloom Richardson grade I, II, III), size (pT1–3), multifocality (no, yes), lymph nodes status (pN0–3), oestrogen receptor (ER) status (negative, positive), progesterone receptor (PR) status (negative, positive), human epidermal growth receptor 2 (HER2/neu) status (negative, positive), type of surgery (lumpectomy, mastectomy), axillary lymph node dissection (no, yes), chemotherapy (no, yes), radiation therapy (no, yes), and endocrine therapy (no, yes). Correlation between variables was assessed using a correlation matrix. The variables PR and ER receptor status showed a high correlation and were combined into hormone receptor status as a single variable [31].

The cause-specific hazard functions after 5 years of follow-up for LRR or SP within the current age groups were determined for the three age groups that are distinguished in the guideline (<60, 60–74, >74 after 5 years of follow-up). The difference in risk was assessed by comparing

the cumulative risks as well as the subhazard ratios (sHRs) from the multivariable analysis. Also, the cumulative incidence functions of the three current age groups for the follow-up years 5–10 were compared with the 5-year incidence of primary breast cancer in the screening population divided in 5-year age groups. To determine the 5-year risk of primary breast cancer in the population that is invited for the biennial screening program (50–75 years), data from the incidence years 2005–2009 from the NCR were used, as were mortality data from Statistics Netherlands [32]. The life table method was used to calculate this risk with adjustments for mortality from other causes and the prevalence of cancer in the population.

By testing the survivor functions (events predicted vs. observed) of both LRR and SP per 5-year age intervals using the log-rank test, alternative cut-offs for age were determined to obtain a greater differentiation in risk between the groups. The difference in risk between the current age groups and when using the new age cut-offs was compared graphically and by the sHRs obtained with competing risks regression, corrected for other explaining variables.

All statistical analyses were performed using STATA 14.0 (StataCorp, College Station, TX).

RESULTS

Of the 18,568 patients, 65% were within primary breast cancer screening age (50–75 years) after 5 years of follow-up. During the 10 years of follow-up, 852 (4.6%) developed an LRR, 868 (4.7%) an SP, and 2,484 (13.4%) a DM as first event. The median follow-up time for the total population was 9.6 years (interquartile range [IQR] 9.0–10.0). For patients with an LRR as a first event, the median disease-free interval (DFI) was 3.7 years (IQR 1.8–6.5). Median DFI before an SP was slightly longer at 4.8 years (IQR 2.3–7.1). Table 1 summarizes the patients, tumour, and treatment characteristics stratified by first event.

Table 1. Patient and tumour characteristics, stratified by event type occurring within ten years after treatment.

		LRR (N = 852)		SP (N = 868)		Total (N = 18,568)	
		N	%	N	%	N	%
Age	<40	81	9.5	44	5.1	1,121	6.0
	40-49	178	20.9	172	19.8	3,684	19.8
	50-74	507	59.5	581	66.9	11,359	61.2
	≥75	86	10.1	71	8.2	2,404	12.9

Table 1. (continued)

		LRR (N = 852)		SP (N = 868)		Total (N = 18,568)	
		N	%	N	%	N	%
Histology	Ductal	690	81.0	674	77.6	14,875	80.1
	Lobular	93	10.9	97	11.2	2,025	10.9
	Other	69	8.1	97	11.2	1,668	9.0
Tumour size	≤ 2 cm	501	58.8	602	69.4	11,249	60.6
	>2-5 cm	321	37.7	238	27.4	6,650	35.8
	>5 cm	18	2.1	21	2.4	517	2.8
	Unknown	12	1.4	7	0.8	152	0.8
Lymph node status	Negative	543	63.7	640	73.7	11,333	61.0
	1-3 positive	229	26.9	150	17.3	4,985	26.8
	>3 positive	63	7.4	64	7.4	1,988	10.7
	Unknown	17	2.0	14	1.6	262	1.4
Tumour grade	I	138	16.2	234	27.0	3,854	20.8
	II	344	40.4	374	43.1	7,667	41.3
	III	298	35.0	198	22.8	5,719	30.8
	Unknown	72	8.5	62	7.1	1,328	7.2
Hormone status	ER&PR -	196	23.0	127	14.6	3,091	16.6
	ER/PR +	632	74.2	709	81.7	14,894	80.2
	Unknown	24	2.8	32	3.7	583	3.1
Her2neu status	Negative	381	44.7	376	43.3	8,108	43.7
	Positive	95	11.2	59	6.8	1,720	9.3
	Unknown	376	44.1	433	49.9	8,740	47.1
Multifocality	No	694	81.5	715	82.4	15,294	82.4
	Yes	118	13.8	119	13.7	2,323	12.5
	Unknown	40	4.7	34	3.9	951	5.1
Type of surgery	Lumpectomy	459	53.9	516	59.4	10,444	56.2
	Mastectomy	393	46.1	352	40.6	8,124	43.8
Axillary lymph node dissection	No	447	52.5	526	60.6	9,140	49.2
	Yes	405	47.5	342	39.4	9,428	50.8
Chemotherapy	No	603	70.8	643	74.1	12,021	64.7
	Yes	249	29.2	225	25.9	6,547	35.3
Radiotherapy	No	359	42.1	279	32.1	6,357	34.2
	Yes	493	57.9	589	67.9	12,211	65.8
Endocrine therapy	No	593	69.6	643	74.1	10,601	57.1
	Yes	259	30.4	225	25.9	7,967	42.9

Abbreviations: ER, oestrogen receptor; PR, progesterone receptor; Her2neu, human epidermal growth factor receptor 2.

Risk of Current Age Groups and Comparison with Screening Population

The cumulative incidence of LRR and SP combined in the first 5 years of follow-up of the complete population was 5.7%. In this period, the cumulative LRR risk, corrected for competing risks, was overlapping for women aged <60 and >74 and slightly higher for women aged 60–74 (Figure 1A). The differences were not significant, as 95%CI were overlapping (data not shown). After 5 years of follow-up, this pattern of the cumulative risk of LRR for the age groups remained the same, unlike the recommendations for follow-up.

The cumulative incidence of SP (Figure 1B) was significantly higher for women aged 60–74 during the 10 years of follow-up than women aged <60 or >74. Subsequently, the cumulative incidence for LRR and SP together followed the same pattern and was higher as well for women aged 60–74 than the risk of women aged <60 and >74 years (Figure 1C). This effect could also be seen in the sHR values from the multivariable analysis (<60 vs. 60–74: sHR 1.07, $p = 0.423$; <60 vs. >74: sHR 0.74, $p = 0.010$). Other factors from the multivariable analysis (Table 2) with both a greater and significant effect on the risk of recurrence than age were receiving endocrine treatment (sHR 0.52, $p < 0.001$, vs. no endocrine treatment), chemotherapy (sHR 0.58, $p < 0.001$, vs. no chemotherapy), and grade of differentiation (grade II: sHR 1.25, $p = 0.021$, vs. grade I; grade III: sHR 1.34, $p = 0.015$, vs. grade I).

Figure 1. Cumulative incidence functions during 10 years of follow-up stratified by age. **(A):** LRR. Abbreviations: FU, follow-up; LRR, locoregional recurrence; SP, second primary.

Figure 1. Cumulative incidence functions during 10 years of follow-up stratified by age. **(B):** SP. **(C):** LRR and SP combined. Abbreviations: FU, follow-up; LRR, locoregional recurrence; SP, second primary.

The cumulative incidence of LRR during the years 5–10 of follow-up for women with a history of breast cancer was 2.7% (95%CI 2.3–3.2), 2.6% (95%CI 2.2–3.1), and 2.1% (95%CI 1.6–2.9) for women aged <60, 60–74, and >74, respectively, all slightly higher than the 5-year risk of a primary tumour in the healthy screening population (ranging from 1.4% to 1.9%). Also, the cumulative incidence of SP was higher, with risks of 3.1% (95%CI 2.7–3.6), 3.7% (95%CI 3.2–4.3), and 2.6% (95%CI 1.9–3.4) for women aged <60, 60–74, and >74, respectively. LRR and SP combined resulted in at least twice the risk of recurrence in women with a history of breast cancer (<60: 5.9%, 95%CI 5.3–6.6; 60–74: 6.3%, 95%CI 5.6–7.1; >74: 4.7%, 95%CI 3.9–5.9), compared with the risk of a primary tumour in the healthy screening population (Figure 2A).

Table 2. Multivariable competing risk regression.

		sHR	95%CI	p-value
Age	<60	Ref.		
	60-74	1.07	0.91-1.25	0.426
	≥75	0.74	0.59-0.93	0.010
Histology	Ductal	Ref.		
	Lobular	1.00	0.78-1.27	1.000*
	Mixed	1.08	0.77-1.52	0.656
	Other	1.10	0.80-1.51	0.550
Tumor size	≤ 2 cm	Ref.		
	>2-5 cm	1.23	1.05-1.45	0.012
	>5 cm	1.32	0.83-2.09	0.242
Lymph node status	Negative	Ref.		
	1-3 positive	1.04	0.81-1.34	0.762
	>3 positive	1.05	0.71-1.56	0.812
Tumor grade	I	Ref.		
	II	1.25	1.03-1.51	0.023
	III	1.34	1.06-1.70	0.014
Hormone status	ER&PR -	Ref.		
	ER/PR +	1.11	0.87-1.40	0.404
HER2neu status	Negative	Ref.		
	Positive	0.96	0.79-1.17	0.688
Multifocality	Yes	Ref.		
	No	1.24	1.01-1.52	0.041
Type of surgery	Lumpectomy	Ref.		
	Mastectomy	1.02	0.74-1.41	0.891
Axillary lymph node dissection	Yes	Ref.		
	No	1.09	0.88-1.36	0.427
Chemotherapy	No	Ref.		
	Yes	0.63	0.51-0.78	<0.001
Radiation therapy	No	Ref.		
	Yes	0.80	0.57-1.11	0.176
Endocrine therapy	No	Ref.		
	Yes	0.51	0.41-0.62	<0.001

* Rounded value.

Abbreviations: CI, confidence interval; ER, oestrogen receptor; HER2neu, human epidermal growth factor receptor 2; PR, progesterone receptor, sHR, sub hazard ratio.

Figure 2. Cumulative incidence functions with 95% confidence intervals (CIs) for **(A)** the current age categories during years 5–10 of follow-up for locoregional recurrence (LRR) and secondary primary tumour (SP) combined, compared with the risk of a primary tumour in the healthy screening population (Δ) having biennial screening, divided in 5-year age categories, and **(B)** LRR and SP combined after 5 years of follow-up using the proposed age cut-offs. Note how the first two risk groups switch: with the proposed cut-offs, the highest risk group (<50) receives annual follow-up after 5 years and the lower risk group (50–69) biennial follow-up. Abbreviations: FU, follow-up.

Alternative Age Cut-offs

As the age-based follow-up recommendations after 5 years of follow-up did not match with the actual risk (as after 5 years of follow-up, the risks of LRR or SP was highest for the age group 60–74 with biennial follow-up, whereas the age group <60 has lower risk and is recommended annual follow-up), alternative age cut-offs were assessed. The cumulative incidence functions for the current age cut-offs during 10 years of follow-up are depicted in Figure 1C. After testing between 5-yearly cut-offs, significant differences in events were found between the age groups <50, 50–69, and >69 years after 5 years of follow-up. The corresponding cumulative incidences in the years 5–10 of follow-up were 6.5% (95%CI 5.4–7.6) for the group aged <50, 6.2% (95%CI 5.6–6.7) for ages 50–69, and 4.9% (95%CI 4.3–5.8) for women >69 years. As the risk is especially high in relatively young women, the new age cut-offs enable that the first risk group (<50 after 5 years) has both the highest risk and the most intensive follow-up recommendation (Figure 2B). So if follow-up recommendations were to be based on age only, the new cut-offs are more in accordance with the risk of LRR and SP. This could also be seen from the multivariable analysis (<50 vs. 50–69: sHR 0.82, $p = 0.050$; <50 vs. >69: sHR 0.63, $p < 0.001$; Table 2).

DISCUSSION

Using competing risk regression, we found that the current age-based recommendations for patients with breast cancer after 5 years of follow-up do not match with the actual risk of LRR and SP: the risk was lower for women aged <60 years after 5 years of follow-up who received annual follow-up, compared with women aged 60–74 receiving less intensive biennial follow-up. This contradiction was caused by the relatively low risk of the 50- to 60-year-old group, which lowered the risk of the complete group, including the age group of younger women (<50 after 5 years of follow-up, <45 at diagnosis) with higher risks. With alternative cut-offs for the age groups (<50, 50–69, >69), this higher-risk group was separated from the women with lower risk (aged 50–60) and more differentiation was achieved, resulting in recommendations that better match the actual risk. When comparing with the 5-year risk of primary breast cancer in different age groups of women without a history of breast cancer that are invited to the biennial national screening program, the risk of LRR and SP after 5 years of clinical follow-up was at least twice as high. Still, other factors than age were of greater influence on recurrence risk and should also be taken into account.

The large size of this study cohort from the population-based NCR strengthens the reliability and generalizability of the results. Because of the required long follow-up

for our study, the data from 2003 and 2005 might not be generalizable to the current situation, as treatments have improved over time, resulting in lower recurrence risk. For example, the addition of trastuzumab to chemotherapy for HER2-positive tumours was not yet advised in the guideline in the year 2003, which means that patients in this cohort did not receive this treatment [3]. Still, the benefit of this treatment in the following years can be supposed by the nonsignificant sHR of 0.96 for HER2-positive tumours. A positive hormonal receptor status, on the other hand, suggested a nonsignificant negative effect (sHR 1.11 for ER/PR+ compared with ER&PR-). However, when the endpoints were assessed separately, we see other (nonsignificant) outcomes: sHR of 0.94 (95%CI 0.71–1.24) for LRR and 1.29 (95%CI 0.99–1.67) for SP.

The probability of recurrence was compared with the risk of a primary tumour in the healthy population and not the hazard rate, as with competing risks the one-to-one relationship between rate and risk is lost (i.e., the hazard of recurrence will not be equal to the risk of recurrence) [33]. Consequently, the way in which covariates (like age) are associated with the outcome may not coincide. The comparison with the healthy screening population was made with different incidence years (2005–2009) than women at risk for recurrence (2008–2013 for 2003 and 2010–2015 for 2005). This could have led to slight changes in risk, but it is unlikely that this has led to different results. With the alternative age cut-off, the recommendations for women aged 50–69 after 5 years of follow-up would be the same in both the follow-up and the screening setting (biennial). The risk of both LRR and SP combined resulted in at least twice the risk of recurrence in women with a history of breast cancer, compared with the risk of a primary tumour in the healthy screening population. This means that patients in the follow-up aged 60–74 undergo the same frequency of visits as patients in the screening setting, who have half the risk. This does not necessarily mean that follow-up should be intensified or that screening should be less intensive; rather, it points out that there is a lot to be gained from personalization. Personalizing screening is of increasing interest and is currently being studied [34,35]. Furthermore, there are some differences between screening and follow-up, as for example women with a history of breast cancer undergo both mammography and a physical examination. Also, primary tumours are thought to grow slower than LRR [36], which leads to a larger sojourn time.

Although many patients with breast cancer report reassurance from frequent follow-up, clinic visits and possible false-positive tests also cause unwarranted effects such as anxiety [7]. A reduction of unnecessary follow-up visits can reduce this discomfort, especially in light of the limited evidence on a possible survival benefit. A personalized

follow-up could also reduce unnecessary use of valuable capacity, shorten the waiting lists for diagnostics tests and other services required for follow-up. The impact of less resource-intensive follow-up has already been assessed and found to be cost-effective, but the differences in the risk of recurrent disease were not considered [37–42]. In this study, we only considered the follow-up visits aimed at detection of recurrent disease in an early stage. No conclusions can be made based on this study for the visits that offer psychosocial care. When a detected tumour would not have become symptomatic during a woman's lifetime, this is considered overdiagnosis [43]. Overdiagnosis increases in the highest age group, as the risk of death due to other causes also rises. Because mammography is less sensitive and specific in women <50 years, the net benefit of follow-up in this age group is probably also lower. However, the longer life expectancy of this group compared with the elderly increases the benefit. Moreover, more sensitive diagnostic tools such as magnetic resonance imaging are progressively more used in patients at higher risk for LRR or SP.

Using the alternative cut-offs for age would lead to more risk-based recommendations, as especially young women (<50 after 5-year follow-up) bear higher risks. These young women tend to have higher-grade primary ductal tumours with positive lymph nodes and to receive endocrine and chemotherapy more often than the older age groups (data not shown). Although the new cut-offs lead to a more risk-based follow-up, there was still overlap in the confidence intervals. As only data on diagnosis and no data on timing and results from previous follow-up testing were available from the NCR, the effect of this more risk-based strategy (e.g., which recurrences would be detected "late") could not be assessed. With stratification only based on age, it is not possible to accurately discriminate low- from high-risk patients. In previous studies, we developed a prediction model for the first 5 years of risk of recurrence that revealed other factors such as receptor status, stage, and treatment that all influence recurrence risks. To achieve a more detailed personalized risk estimate after 5 years of follow-up, multiple risk factors should be taken into account. The INFLUENCE nomogram is a prediction model and web-based nomogram (www.utwente.nl/influence) for individual time-dependent LRR risk for 5 years [8]. It was developed based on 37,278 patients diagnosed with early breast cancer between 2003 and 2006. The model was also externally validated and provides valid and reliable estimates for patients with a follow-up of 5 years [44]. However, it does not include the risk on SP. When this model is combined with SP risk and accurate thresholds, personalized follow-up schedules based on estimated individual risks can be offered. Ideally, comorbidity should be taken into account as well. However, evidence for this is limited and practice guidelines are missing [2].

Figure 3. Examples of risk groups to illustrate the imbalance between the risk and recommendations based on age-related thresholds. **(A):** Cumulative incidence of locoregional recurrence (LRR) and secondary primary tumour (SP) combined over 10 years of follow-up using the proposed age cut-offs after 5 years and the corresponding recommendations. **(B):** Cumulative incidence of combined LRR and SP of the entire population to determine equally spaced risk intervals per visit, to propose a follow-up visit only when the risk level is reached (not at set time periods). Abbreviation: FU, follow-up.

Figure 3. Example of risk groups to illustrate the imbalance between the risk and recommendations based on age-related thresholds. **(C):** Cumulative incidence of LRR and SP combined with 95% confidence intervals for two example risk groups based on age (<50) and endocrine therapy (yes/no), showing significant differences in risk within one age group. On the cumulative incidence functions, the risk intervals for the first five visits (as depicted in B) are projected. Based on these simple thresholds, the high risk group might benefit from more frequent visits, as it reaches the risk level of the entire population (visit 5) already after 3 years, whereas it takes around 7 years for the lower risk group. However, these thresholds only take into account the risk and current recommendations, not the benefits and harms. Abbreviation: FU, follow-up.

A simple example of thresholds would be to use the cumulative incidence levels after 5 years of follow-up of the newly defined groups based on the alternative age cut-offs (Figure 3A) as risk thresholds for the follow-up frequency (annual, biennial, or consider stopping hospital follow-up). Subsequently, cumulative incidence level of the complete population during the first 5 years (5.74%) could be divided in five equal intervals (1.15% per annual visit) and used to determine when a follow-up visit should take place: instead of set yearly intervals, only when the risk level is reached (Figure 3B). When projecting these thresholds on two patient profiles based on age (<50) and endocrine treatment (yes, no), it can be seen that although the two groups receive the same annual follow-up in practice, the risk of women with endocrine therapy is half that of women without and below the risk level of women aged >69 (Figure 3C).

Although there is a difference in risk using other age cut-offs, the differences are not large. This raises the question whether there should be a difference in recommendation at all

and exemplifies that age, or any single risk factor for that matter, is not able to capture the risk differences in women at risk for recurrence and is not sufficient for determining follow-up. The above thresholds are based on age and the current recommendations. Better would be to take into account the clinical relevance of the risk, as well as the growth rate of tumours and the metastatic potential (e.g., it is better to detect a triple-negative tumour as early as possible, and for a luminal A tumour, detection is less urgent). However, this was meant to give insight into the room for improvement of follow-up. In a more comprehensive model for follow-up, besides taking into account the individual risk of recurrent disease, there should be a weighted balance between the possible benefits (earlier detection and corresponding survival) and harms of follow-up (testing itself, false positives, overdiagnosis, and financial toxicity) that should be addressed to get toward personalized risk-based follow-up combined with informed clinical decision making. Moreover, part of the follow-up consists of the identification of need of psychosocial support, which could be tailored based on outcomes of quality of life surveys and patient preferences.

CONCLUSION

The current consensus-based follow-up recommendations after 5 years (annual for <60 years after 5 years of follow-up, biennial for 60–74, consider stopping >74) use suboptimal age cut-offs leading to an imbalance between risk of LRR and SP and intensity of the follow-up following the 5 years of clinical follow-up. Patients aged 50–60 years have a lower risk for recurrence compared with patients <50 and could have a less intensive schedule. The proposed alternative cut-offs (<50, 50–69, >69) will lead to a more balanced risk-based follow-up frequency taking into account the risk of both LRR and SP and will be a start toward more efficient allocation of resources. However, to get truly personalized follow-up, more risk factors as well as the benefits and harms of follow-up should be taken into account to provide accurate individualized risk estimates and follow-up schedules.

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contact, and according to local regulations in The Netherlands (WMO), only studies with high burden for patients have to be reviewed.

AUTHOR CONTRIBUTIONS

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DISCLOSURES

Gabe S. Sonke: AstraZeneca, Merck, Novartis, Roche (RF [to institution]);

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Part **III**

General discussion

9

General Discussion

SUMMARY

This thesis provides a comprehensive description of the impact of the Dutch screening programme in the context of an ageing society with an increasing background incidence of breast cancer. The contribution of the screening programme to the detection of early stage cancers and smaller tumours was studied, as was its effect on the disease-free interval (including tumour-free margins and disease recurrence) and overall survival (OS). For Chapter 2 to 6 relevant data from the Netherlands Cancer Registry (NCR) were linked to corresponding data from the Dutch breast cancer screening programme, Chapter 7 and 8 are based on data from the NCR only.

Chapter 2 describes a study into the effects of different definitions of advanced breast cancer on the percentages of detected cancers during a steady-state biennial screening programme. This was achieved by retrieving data on invasive tumours and ductal carcinoma in situ (DCIS) for women aged 49–74 years and diagnosed with breast cancer between 2006 and 2015. We then classified any breast cancers detected during this period as screen-detected (diagnosed <24 months after positive screening), interval (diagnosed <24 months after negative screening), or non-screened (diagnosed ≥ 24 months or never screened). For the core results, three definitions of advanced breast cancer were used for comparison: TNM staging (stages III–IV, compared to stage 0-I-II); NM staging (tumours with positive lymph nodes and/or metastasis, compared to NOM0); and T-size staging (invasive tumour size ≥ 15 mm, compared to invasive tumours <15 mm and DCIS). We performed multivariable logistic regression analyses adjusted for age, diagnosis year, and socioeconomic status, assuming a 10% overdiagnosis rate. In a secondary analysis, the assumption of overdiagnosis was varied from 0% to 30%. In this first study, we included 46,734 screen-detected, 17,362 interval, and 24,189 non-screened breast cancers. By TNM stage, 4.9% of screen-detected breast cancers were advanced, compared with 19.4% and 22.8% of interval and non-screened breast cancers, respectively ($p < 0.001$). Applying the other definitions led to higher percentages of advanced breast cancer being detected. Interval and non-screened breast cancers had 2- to 5-times increased risks of being advanced depending on the definition and assumed overdiagnosis rate. However, irrespective of the definition, the screen-detected breast cancers were less often of advanced stage compared with interval and non-screened breast cancers. These findings indicated that there was a stage shift to early detection, and as such, provided support for the potential of screening to reduce the treatment-related burdens and mortality associated with breast cancer.

The effect of screening on breast cancer burden is described in **Chapter 3** among women aged ≥ 49 years and diagnosed with breast cancer between 2006 and 2011. Cancers were defined as screen-related (diagnosed < 24 months after screening) or non-screened (all other cases) and two cut-offs were used to define advanced breast cancer: TNM stage (stage III–IV) and T-size alone (≥ 15 mm), as described in Chapter 2. The incidence was adjusted for age before using logistic regression to compare groups. Of the 72,612 included women diagnosed with breast cancer, 44,246 (61%) had screen-related breast cancer. By TNM stage, advanced cancer was almost three times as likely to be at an advanced TNM stage in the non-screened group compared with the screen-related group (38 and 94 per 100,000; odds ratio [OR]: 2.86, 95% confidence interval [95%CI]: 2.72–3.00). By T-size, the incidence of advanced cancer was higher overall, and was significantly higher in non-screened women than in screened women (210 and 169 per 100,000; OR: 1.85, 95%CI: 1.78–1.93). These data on actual screening attendance indicated that the incidence of advanced breast cancer was significantly higher in non-screened women than in screened women, which was consistent with our expectation that screening would cause a stage shift toward early detection. Conflicting with the ongoing debate about the utility of breast cancer screening programmes, data from this study indicated that breast cancer screening is a valuable tool that can reduce the disease burden in women.

In **Chapter 4**, the effect of introducing Full-field digital mammography (FFDM) to replace screen-film mammography (SFM) in the breast cancer screening programme is described. This was considered essential because this technological advance brings clear advantages, such as improved image quality, the option to adjust contrast, and improved transfer capabilities. Therefore, we included data for 902,868 women attending the Dutch breast cancer screening programme, region North, in the period 2004–2010 (i.e. the transition from SFM to FFDM) and described performance indicators and tumour characteristics of screen-detected and interval cancers. After initial screens, the recall rates were 2.1% for SFM and 3.0% for FFDM ($p < 0.001$), while the positive predictive values were 25.6% and 19.9%, respectively ($p = 0.002$). Detection rates were similar, as were all performance indicators after subsequent screens. Similar percentages of low-grade DCIS were found for SFM and FFDM, but invasive cancers diagnosed after subsequent screens with FFDM were more often high-grade ($p = 0.024$) or ductal type ($p = 0.030$). The incidence rates of interval cancers were similar for SFM and FFDM after initial (2.69/1000 versus 2.51/1000; $p = 0.787$) and subsequent screens (2.30 versus 2.41; $p = 0.652$), and tumour characteristics remained similar. Thus, FFDM performed as well as SFM in breast cancer screening, resulting in similar rates of screen-detected and interval cancers. The lack of increase in cases of low-grade DCIS also suggested that overdiagnosis was unlikely. Nonetheless,

after initial screening, which account for 12% of all screens, FFDM did result in a higher recall rate and a lower positive predictive value (PPV), both of which require attention in future research.

Positive tumour margins after breast-conserving surgery (BCS) are used as the main criterion for determining the successful surgical treatment of localized primary breast cancer. The national guideline in the Netherlands recommends that the rate of positive margins should not exceed 30% for DCIS and 15% for invasive cancers. In **Chapter 5**, we determined whether BCS resulted in fewer positive margins in cases of screen-detected than clinically detected breast cancer. Furthermore, the choice of subsequent therapy was studied based on the finding of positive margins after initial BCS. The sample comprised 1,537 women from region North and East of the screening programme merged with the NCR, aged 50–75 years, who underwent BCS for invasive breast cancer between July 2008 and December 2009. We identified 873 women with screen-detected cancers (57% of the original sample). Next, the correlations of margin status to screening history, clinical factors, and pathological findings were evaluated by multilevel analysis. This revealed that screen-detected cancers were significantly smaller (87% versus 69%; i.e. T1 tumours <2 cm), more often well differentiated (33% versus 26%), confirmed pre-operatively (98% versus 96%), diagnosed in a nonteaching hospital (60% versus 66%) and more often had negative lymph nodes (80% versus 68%). The resection margins were positive in 170 women from the original sample. Multivariable analysis indicated that the presence of positive margins was predicted by hospital, tumour size, multifocality, positive lymph nodes and absent pre-operative confirmation. However, women with screen-detected cancer did not have a lower risk of having positive margins after BCS than women with clinically detected breast cancer. Positive margins only occurred in 11% of women with invasive tumours, well below the percentage recommended by the national guideline. The presence of encouraging factors by screen-detected breast cancer such as a smaller tumour size, unifocality, negative lymph nodes and the presence of pre-operative confirmation should not lead to performing a more sparing excision than is considered usual for comparable clinically detected breast cancer.

Recent registry-based studies have reported improved survival with breast conserving therapy (BCT; i.e. BCS followed by moderate-dose radiation therapy) compared to mastectomy for early breast cancer. Given that these studies did not report either the long-term OS or the breast cancer-specific survival (BCSS), they may have overestimated the effect of BCT. Therefore, in **Chapter 6**, we evaluated the 10-year OS and BCSS and compared the results after BCT and mastectomy in Dutch women with early breast cancer.

We included all women in the NCR diagnosed with primary invasive breast cancer (T1-2, N0-1, M0) between 2000 and 2004 if they received either treatment option, irrespective of axillary staging, dissection, or adjuvant systemic therapy use. The BCSS was estimated by calculating the distant metastasis-free survival (DMFS) and the relative survival (RS; i.e. calculating excess mortality ratios using life tables of the general population) for the 2003 subcohort with complete follow-up. OS was calculated at the level of the total cohort. Multivariable Cox proportional hazard analysis was used to estimate the HRs for 10-year OS and DMFS. Multiple imputation was performed to account for missing data. Of the 37,207 women in the total cohort, 21,734 (58.4%) underwent BCT and 15,473 (41.6%) underwent mastectomy. BCT was significantly associated with a superior 10-year OS ($HR_{\text{adjusted}} 0.81$ (95% CI 0.76-0.86), that remained significant in each T and N category. DMFS and RS were calculated for the 2003 subcohort (n=7,552) which was considered representative of the entire cohort. Compared to mastectomy, BCT showed much superior 10-year DMFS ($HR_{\text{adjusted}} 0.74$ (95% CI 0.58-0.94) and RS ($EMR_{\text{adjusted}} 0.60$ (95% CI 0.42-0.85) for T1N0 cancers only. This potentially indicates an effect of confounding by severity in OS. These results support the contention that BCT is at least equivalent to mastectomy concerning survival outcomes.

In the Netherlands, breast cancer patients are treated and followed-up for at least 5 years after diagnosis and all women aged 50-74 years are invited for biennial mammography by the screening programme. However, although attending both is suboptimal, the relation between these assessments had not previously been established. In **Chapter 7**, we therefore evaluated the potential factors that influenced women to attend the screening programme during (overlap) and after their outpatient follow-up. Data were included for women with breast cancer aged 50-74 years and treated for primary breast cancer between 1996 and 2007 and linked to data of the screening program, region North. Cox regression analyses were used to study any possible overlap during the outpatient follow-up, attendance at the screening programme after discharge from follow-up, and the factors influencing these choices. In total, 11,227 women with breast cancer were included, of whom 19% attended the screening programme after breast cancer treatment, with 4.4% doing so within 5 years and 15.4% doing so after more than 5 years. Several factors independently influenced attendance during and after the 5-year follow-up period with positive hazard ratios (HRs) for interval tumours (during: 0.77, 95%CI 0.61-0.97; after: 0.69, 95%CI 0.53-0.88; ref: screen-detected tumours), receiving adjuvant radiation therapy (during: 0.65, 95%CI 0.47-0.90; after: 0.66, 95%CI 0.47-0.93; ref: none) and diagnosis of DCIS (during 1.67, 95%CI 1.25-2.23; after 1.39, 95%CI 1.05-1.85; ref: stage I tumours). By contrast, non-screen related tumours (HR 0.41, 95%CI 0.29-

0.58) and recent diagnosis (HR 0.89 per year, 95%CI 0.86-0.92) were only associated with overlap attendance within 5 years. To avoid overlap and low attendance after outpatient follow-up, women with breast cancer should be informed that attending the screening programme is not necessary during outpatient follow-up. Efforts should also continue to ensure that an appropriate screening routine is adopted after discharge. Improving the relationship between outpatient follow-up and screening should be central in our thoughts when addressing these issues.

Beyond the 5 years of follow-up after breast cancer treatment, Dutch consensus-based recommendations advocate annual, biennial, and no follow-up for women aged <60 years, 60-75 years, and >75 years, resp. However, it was unclear how these recommendations related to the actual risks of recurrence and second primary breast cancer in the general screening population. In **Chapter 8** we therefore selected 18,568 women from the NCR who had been diagnosed with early breast cancer in 2003 or 2005. Competing risk regression was then used to estimate the cumulative incidence function of locoregional recurrence (LRR) and second primary breast tumour (SP) for each age group during follow-up 5-10 years after treatment. Risks were compared against those in the screening population with no history of breast cancer and alternative age cut-offs were determined by log-rank tests. Among women aged <60, 60-74, and >74 years, the respective cumulative incidence rates were 2.7%, 2.6% and 2.1% for LRR compared to 3.1%, 3.7% and 2.6% for SP. The cumulative risk for LRR and SP together was lower in women aged <60 years under annual follow-up (5.9%, 95% CI 5.3-6.6%) than for women aged 60-75 years receiving biennial visits (6.3%, 95% CI 5.6-7.1%). Although several risk factors other than age showed greater differentiation in risk, age cut-offs <50, 50-69 and >69 years better differentiated the risks of both LRR and SP by 6.5%, 6.2% and 4.9%, respectively. All age-based LRR and SP risks were higher when compared with the 5-year risk of a primary tumour in the healthy screening population (1.4%-1.9%). Thus, it was concluded that the current consensus-based follow-up recommendations use suboptimal age cut-offs because recurrence risk is not influenced by age alone. If we are to individualise follow-up appropriately, there is a need to take other factors into account. However, if follow-up by age should adopt the evidence based cut-offs reported in this study, it can be a start towards risk-based follow-up and efficient resource allocation.

HOW CAN WE BEST MONITOR THE BREAST CANCER SCREENING PROGRAMME?

The main goal of a breast cancer screening programme is to reduce the mortality associated with breast cancer. However, it is difficult to study the effect of screening on mortality because not only is survival high, but also risk factors and treatments influence outcomes [1-3]. This then raises the question as to whether another endpoint can be identified that is more suited to study into the effects of screening. Most breast cancer deaths occur in women diagnosed with advanced disease in whom there has been spread to other organs [4], with screening programmes aiming to detect the disease before it reaches this stage [5]. Therefore, the incidence of advanced breast cancer may represent a suitable proxy for mortality, and potentially replacing it as the main endpoint when estimating the effect of screening. This proxy also benefits from the facts that stage can be determined at diagnosis, that international coding rules exist, that it is independent of treatment, and that it is not influenced by risk factors [6-9]. Furthermore, because the screening programme's design has not been changed since 2013, and because it has reached a steady-state situation, no changes in incidence or tumour stage are expected [10]. In this thesis, stage was considered a substitute endpoint for effectiveness based on these arguments. By demonstrating that advanced breast cancer was less common in the screened population under several definitions of advanced stage, it was shown that screening affected the incidence of advanced breast cancer [11,12].

Currently, the impact of the screening programme is described in an annual 'national evaluation of breast cancer screening in the Netherlands' report produced by IKNL and commissioned by RIVM [13]. Because the results of our studies indicate that stage at diagnosis is a useful substitute endpoint and proxy for mortality, we recommend adding more information to this report on tumour stage at the time of diagnosis for screen-detected and interval tumours. Although this improved insight into the change in occurrence of advanced stage cancers is important, it must also be ensured that we gain better insight into the incidence of DCIS. Technical advantages, such as the introduction of FFDM, mean that we can expect more DCIS to be diagnosed, that may not otherwise have become clinically apparent or relevant. This may, in turn, lead to so-called overdiagnosis and unnecessary monitoring or treatment that increase the burdens on both patients and the health care system (professionals and costs). In this situation, efforts would be needed to reduce the risk of overdiagnosis. However, when we studied the effect of implementing FFDM in the north of the Netherlands, there was no increase in the

incidence of low-grade DCIS associated with its introduction [14], which conflicted with results for other regions [10].

Efforts are currently being made to gain insight into the characteristics of DCIS that determine prognosis. It is anticipated that this will help to identify the number of DCIS lesions that will never contribute a hazard to health, particularly in cases of non- to slow-growing low-grade DCIS. Specifically, the LORD study aims to evaluate the safety of active surveillance by annual FFDM for 10 years in women with low-risk DCIS [15]. By delivering annual mammography after surgery or as active surveillance, the results of this study should improve our understanding of not only the development of DCIS but also the safety of omitting surgery (i.e. less overtreatment). The burdens and costs of active surveillance will also be included, shedding further light on the impact of these key aspects on patients and the health care system.

THE ROLE OF METHODOLOGY WHEN EVALUATING BREAST CANCER SCREENING

To evaluate the effects of a screening program, it is crucial to know exactly what cancers are diagnosed in screened or non-screened women. Other observational studies have previously evaluated how the screening programme affected the incidence of both early and advanced breast cancer, but did not link tumour data to the screening mammography result at the level of the individual patient. Instead, they relied on approximations of attendance and screening detection, often based only on groups of women in age categories invited for screening [16-23]. We found just one study using data about screening attendance at an individual level, and it showed that there was a lower rate of advanced cancer among screened women [24]. Our method of linking data from the NCR and screening programme at an individual level is well established and is often used in national evaluations and audits of the breast cancer screening programme. Considering the limitations of existing research, we are convinced that this method offers the most accurate results for evaluating screening.

Studying the incidence of advanced stage breast cancer in a population over a specific time period, without including the relevant attendance data, may have biased the results. This could have resulted from stage migration toward higher stages in response to diagnostic innovations and progress. For example, stage migration was reported following the introduction of the sentinel node biopsy, where lymph nodes were examined more thoroughly, leading to the discovery of more lymph node metastases [25]. Other more

precise methods of detecting distant metastasis, such as FDG-PET scanning, may also result in a stage migration towards more advanced stages thanks to their ability to diagnose distant metastasis that may not be evident when using older techniques. This leads to a stage shift towards stage IV, which included patients with metastatic disease. Additionally, stage III then comprises the relatively more favourable stage III patients. This effect dilutes the beneficial impact of screening on lowering the incidence of advanced disease. The studies in this thesis all benefitted from including information at an individual patient level, and as such, more accurately reflected the true status.

THE NEED FOR HIGH-QUALITY AND INTEGRATED DATA SOURCES

The NCR was the main source of data in this thesis [26]. This registry contains nationwide population-based data for all patients diagnosed with cancer since 1989 and is known for its high abundance, completeness and quality of its data. Nationally and internationally the NCR has a strong track record and is considered one of the most comprehensive population-based cancer registries in Europe, benefitting from inclusion of data for all tumour types together with data about stage, treatment and vital status. However, the registry does lack data on tumours that are not pathologically confirmed and are only mentioned on a death certificate. The NCR collaborates with the International Agency for Research on Cancer [27] and the European Network of Cancer Registries [28]. On request, the NCR will provide anonymous data for reports on cancer incidence to researchers in Europe and beyond. NCR data are thereby available for use in scientific research after submission of the research protocol and approval of the study by the Privacy Review Board of the NCR. Our ability to link the data of the NCR and the Dutch breast cancer screening programme provided a unique dataset for screening attendance and detection method at an individual level.

FOLLOW-UP AND BREAST CANCER RECURRENCE

Treatment options must be discussed after a diagnosis of breast cancer with recommendations from the Dutch breast cancer guideline [29], basing such discussions on tumour stage and the age of the women. At present, BCT and mastectomy are the two main surgical options for early stage non-metastatic breast cancer. However, decisions are not always clinical: on the one hand, the need for radiation therapy after BCS means that some women may not opt for BCT; on the other hand, mastectomy can be considered the safer option because the whole breast is being removed, which seems to prevent the

growth of recurrent breast cancer. However, even after mastectomy some residual breast tissue remains in which local recurrence can occur [30]. Although local recurrence can occur after both surgical options, the rate of a local recurrence within 5 years is as low as 2.6% after BCT and 3.5% after mastectomy [31]. Moreover, we showed that there was no difference in either the 10-year OS or 10-year BCSS between these surgical options [32], with BCT benefitting from being associated with less morbidity and fewer surgical complications [33,34].

The data presented in this thesis indicated that BCT may be the preferred option for most women with early stage breast cancer. Nevertheless, this might not account for patients with a contraindication for radiation therapy or for specific groups of patients with a higher risk of recurrent disease, such as carriers of gene mutations, or patients with familial predisposition. Recent developments in the use of neo-adjuvant treatment options might further increase the opportunities to use BCT if systemic treatment can make the tumour smaller or even completely undetectable. We must also account for the fact that screening results in the diagnosis of more early stage tumours, and that this may lead to a further increase in the use of BCT. Conversely, the use of MRI could reveal more cases of multifocal tumours which could lead to a preference for mastectomy [35,36], as could the good cosmetic results of direct reconstruction after mastectomy [37]. Such issues will always mean that there is a balance to be struck between the use of BCT and mastectomy, and it is at this point in the decision process that patient preferences should play a key role.

After diagnosis and treatment, the guideline recommends that breast cancer patients receive standard outpatient follow-up (follow-up visits in the outpatient clinic for 5 years after treatment) for the first 5 based on age [29]. After this time, patients can be discharged from outpatient follow-up and attend the screening programme provided that they are eligible. However, patient allocation to outpatient follow-up and screening has not been clearly established, meaning that it is possible for women to receive an invitation for screening during the first 5 years of follow-up. Attending both the screening programme and the outpatient follow-up is not desirable for either the woman, who receives unnecessary radiation from extra mammography, or the health care system, which is burdened by inefficient resource allocation. We found that current allocation procedures can be improved to reduce these avoidable burdens [38], possibly by developing a more appropriate screening routine after discharge that is based on mutual data exchange.

Current risk groups used in the outpatient follow-up were decided by consensus and based on age cut-offs, but it has been uncertain whether they capture true differences in the risk of recurrence. Ideally, groups should be clearly differentiated so that the frequency of follow-up visits is related to the risk. As personalised treatment and follow-up will become the standard of care, it will be important to know how the current age-based recommendations on follow-up schedules correspond to the actual hazard and risk of recurrence after 5 years. However, the findings in this thesis indicated that current age cut-offs do not correspond with the actual risk of recurrence. Several other factors, such as higher tumour grade, receiving hormonal therapy, or receiving chemotherapy better differentiated risk than age. In the future, these factors, together with age and other factors that are as yet unknown, will need to be considered if we are to individualise follow-up. The Influence nomogram uses these factors to predict the annual risk of local or regional recurrence and can be used to identify the most suitable intensity of follow-up for a given patient (www.evidencio.com/models/show/774) [39,40]. A first step toward a more risk-based follow-up may be to use the alternative age cut-offs reported in Chapter 7. In addition, improving the relation between outpatient follow-up and the screening programme could help with efforts to personalise follow-up and improve the efficiency of resource allocation. When patients who have been treated for breast cancer (re)enter the screening programme after the 5-year period in outpatient follow-up, radiologist will benefit from mammography results performed during follow-up being available as a reference. This could be facilitated by making the exchange of mammography images and reports easier between hospitals and screening units.

FUTURE PERSPECTIVES

Over coming years, it is anticipated that personalised care will become the new standard, encompassing screening, diagnosis, treatment, and follow-up. The key advantage is that, if implemented properly, patients should receive the optimal level of personalised care, with exactly the right number of screening examinations and treatments delivered at the right moment based on individual requirements. Moreover, personalised care should reduce the unnecessary use of resources, which in turn, should lead to a reduction in costs.

The first steps toward personalised screening have been made, with recommendations already in place for carriers of gene mutations (e.g. BRCA1/2, PTEN, TP53, CHECK2, and so on) and to invite them for an annual MRI or mammography, depending on their age [29]. More recently, further steps have been taken toward personalised screening with the DENSE trial studying a subgroup of women invited for screening with extremely

dense breasts [41]. The study showed that the use of supplemental MRI screening in women with extremely dense breast tissue and normal mammography findings resulted in significantly fewer interval cancers being diagnosed over a 2-year screening period when compared with the use of mammography alone. Further personalisation will require that factors other than breast density be considered, such as lifestyle factors or specific features on mammograms [42,43]. Any future developments regarding personalised screening will necessitate a shift in the organisation of the screening to accommodate the more personalised invitation schedule, and this will have a knock-on effect on the contents of the annual report on the national breast cancer screening programme. This may require indicators being presented by risk group.

Moreover, monitoring the screening programme can be improved by collecting outcome data in a more uniform way at a national level. Regularly linking data from the screening programme to the NCR will remain important as a means of providing data on screening status at an individual level. Furthermore, incorporating stage at diagnosis can help when evaluating the screening programme at a national level because it is a short-term outcome that is independent of treatment. Moreover, the performance of the screening programme might be enhanced by using artificial intelligence to read images. There is hope that such technology could help detect irregularities, result in fewer healthy women being recalled due to false alarms, and improve how radiologists' read breast cancer screening mammograms. An example of such an approach can be seen in the aiREAD project [44].

As survival increases due to earlier detection and better treatment and follow-up, the role of long-term patient care is becoming more important. However, if we are to optimise personalised care in the longer term, it is essential that we have accurate data about locoregional recurrence and distant metastases. With increasing digitalisation, computational power, and data-availability, it should become possible to combine multiple data sources. A nice example is the development of the Personal Health Train by IKNL, that enables people to use, combine and reuse health data from various sources without actually pooling the data in one database [45]. Moreover, the ability to link data on recurrence and distant metastasis regularly into the NCR will help to lower registration burden and will offer more possibilities to study their occurrence in close relation to the treatment, and perhaps even to other risk factors, such as body mass index, smoking and other life style factors. It is anticipated that such data will trigger change in the current age-based follow-up schedules toward an even more personalised follow-up than is obtainable using the Influence nomogram. Attendance at the screening programme after

the 5 years of outpatient follow-up, and the exchange of mammograms between hospital and screening units, should also be integrated in these guideline recommendations.

In the Netherlands, the breast cancer guideline has now been digitalised in Oncoguide and is summarised in decision trees in open access software (www.oncoguide.nl). Nomograms and tools can certainly be used to help patients make choices regarding treatment. Many nomograms have been developed over recent years to predict specific outcomes for patients with specific characteristics. As such, efforts are currently being made to incorporate the relevant nomograms into the Dutch guideline recommendations in Oncoguide. Furthermore, decision aids are being developed to help inform patients about the benefits and harms of each treatment. An example is the PATIENT+ decision aid, that helps patients choose between BCT and mastectomy, whether to undergo breast reconstruction, and whether adjuvant treatment is suitable [46]. This provides patient-oriented information on the benefits of each treatment, as well as information on survival, recurrence rates and cosmetic satisfaction (www.keuzehulp.info/pp).

Each of these developments can be used to personalise patient care and help patients and health care professionals make informed decisions about the most suitable treatment and follow-up. However, all current and future objectives will only succeed if close involvement is maintained among scientists, patients and professionals. Our mutual aim must be to optimise the entire care trajectory and to reduce the impact of cancer, starting at screening and diagnosis, continuing through treatment and appropriate follow-up, and finally with end of life care.

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Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Borstkanker is de meest voorkomende vorm van kanker bij vrouwen, zowel wereldwijd als in Nederland. Het aantal nieuwe diagnoses borstkanker in Nederland is gestegen van ongeveer 10.000 in de jaren '90 tot ruim 17.000 in 2018, waarvan in bijna 15.000 gevallen een invasieve borstkanker werd gediagnosticeerd en in ruim 2.000 gevallen een ductaal carcinoma in situ (DCIS, wat wordt beschouwd als een voorstadium van borstkanker). Daarentegen daalt in Nederland de kans om te overlijden aan borstkanker. In recente jaren overleden ongeveer 3.100 vrouwen per jaar aan borstkanker, vergeleken met 3.500 vrouwen per jaar in de periode 2001-2010. In 2018 waren er 135.000 vrouwen in leven in Nederland die in de voorgaande 10 jaar de diagnose borstkanker kregen.

Het opsporen van borstkanker in een vroeg stadium, een behandeling op maat passend bij de patiënt- en tumorkenmerken, en de beste schema's voor nacontroles na afloop van de behandeling zijn allemaal van belang om de zorg voor deze patiënten te optimaliseren. Ook de ontwikkeling van nieuwe behandelingen speelt hierbij een rol. In dit proefschrift beschrijf ik in deel 1 het effect van het bevolkingsonderzoek borstkanker op het stadium van de borstkanker bij diagnose. In deel 2 wordt ingegaan op de chirurgie en de gevolgen op langere termijn tot 10 jaar na diagnose, waarna in deel 3 wordt afgesloten met een samenvatting en discussie.

Hoofdstuk 1 is een algemene introductie en leidt het onderzoek beschreven in dit proefschrift in. Alle studies in dit proefschrift zijn uitgevoerd met gegevens uit de Nederlandse Kankerregistratie (NKR). De NKR bevat gegevens over vrijwel alle gediagnosticeerde kankers in Nederland sinds 1989. In het kader van het bevolkingsonderzoek borstkanker worden alle vrouwen in Nederland tussen de 50 en 74 jaar elke twee jaar uitgenodigd om een mammogram te laten maken. Voor de studies in hoofdstuk 2 t/m 5 en hoofdstuk 7 werden de gegevens uit de NKR gekoppeld aan de gegevens van het bevolkingsonderzoek. Deze koppeling van de data van de NKR en het bevolkingsonderzoek gebeurt op individueel niveau, volgens een methode waarbij de privacy gewaarborgd blijft. Dit leidt tot de unieke situatie dat het mogelijk is om precies te bestuderen wie naar het bevolkingsonderzoek is geweest, en wat de relatie is tussen een gediagnosticeerde borstkanker en de screening in het kader van het bevolkingsonderzoek. Hierdoor kunnen er drie groepen worden gedefinieerd. Een screen-gedetecteerde borstkanker is een borstkanker die gediagnosticeerd is na een doorverwijzing vanuit het bevolkingsonderzoek. Een intervalekanker wordt gediagnosticeerd tussen twee onderzoek rondes in en binnen 24 maanden na een

screeningsmammogram waarop geen afwijkingen werden gezien. De overige borstkankers zijn niet aan de screening gerelateerd, maar zijn gediagnosticeerd bij een vrouw die niet heeft deelgenomen aan het bevolkingsonderzoek of worden meer dan twee jaar na het onderzoek gediagnosticeerd.

In **hoofdstuk 2** wordt het percentage hoog stadium borstkanker beschreven, uitgesplitst naar de drie bovengenoemde groepen: screen-gedetecteerde borstkankers, intervalekankers en overige borstkankers. Uit dit hoofdstuk blijkt dat deelname aan het bevolkingsonderzoek statistisch gezien leidt tot een lager stadium van borstkanker bij diagnose. Om dit te kunnen bepalen werden drie verschillende definities van hoog en laag stadium gebruikt. Deze definities werden gebaseerd op basis van de kenmerken van de tumor, het aantal lymfeklieren en het voorkomen van metastasen bij diagnose, waarbij een hoog stadium betekent dat de kenmerken van de tumor ongunstiger zijn. Voor dit onderzoek werden de gegevens geselecteerd van alle vrouwen tussen de 49 en 74 jaar, die tussen 2006 en 2015 de diagnose borstkanker kregen. Uit dit onderzoek blijkt dat het percentage hoog stadium borstkanker in de intervalekankers en de overige borstkankers groter is dan in de screen-gedetecteerde borstkankers, en dit resultaat is bij elk van de drie definities van hoog en laag stadium zichtbaar. Wel gaf elke definitie een andere grootte van het effect: afhankelijk van de gebruikte definitie was de kans twee tot vijf keer zo hoog dat een intervalekanker of een overige borstkanker een hoog stadium had. Vervolgens werd in dit onderzoek gecorrigeerd voor overdiagnose. Overdiagnose houdt in dat er borstkanker wordt gediagnosticeerd waar een vrouw tijdens haar leven geen last van zou hebben gekregen. Daarbij is het uitgangspunt dat overdiagnose alleen voorkomt bij tumoren met een laag stadium. Omdat niemand weet wat het exacte percentage overdiagnose is, werd daarvoor in dit onderzoek gecorrigeerd door 10% en 30% van de tumoren met een laag stadium als overdiagnose te oormerken en de analyses te herhalen voor beide percentages. Ook na deze correcties bleef de conclusie hetzelfde dat screen-gedetecteerde borstkankers vaker een laag stadium hadden.

In **hoofdstuk 3** wordt specifiek gekeken naar de incidentie (het aantal diagnoses per 100.000 vrouwen) van hoog stadium borstkanker. Deze studie laat zien dat vrouwen die deelnamen aan het bevolkingsonderzoek naar borstkanker significant minder vaak een hoog stadium borstkanker hadden bij diagnose in vergelijking met vrouwen die niet of onregelmatig deelnamen aan de screening. Om dit te kunnen onderzoeken werden de vrouwen ingedeeld in twee groepen: de eerste groep bestond uit vrouwen met borstkanker, die in de twee jaar voorafgaand aan de diagnose hadden deelgenomen aan het bevolkingsonderzoek (screen-gedetecteerde of intervalekankers). De tweede

groep bestond uit vrouwen met borstkanker, die meer dan twee jaar geleden hadden deelgenomen of die niet hadden deelgenomen (overige borstkanker). Per groep werd berekend hoeveel vrouwen een hoog stadium borstkanker hadden per 100.000 vrouwen. Vrouwen die deelnamen aan het bevolkingsonderzoek naar borstkanker hadden minder vaak een hoog stadium borstkanker bij diagnose, waardoor bij deze vrouwen waarschijnlijk een minder zware behandeling mogelijk was.

Het bevolkingsonderzoek borstkanker kan ook worden gemonitord door prestatie-indicatoren te bestuderen. Met deze prestatie-indicatoren wordt het functioneren en de kwaliteit van het bevolkingsonderzoek in beeld gebracht. De belangrijkste indicatoren zijn het verwijscijfer, de positief voorspellende waarde, het detectiecijfer en het aantal interval tumoren per 1.000 onderzochte vrouwen. Deze prestatie-indicatoren kunnen worden gebruikt om de overgang van analoge mammografie naar digitale mammografie te onderzoeken. Digitale mammografie heeft tussen 2004 en 2010 de voorheen gebruikte analoge mammografie vervangen vanwege de technologische ontwikkelingen, zoals mogelijkheden om het contrast aan te passen, betere beeldkwaliteit en sneller en eenvoudiger uitwisselen van mammografiebeelden. **Hoofdstuk 4** laat zien dat, in deze begin periode van digitale mammografie binnen het bevolkingsonderzoek, digitale mammografie statistisch gezien even goed presteerde als analoge mammografie in de regio van het Bevolkingsonderzoek Noord. Wel leidde digitale mammografie in deze begin periode bij de groep vrouwen die voor de eerste keer deelnam aan het bevolkingsonderzoek (goed voor 12% van alle screeningsonderzoeken per jaar), tot een hoger aantal doorverwijzingen en een lagere positief voorspellende waarde, maar bleef het detectiecijfer vergelijkbaar. Bij de groep die deelnam in een volgende ronde waren de uitkomsten van deze indicatoren vergelijkbaar, wat aangeeft dat er evenveel borstkanker werd opgespoord met digitale als met analoge mammografie. De incidentie van intervalkankers was vergelijkbaar voor analoge en digitale mammografieën.

Deel 2 van dit proefschrift gaat in op de chirurgie en de gevolgen op langere termijn tot 10 jaar na diagnose. In **hoofdstuk 5** is onderzocht of er bij vrouwen met een screen-gedetecteerde borstkanker minder vaak tumorweefsel in de chirurgische snijvlakken zit, dan bij vrouwen met borstkanker gediagnosticeerd op basis van klachten (intervalkanker en overige tumoren). Deze studie laat zien dat bij beide groepen even vaak tumorweefsel achterbleef. Wel bleek dat een kleine screen-gedetecteerde borstkanker vaker een in situ component had die nog in de snijvlakken achter was gebleven dan kleine klinisch-gedetecteerde tumoren. Een in situ component wordt beschouwd als een voorstadium van borstkanker en is vaak sprieterig van vorm. Daardoor is het lastig om deze in zijn geheel

te verwijderen bij een operatie. Aangezien de aanwezigheid van tumor in de snijvlakken een heroperatie tot gevolg kan hebben, is het van belang dat een screen-gedetecteerde borstkanker en een borstkanker gediagnosticeerd op basis van klachten met dezelfde tumorkenmerken (bv. grootte en stadium) met eenzelfde ingreep wordt verwijderd.

In **hoofdstuk 6** wordt de 10-jaars algehele, metastasevrije en relatieve (overleving vergeleken met de algemene Nederlandse populatie) overleving van patiënten met tumoren tot vijf cm met maximaal drie aangedane lymfeklieren (borstkanker stadium T1-2N0-1) beschreven. Uit deze studie blijkt dat borstsparende chirurgie gevolgd door radiotherapie een minstens gelijke overleving heeft vergeleken met patiënten die een amputatie ondergingen. Analyse van de verschillende subgroepen van tumor- en klierstadium gaf eenzelfde resultaat. Alleen in de subgroep van patiënten met een tumor tot twee cm, zonder aangedane klieren (T1N0) bleek er een voordeel te zijn van de borstsparende behandeling.

Na de behandeling voor borstkanker blijven patiënten nog vijf jaar onder controle in het ziekenhuis. Als de eerste vijf jaar van nacontrole na borstkanker voorbij zijn, zijn de Nederlandse richtlijnen voor nacontrole vanaf het zesde jaar na diagnose gebaseerd op de leeftijd van de vrouw op dat moment. Voor vrouwen tot 60 jaar geldt een jaarlijkse follow-up, voor vrouwen in de leeftijd 60 tot 75 jaar een tweejaarlijkse follow (na een mastectomie kan dit via het bevolkingsonderzoek) en géén follow-up voor vrouwen boven 75 jaar. In **hoofdstuk 7** wordt de relatie beschreven tussen de nacontrole in het ziekenhuis en deelname aan het bevolkingsonderzoek. Uit het onderzoek blijkt dat van de 11.227 geselecteerde vrouwen met borstkanker tussen 1996 en 2007, 19% na de behandeling deelnam aan het bevolkingsonderzoek. Vier procent daarvan nam deel binnen vijf jaar na de diagnose, in de periode dat ze ook nog onder controle staan in het ziekenhuis. Vrouwen met een in situ tumor of een screen-gedetecteerde borstkanker bezochten het bevolkingsonderzoek relatief vaker binnen de vijf jaar, terwijl vrouwen die adjuvante radiotherapie ontvingen juist minder vaak deelnamen. Uit deze resultaten blijkt dat de afstemming tussen de nacontrole in het ziekenhuis en het bevolkingsonderzoek verbeterd kan worden. Ten eerste kunnen vrouwen beter worden geïnformeerd dat het niet nodig is om aan het bevolkingsonderzoek deel te nemen gedurende de eerste vijf jaar nacontrole, zodat er geen dubbele diagnostiek plaatsvindt. Ten tweede kunnen er inspanningen worden gedaan waardoor het makkelijker wordt om de implementatie van de bovengenoemde richtlijnen te kunnen optimaliseren na afloop van de eerste vijf jaar nacontrole. Zo wordt er verder nagedacht over de mogelijkheid om mammogrammen uit te wisselen tussen het ziekenhuis en het bevolkingsonderzoek. De mammogrammen

die in de nacontrole in het ziekenhuis zijn gemaakt, kunnen dan worden betrokken in de beoordeling van het screeningsmammogram, wat voor de screeningsradioloog bijzonder behulpzaam is.

Hoofdstuk 8 gaat verder in op de nacontrole na afloop van de eerste vijf jaar en beschrijft hoe deze richtlijnen zich verhouden tot het risico op terugkeer van de ziekte (locoregionaal recidief, metastasen of tweede primaire borstkanker). Deze studie laat zien dat het risico op terugkeer niet overeenkomt met de frequentie van de nacontrole in de huidige leeftijdsgroepen, zoals in de huidige richtlijn staat beschreven. In de NKR zijn de gegevens over het voorkomen van een lokaal of regionaal recidief of het optreden van metastasen door de registratiemedewerkers verzameld voor vrouwen met borstkanker in bepaalde diagnosejaren. Voor deze studie werden 18.568 vrouwen geselecteerd met de diagnose borstkanker in 2003 of 2005, waarbij de terugkeer van ziekte was geregistreerd tot 10 jaar na de oorspronkelijke diagnose. Er werd bestudeerd hoe vaak de ziekte lokaal terugkeerde in de periode vijf tot 10 jaar na de diagnose en dit werd vergeleken met de frequentie van de nacontroles zoals ze in de richtlijn worden beschreven. Het risico na vijf jaar was lager voor vrouwen jonger dan 60 jaar (die een jaarlijkse controle ondergaan), terwijl het risico hoger was bij vrouwen van 60 tot 74 jaar (die tweejaarlijks een mammogram krijgen). Deze contradictie wordt veroorzaakt door het relatief lage risico in de (grotere) groep 50-60-jarigen die het risico voor de gehele groep verlaagden, inclusief de groep jonge vrouwen (jonger dan 45 jaar bij diagnose) met een hoger risico. Als de nacontrole zou worden ingedeeld op basis van leeftijd, zouden alternatieve afkappunten (<50, 50-69, >69) de risicogroepen beter onderscheiden. Andere factoren, waaronder systemische behandelingen, bleken een grotere impact te hebben op het risico van terugkeer van de ziekte en dienen ook te worden meegenomen bij de inrichting van de nacontrole. Uiteindelijk kan dit mogelijk leiden tot een meer op risico gebaseerde follow-up met een efficiënter en meer gebalanceerd gebruik van de zorgcapaciteit.

In de discussie (**hoofdstuk 9**) wordt ingegaan op het uiteindelijk doel van het bevolkingsonderzoek borstkanker om de sterfte aan borstkanker te reduceren. Dit is echter lastig te onderzoeken gezien de hoge overleving en de invloed van andere risicofactoren en de behandeling. Dit leidt tot de vraag of er een ander eindpunt kan worden gedefinieerd om het effect van het bevolkingsonderzoek te evalueren. Aangezien de sterfte aan borstkanker voornamelijk voorkomt in vrouwen met een hoog stadium borstkanker en het bevolkingsonderzoek zich richt op de diagnose in een lager stadium, is het een mogelijkheid om de incidentie van hoog stadium als vervangend eindpunt aan te merken. In dit proefschrift hebben we daar een aanzet voor gedaan.

Tevens wordt ingegaan op de gebruikte data uit de NKR en het bevolkingsonderzoek. De NKR krijgt de eerste pathologische bevestiging van de diagnose kanker aangeleverd door PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief), waarna de signalering wordt aangevuld door de medische registraties van de ziekenhuizen. Vervolgens registreren speciaal opgeleide registratiemedewerkers van IKNL de benodigde items in de NKR, gebruik makend van de gegevens uit het elektronisch patiëntendossier. Dit leidt tot een NKR die nationaal en internationaal bekend staat om zijn uitgebreidheid, volledigheid en hoge kwaliteit. Ook de data van het bevolkingsonderzoek borstkanker zijn landelijk dekkend. De kwaliteit van de gebruikte databronnen is van belang om resultaten goed te kunnen duiden. De koppeling van deze datasets op individueel niveau is cruciaal om het bevolkingsonderzoek borstkanker goed te kunnen evalueren.

Naar de toekomst kijkend zal de zorg de komende jaren naar verwachting verder worden gepersonaliseerd. Dit zal zowel effect hebben op de keuze van de behandeling als op de controle schema's daarna. De verwachting is dat de keuze voor borstsparende therapie of amputatie altijd zal blijven afhangen van medische kenmerken (tumor kenmerken, aanvullende behandelingen of reconstructies, en eventuele contra-indicaties) en ook de voorkeur van de patiënt zal hierbij een belangrijke rol spelen. Na afloop van de behandeling zal ook de nacontrole kunnen worden gepersonaliseerd door bijvoorbeeld het risico op terugkeer te combineren met de frequentie van de nacontrole.

Samenvattend laat dit proefschrift zien dat het bevolkingsonderzoek leidt tot minder hoog stadium borstkankers bij diagnose, ook als hierbij rekening wordt gehouden met enige mate van mogelijke overdiagnose. De twee belangrijkste behandelopties voor kleine tumoren, borstsparende operatie met radiotherapie of amputatie, zijn gelijkwaardig qua overleving. Daarnaast laat het proefschrift zien dat de afstemming tussen het bevolkingsonderzoek en de nacontrole in het ziekenhuis na afloop van de behandeling van borstkanker kan worden verbeterd. Met deze nieuwe inzichten draagt dit proefschrift bij aan het verder verbeteren van een vroege opsporing van borstkanker, de juiste behandeling, en het optimaliseren van de schema's voor nacontroles na afloop van de behandeling. Deze factoren zijn gezamenlijk van belang om de zorg voor deze patiënten zo optimaal mogelijk te maken en de impact van borstkanker te verminderen.

List of publications

LIST OF PUBLICATIONS

Publications included in this thesis

de Munck L, Siesling S, Fracheboud J, den Heeten GJ, Broeders MJM, de Bock GH. Impact of mammographic screening and advanced cancer definition on the percentage of advanced-stage cancers in a steady-state breast screening programme in the Netherlands. *Br J Cancer*. 2020 Jul 9. 10.1038/s41416-020-0968-6. Epub 2020 Jul 9.

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About the author

ABOUT THE AUTHOR

Curriculum Vitae

Linda de Munck werd geboren op 2 maart 1975 in Assen. In 1993 behaalde zij haar VWO-diploma aan het Zernike College te Groningen, en na haar eindexamen ging zij een jaar naar highschool aan de Peter Skene Ogden Secondary School in 100 Mile House, British Columbia, Canada. Terug in Nederland startte Linda met de studie Farmacie aan de Rijksuniversiteit Groningen en zij rondde deze studie af in 2001 binnen de afstudeerrichting Sociale Farmacie en Farmaco-epidemiologie. Zij schreef haar afstudeerscriptie getiteld “Antidepressants – a cohort study on the risk of malformations and preterm delivery” bij het Danish Epidemiology Science Centre, University of Aarhus, Denemarken.

In 2001-2002 studeerde Linda Informatiedienstverlening en -management, waar zij haar propedeuse behaalde. Vervolgens startte zij in 2002 als onderzoeker bij het Integraal Kankercentrum Nederland (IKN) in Groningen. Daar was zij betrokken bij onderzoeksprojecten over diverse tumorsoorten en bij het analyseren van klinische trials. Tevens werd zij betrokken bij de evaluatie van het bevolkingsonderzoek borstkanker, toen nog op regionaal niveau. Linda startte haar promotieonderzoek in 2009, naast haar werk als onderzoeker. Gedurende haar promotietraject volgde Linda diverse cursussen binnen de opleiding tot Epidemioloog B.

Sinds de fusie van de regionale kankercentra tot Integraal Kankercentrum Nederland (IKNL) in 2011 is borstkanker haar aandachtsgebied. Hierbij heeft zij een divers takenpakket, van de scholing van datamanagers tot analyses en interpretatie van de gegevens van de Nederlandse Kankerregistratie. Ook heeft zij een aantal werkzaamheden voor de landelijke evaluatie van het bevolkingsonderzoek borstkanker onder haar hoede. Sinds 2016 is Linda lid van de ‘Werkgroep Kwaliteit, Monitoring & Informatiehuishouding’ met betrekking tot het bevolkingsonderzoek borstkanker van het RIVM. Vanaf 2017 verzorgt zij de jaarlijkse ‘Monitor bevolkingsonderzoek borstkanker’. Na afronding van dit promotietraject zal Linda haar aandachtsgebied binnen IKNL op borstkanker houden.

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