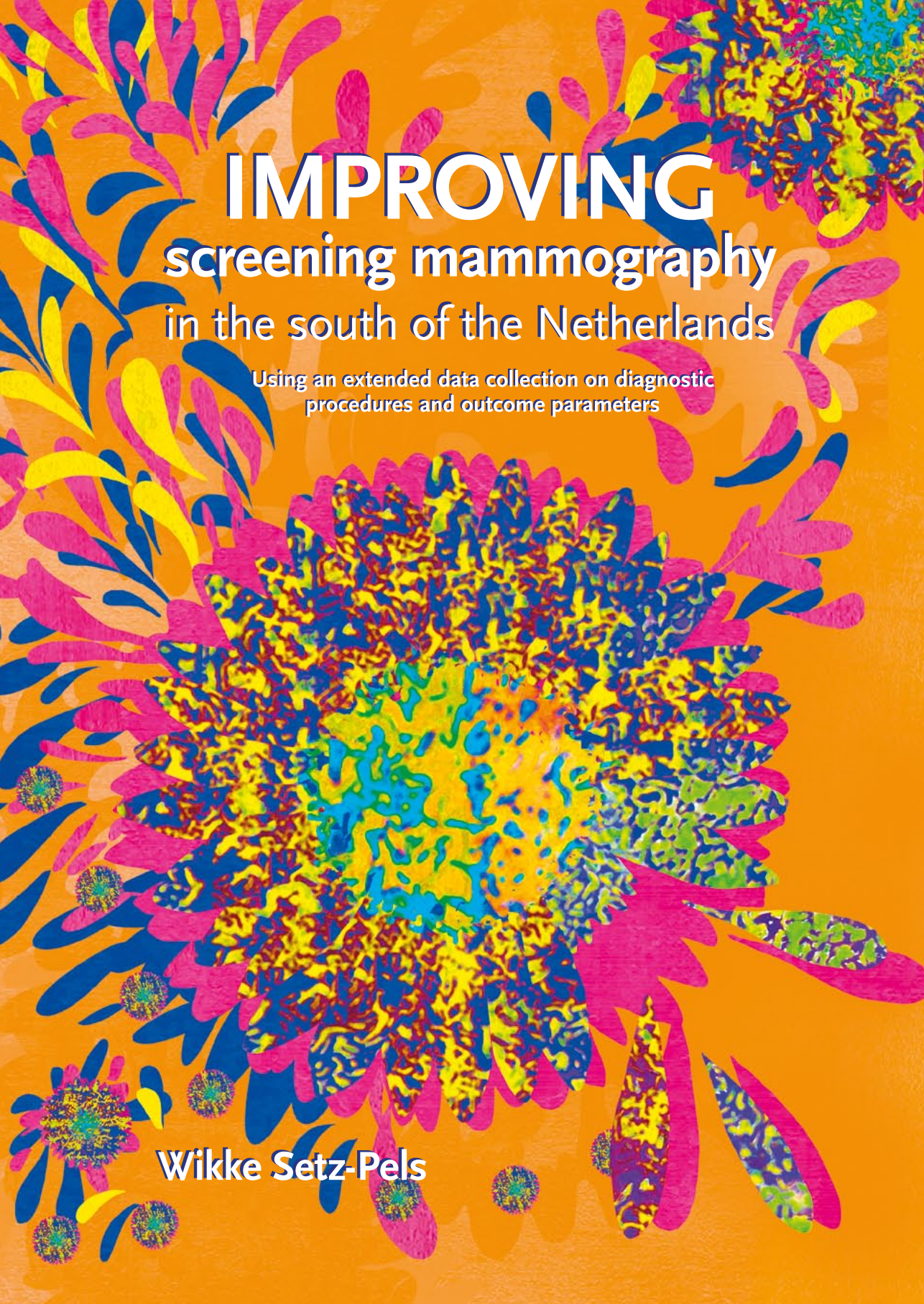
# IMPROVING
## screening mammography
## in the south of the Netherlands

Using an extended data collection on diagnostic procedures and outcome parameters



Wikke Setz-Pels

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# IMPROVING
## Screening Mammography
## in the South of the Netherlands

**Using an extended data collection on diagnostic procedures and outcome parameters**

**Het verbeteren van de mammografische borstkankerscreening in het zuiden van Nederland**
met een uitgebreide gegevensverzameling inzake diagnostiek en uitkomstparameters

**PROEFSCHRIFT**

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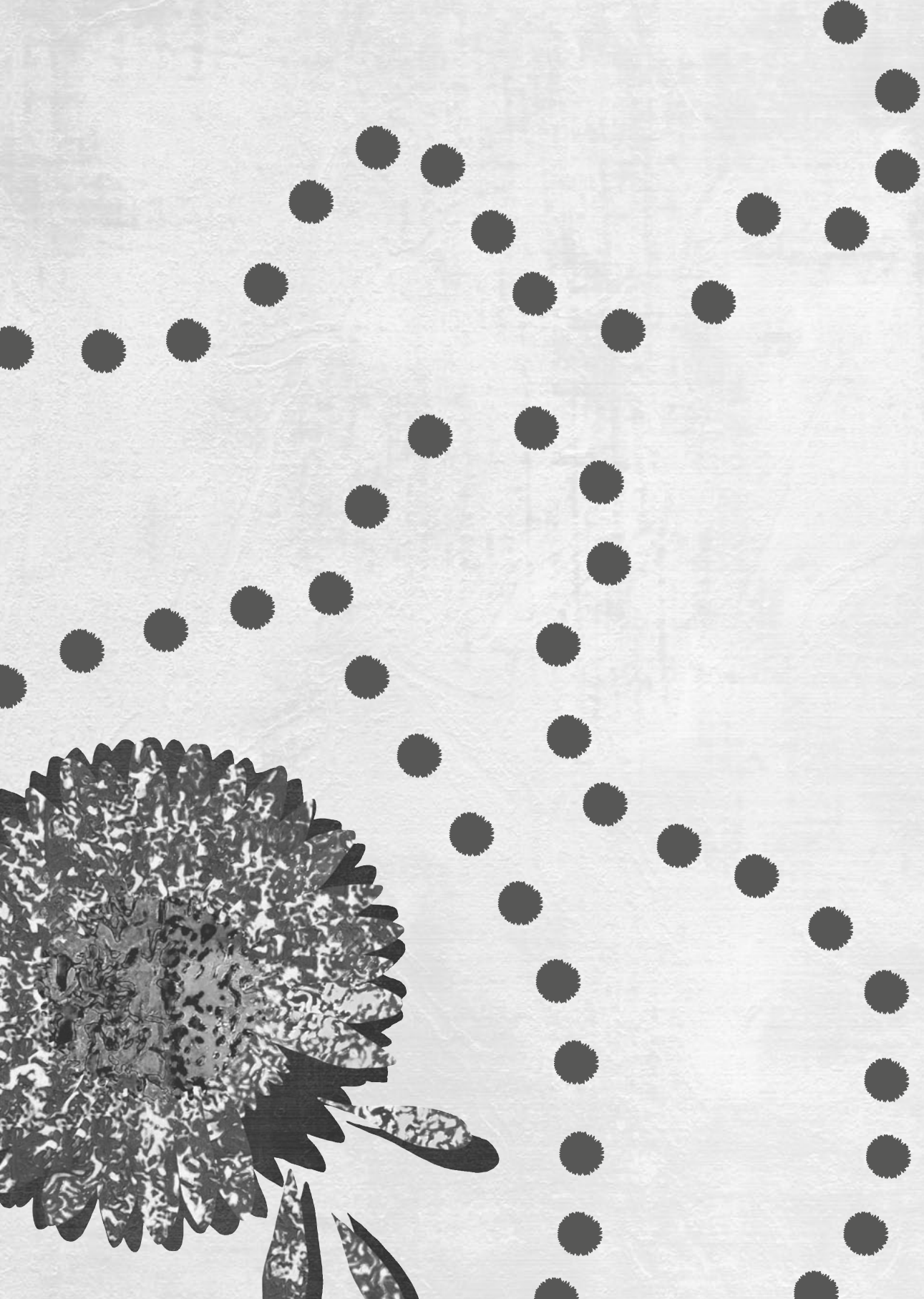
# Contents



# Chapter 1

## General Introduction

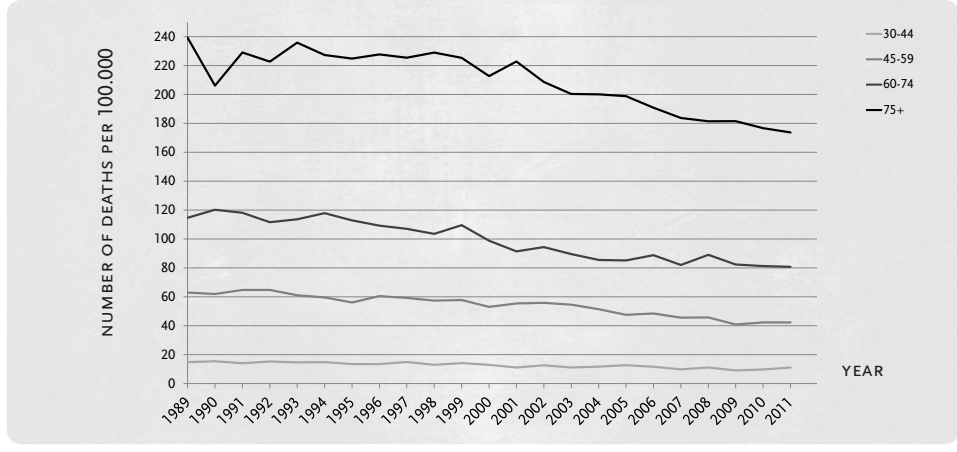
## RATIONALE

The motivation for this thesis is to reflect on opportunities to improve breast cancer screening in the Netherlands. The regional studies reported in this thesis can be placed within a broader framework of research on the effectiveness of national screening programmes, as well as within a more narrow framework of ways to improve this long settled institution of preventive health care in the Netherlands. This work will not give the answers to all questions that can be and have been asked concerning 'the good and the bad' in screening mammography. However it is unlikely that breast cancer screening will come to an end in the Netherlands in the near future. It is considered an important part of women's health care in our country for already more than 2 decades now and women show much confidence in the programme as is reflected by the high participation rates and their conviction that it is an effective way of reducing the risk of dying from breast cancer. Therefore in this thesis we explored possible weaknesses in the present screening programme and opportunities for improvement.

## BREAST CANCER

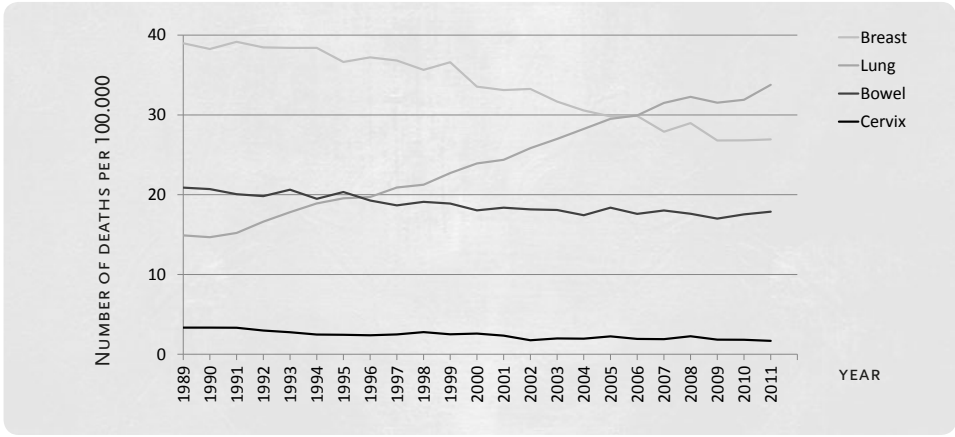
Worldwide breast cancer is the most common cancer diagnosed in women. A woman born in the Netherlands has a 1 in 8 chance of being diagnosed with breast cancer during her lifetime[1]. The incidence of invasive breast cancer in the Netherlands is 134 per 100,000 women per year (European Standardized Rate (ESR) 2011), which is among the highest in Europe[2]. As a comparison, the average incidence in Europe is 94 per 100,000 per year[3]. Breast cancer mortality is high, with a relatively high proportional mortality at middle age (Figure 1a). The breast cancer mortality rate has decreased over the last decades and breast cancer is now the second most common cause of cancer death for women in the Netherlands, with lung cancer being the most common cause after the year 2006 (Figure 1b).

FIGURE 1A. Age-specific mortality of invasive breast cancer in the Netherlands



◂ *fig 1A: Source: www.ikcnet.nl*

FIGURE 1B. Cancer specific mortality in the Netherlands




*Source www.ikcnet.nl*

The risk of breast cancer increases with age and is associated with numerous risk factors including

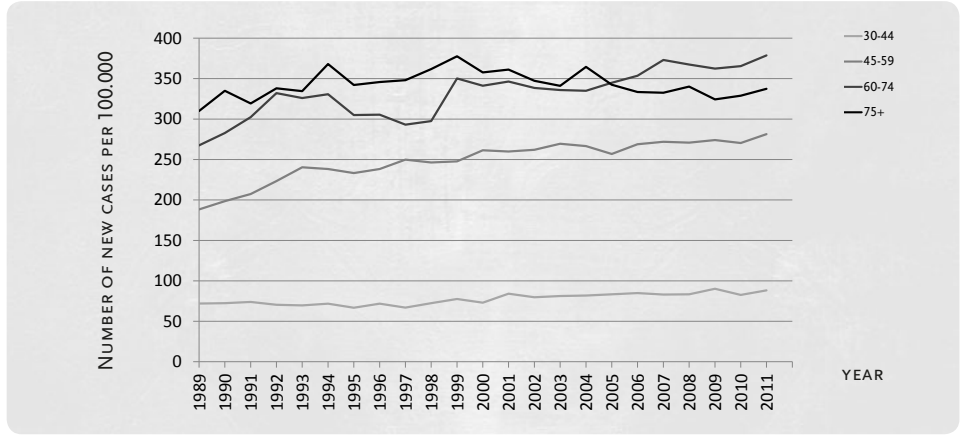
- positive family history (more than one family member, or breast cancer diagnosis at young age (<50 years)), and especially some genetic mutations including BRCA1 and BRCA2 mutations[4,5]
- high density of breast tissue[6]
- exposure to hormonal factors, including endogenous and exogenous exposure to estrogen[7]
- postmenopausal obesity[8]
- a sedentary lifestyle[9]
- alcohol consumption, smoking, white race[10, 11]

A substantial increase in the incidence of breast cancer (invasive and in situ breast cancer) has been observed in the last decades, from 85 per 100,000 women per year (ESR) in 1975 to almost 155 per 100,000 per year in 2011[2] (see also Figure 2a and 2b with age-specific incidence of invasive and in situ cancers). This increase can partly be explained by the incorporation of the national screening programme, increased awareness, and adverse changes in hormone related risk factors including particular patterns in childbearing and breast feeding (increasing age at first birth, lower parity and shorter duration of or no lactation)[12], and increase in postmenopausal obesity[13].



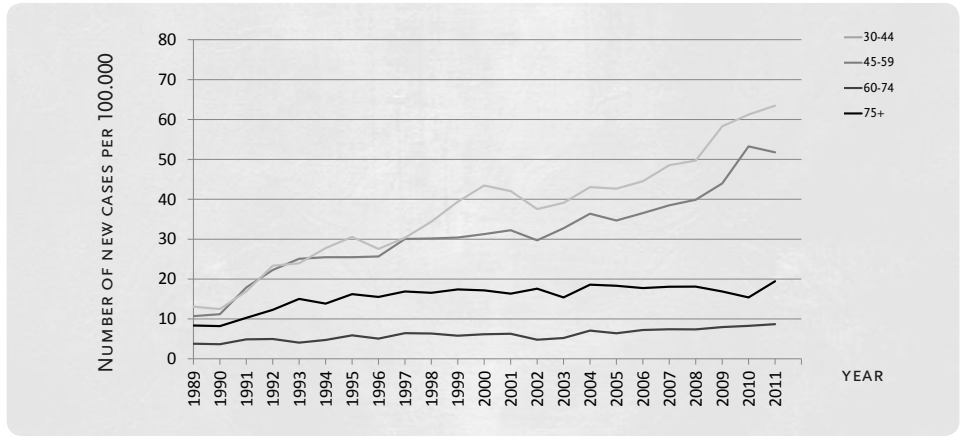


FIGURE 2A. Age-specific incidence of **invasive breast cancer** in the Netherlands




*Source: www.ikcnet.nl*

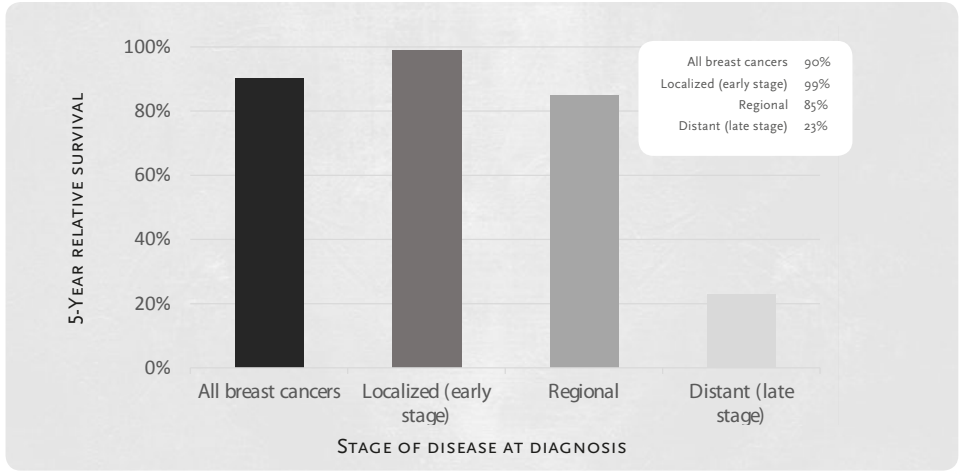
FIGURE 2B. Age-specific incidence of **in-situ breast cancer** in the Netherlands




*Source: www.ikcnet.nl*

The most important determinant of outcome for women with breast cancer remains tumour stage of breast cancer at diagnosis (Figure 3 and Table 1). Increasing tumour size and lymph node invasion will decrease long term survival. Among women with non-metastatic breast cancer, the risk of distant recurrence is most strongly correlated with the number of axillary nodes involved, followed by tumour size[14].

FIGURE 3. 5-year relative survival: breast cancers diagnosed 1999-2003




*Source: Connecticut Tumor Registry*

TABLE 1. Tumour stage related to TNM classification (UICC staging breast cancer)

| Stage | TNM classification | | |
|---|---|---|---|
| | Tumour size | Tumour positive lymph nodes | Distant metastasis |
| Stage 0 | DCIS | No | Mo |
| Stage I | T1 (<2cm) | No | Mo |
| Stage II | T1<br>T2 (2-5cm) | N1 (moveable)<br>To-1 | Mo |
| Stage III | Any T<br>T3-4<br>(>5 cm or extension to skin or chest wall) | N2 (fixed)-N3<br>(infraclavicular, internal mammary chain)<br>Any N | Mo |
| Stage IV | Any T | Any N | M+ |

## BREAST CANCER SCREENING IN THE NETHERLANDS

Because of the strong correlation between tumour size and the extent of axillary spread[15,16], it is thought that by diagnosing a cancer earlier, before it becomes palpable, the risk of dying from it can be decreased. Although several methods for early detection exist, until now mammography has been proven to be the most cost effective tool for examining postmenopausal women with an average risk for breast cancer[17]. For experienced radiologists the mean (programme) sensitivity of mammography is above 70% and







the mean specificity is more than 95%[18,19]. The sensitivity of mammographic testing is dependant of patient related determinants, as well as screening situation and image related determinants (Table 2).

TABLE 2. Factors influencing screening performance

| | Determinants of screening sensitivity |
|---|---|
| Patient related | Breast density<br>Previous breast surgery |
| Image related | Image quality (radiographer dependent)<br>Number of views<br>Screening round<br>Screen film or digital screening |
| Screening situation related | Screening method (single vs. double reading)<br>Radiologist performance<br>Screening interval<br>Breast cancer prevalence |

Before deciding on the implementation of service screening in the Netherlands cost effectiveness analyses were conducted. In the Netherlands this analysis was based on the results of pilot projects in Utrecht[20, 21] and Nijmegen[22], which both started in 1975. The results from the first world-wide randomised breast cancer trials in New York (1963) and Sweden (1977) were included in the analyses as well[23,24]. The analyses (based on the MISCAN model (MIcrosimulation Screening Analyses, a model with continuous time and discrete events that stimulates a dynamic population) predicted that screening women of 50-70 years at a 2-year interval would reduce breast cancer mortality and might be cost-effective[25]. The results of the randomised controlled trials reported a reduction in breast cancer mortality between 20-30%[23,24,26], 7-12 years from entry in the trials. The Dutch national screening programme started around 1990 and originally was targeted to women aged 50-69 years. It was fully implemented in the whole country in 1995, in last instance in Eindhoven and Groningen. The national screening programme implies that all eligible women are biennially invited for screening mammography. From 1998 onwards the age limit was extended to 75 years. This extension was predicted to prevent extra cancer deaths, against a reasonable increase of the screening risks[27]. The costs of the Dutch breast cancer screening programme are moderate, currently about 55 euro per screening examination[28]. For screening mammography a value of 2,200 euro per QALY

(Quality Adjusted Life Years) is determined in cost-utility analyses (performed in 2007)[29]. In the Netherlands the upper-limit for a screening programme to be considered as cost-effective is set at 20,000 euro per QALY.

The decision to screen an asymptomatic population for a disease involves weighing benefits against the potential harms. In the case of breast cancer screening, the most important benefits are the reduction of the mortality through earlier detection of disease, as well as a reduction in morbidity because of less invasive and/or aggressive therapeutic options. The harms include financial costs, but also the disadvantages of the screening regimen itself, including radiation risk, pain at mammography and inconvenience, as well as anxiety and distress because of (false positive) referral. Another important issue is the risk of overdiagnosis, as certain screen detected cancers, would never have become clinically evident or lethal, if left undiscovered[30]. The benefits to harms ratio varies with the age of the screened women.

## NETB
## (National Evaluation Team Breast cancer screening in the Netherlands)

Since the start of the nation-wide breast cancer screening programme in the Netherlands, the screening performance has been monitored and evaluated by the National Evaluation Team for Breast cancer screening (NETB). Since 2006 the National Institute of Public Health and the Environment (RIVM) is responsible for the coordination if the Dutch breast cancer screening programme (Figure 4). Screening can only be effective if certain criteria are met. For screening to be effective in reducing breast cancer mortality, sufficiently high re-attendance rates, but also repeated sequential screening with adequate intervals are essential. The referral rate and detection rate, the tumour stage distribution of screen-detected compared to clinically diagnosed breast cancers, and the rate of interval cancers should be evaluated accurately and timely to see if the programme is meeting its objectives. The monitoring of the Dutch breast cancer screening programme is based on regional data, aggregated annually on a national level, additional data from Statistics Netherlands and the data provided by the Netherlands Cancer Registry (NCR). In 2010, the former 9 breast cancer screening organisations merged to 5 new regional organisations for cancer screening, including cervical and (future) colorectal cancer screening. In 2010, the screening mammograms were read by 17 radiologists' reading units in total[31].

During more than two decades of screening within the Dutch breast cancer screening programme (from 1990 until 2011), over 14 million screening examinations have been performed. Currently, about 1 million women are invited each year and around 82% of them actually attend the programme. Changes in key performance indicators between

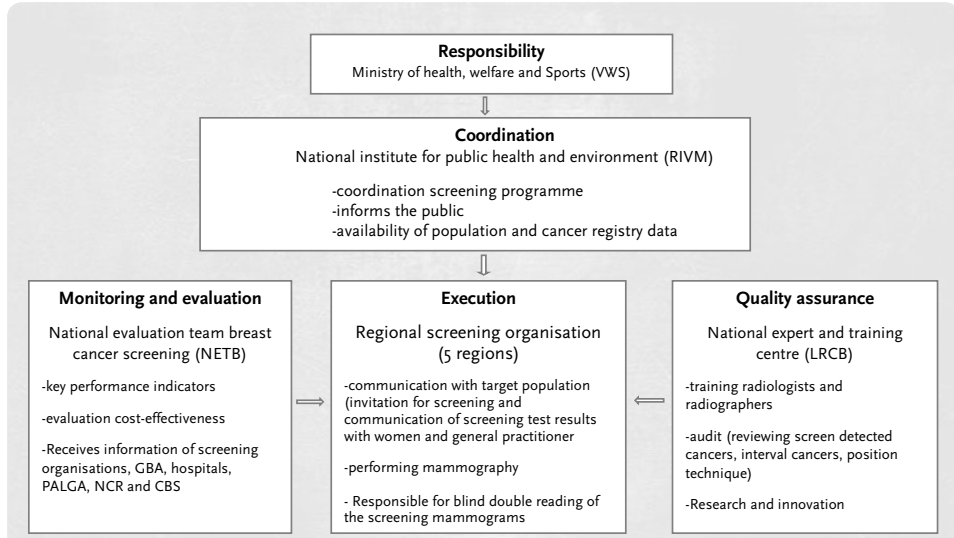






1998 en 2010 are mentioned in Table 3. A small increase in the proportion of patients with positive axillary lymph nodes was noted, probably because of stage migration since the introduction of the sentinel node procedure[32].

FIGURE 4. Organisation of breast cancer screening in the Netherlands




*Source: www.lrcb.nl and www.rivm.nl*

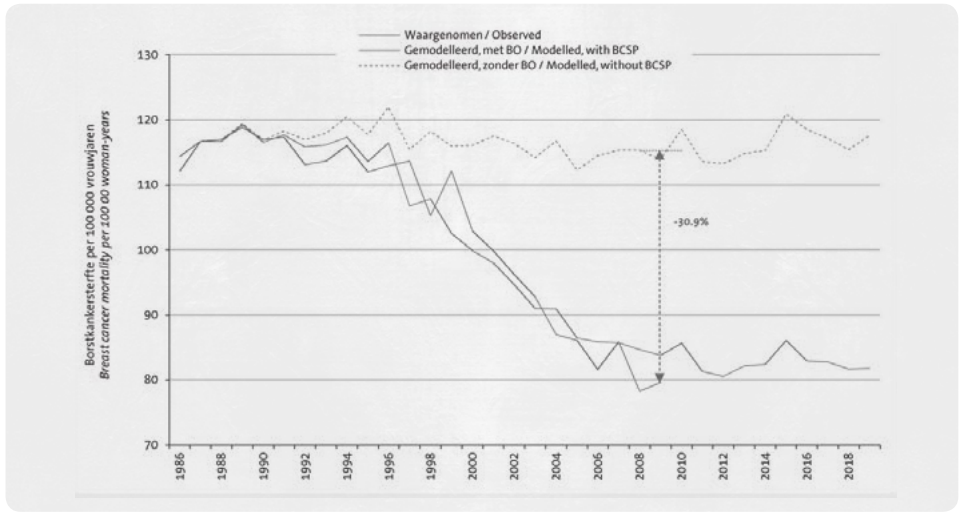
TABLE 3. Key performance indicators of the screening programme in 1998 and 2010.

| Key performance indicators | Year 1998 | Year 2010 |
|---|---|---|
| Referral rate per 1000 women screened | 9,9 | 20,2 |
| Detection rate per 1000 women screened | 4,8 | 5,9 |
| In situ cancers (DCIS) | 14,3% | 20,4% |
| Initial screening round | | |
| -T1N- | 57,5% | 58,2% |
| -T1N+ | 15,3% | 17,3% |
| -Advanced (≥T2) | 23,1% | 23,6% |
| -unknown | 3,8% | 0,0% |
| Subsequent screening rounds | | |
| -T1N- | 64,0% | 66,6% |
| -T1N+ | 12,8% | 14,9% |
| -Advanced (≥T2) | 20,5% | 17,8% |
| -unknown | 2,8% | 0,7% |

*Source NETB report 2012*

In 2010 breast cancer mortality had decreased by 31% (among women aged 55-79 years) compared with the mean annual (pre-screening) rate in 1986-1988. The observed breast cancer mortality rate was slightly lower than the predicted rate based on the previously mentioned MISCAN model (Figure 5)[31,28]. However the share of the screening programme to the mortality reduction as compared to the impact of adjuvant systemic therapy, has not been determined yet, and estimates vary from 50% [33] to virtually zero [34,35].

FIGURE 5. **Observed and predicted breast cancer mortality among women aged 55-79 years, 1986-2009 (Based on the MISCAN model).**




*Source: NETB report 2011*

## DEVELOPMENTS IN BREAST CANCER MANAGEMENT AND SCREENING

### Breast cancer treatment

Past, present and future developments in early detection and treatment of breast cancer, may affect the benefit-risk ratio of mammography screening. Treatments of breast cancer have improved remarkably since the publication of the results of the previously mentioned screening trials. In particular, treatment by (neo) adjuvant systemic and hormonal therapies has intensified[36]. Chemotherapy was introduced in the late 1970's, first for patients with positive axillary lymph nodes and since 1998 also for a substantial part of the lymph node-negative patients, mainly depending of age and tumour grade. Besides the more widespread use of chemotherapy a shift toward more effective treatment regimens and combinations of drugs took place, both in the palliative and adjuvant setting. Major changes also took place in the endocrine treatment of breast cancer. From 1980 onwards tamoxifen (estrogen





receptor modulator) was increasingly used for women with hormone receptor positive breast cancer[36]. In addition rapid implementation of immunotherapy (trasuzumab), in conjunction with chemotherapy for women with HER2-positive breast cancer, took place in 2006[37]. Overall, the use of adjuvant systemic therapy increased from 15% to 49% for patients diagnosed with breast cancer, respectively before 1984 or after 1996[38].

Similar progress has been made with respect to radiotherapy, including the development of sophisticated techniques to minimize the risk of late toxicity. The increased use from the 1980's onward is closely related to the increased use of breast conserving therapy[39]. From this it becomes clear that both earlier diagnosis due to screening and advances in breast cancer treatment have played a role in the reported declining mortality rates of breast cancer.

### Breast cancer awareness

Breast cancer awareness has increased substantially over the last decades. Studies have shown that women tend to overestimate their risk of developing breast cancer[40, 41] and one may argue that this overestimation may partly be due to elaborate coverage of breast cancer in the mainstream media[42]. Increased awareness may also increase the extent of opportunistic screening, which can negatively influence the effectiveness of service screening.

### Breast cancer screening related harms

Inevitably, screening for breast cancer has certain drawbacks. Because it is offered to an asymptomatic population, the risks should be kept to a minimum and be in balance with the harms. Overdiagnosis and related overtreatment is probably the most controversial harm of breast cancer screening. The incidence of ductal carcinoma in situ (DCIS) has increased at a fast rate, mainly due to the introduction of breast cancer screening[43] (see also figure 2b), and despite the relatively benign, non-invasive, nature of DCIS, all patients are treated with surgery and adjuvant radiotherapy is routinely given to patients undergoing lumpectomy. Another potential harm of breast cancer screening is the risk of a false positive referral. Studies have shown that a false positive referral can cause substantial distress and anxiety[44,45], and could negatively influence the re-attendance to the screening programme. The likelihood to re-attend the programme does not appear to be affected by the level of work-up (imaging or biopsy)[46,47], although the degree of distress can be related to the invasiveness of the assessment[48]. The risk of experiencing a false positive screen varies widely between countries, and figures between 20 and 50% have been reported during a screening period of up to two decades[49, 50].

## Interval cancers

Missed breast cancers are inevitably related to screening. It is important to differentiate between true interval cancers and cancers missed at previous screening mammography. About 20-30% of breast cancers among screened women is estimated to emerge as 'interval' cancers, however 18-29% of these cancers appear to have been overlooked at previous screening mammography[51], and thus do not represent true interval cancers. True interval cancers are those cancers where no sign of disease could have been detected at previous screening mammography, thus representing cancers which have progressed above the detection level after the latest screen. A missed cancer may be related to failures in both perception and interpretation of mammographic findings[19]. Since the essence in the concept of screening mammography is the early detection of breast cancer, a delay in the diagnosis might lead to a more advanced stage of the disease, which could diminish treatment options, and result in a worse prognosis[52]. Unfortunately, a delay in the diagnosis of breast cancer is frequently encountered, either as a result of missed breast cancer at screening, or a delay in diagnosis after referral, due to inadequate work-up[53,54]. Delays in diagnosis and errors in the diagnostic work-up are the most common complaint nowadays in medico-legal issues in breast imaging in the UK[55] and by far the most common generic cause of malpractice suits against radiologists in the US[56].

## Breast cancer diagnosis and management

Several developments in breast cancer diagnosis and management have been established in the last decades. Fine needle aspiration cytology was gradually replaced by core needle biopsies for solid lesions. The use of open surgical biopsy rates significantly dropped, from over 28% in 1996 to 2% in 2009 in the BOZ region[57] as a result of the introduction of core biopsy around the year 2000 with high diagnostic accuracy[58, 59], and vacuum assisted biopsies around 2004. Magnetic resonance mammography was gradually implemented in breast care since 2000. Between 2002 and 2007 multidisciplinary teams (including a surgeon, radiotherapist, radiologist, pathologist and breast care nurse) were set up in every hospital to facilitate a comprehensive discussion of the clinical, radiological and biopsy findings of each referred woman.

## Transition screen film to digital mammography

In the Netherlands all screening units had completed the transition from screen-film to digital screening mammography before the end of 2010, when 94% of all screens were digital[31]. Recent studies showed that the transition to digital screening resulted in an enhanced cancer detection rate for both DCIS and invasive cancers, although an increase in referral rate and a related decrease in positive predicted value was seen as well[60,61]. The referral rate increased from 1.5% (screen film mammography, SFM) to 3% (full-field digital







mammography, FFDM) and the positive predicted value (PPV) decreased from 31.6% (SFM) to 21.9% (FFDM)[62].

## Breast cancer screening debate

For almost 15 years now, the effectiveness of breast cancer screening has been under debate. In 2000 the extent of breast cancer mortality reduction through screening was called into question in a Cochrane review by Götzsche et al[63], because of supposed poor internal validity of several studies. The doubt that was caused by the Cochrane review among the general public and in the medical community, resulted in an investigation by the screening committee of the Dutch Health Council, on request of the Dutch minister of Health, Welfare and Sports. The conclusion of its investigation was that the arguments from the Cochrane Review were not persuading enough to stop breast cancer screening[64]. Since then several other studies have refuted the conclusions of the Cochrane centre as well[65]. However the discussion is not over yet, and more recently Kalager et al[66] and Autier et al[67] again have questioned the magnitude of the impact of screening on breast cancer mortality and Bleyer and Welch highlighted the extent of screening related overdiagnosis (and related overtreatment)[68]. A truly objective measurement of the mortality reduction resulting from screening mammography seems very hard to realize, considering the fact that a new randomised controlled trial will no longer be possible and all non-randomized alternatives suffer from bias specifically related to screening studies, including difficulties to rule out lead time bias and length time bias and to account for the effect of adjuvant systemic therapy.

# RELEVANCE AND AIMS OF THESIS

The breast cancer screening programme in the Netherlands is a valuable and appreciated institution. Nevertheless breast cancer screening has proven to be more complicated than envisioned originally. To save lives of some women, many more have to undergo repeated testing, with many of them experiencing subsequent worries after referral and stress related to false positive screening results. Moreover an indefinite proportion of women will experience the diagnosis and treatment of a cancer that would not have become lethal. Despite these drawbacks participation rates continue to be high and new screening programmes are being started, not only for the early detection of breast cancer, but also for cervical and colorectal cancer. In the light of all developments in screening mammography the main objective of this thesis is to assess which aspects in the screening process need further improvement to increase the net effect of the screening programme. The aim of this thesis is to explore how to improve the effectiveness of the breast screening programme in the South of the Netherlands, focussing on bilateral

breast cancer at screening mammography and those women experiencing a false positive referral. Improvements could be achieved concerning cancer detection, work-up after referral and screening re-attendance.

**Part one** (chapter 2 and chapter 3) covers the detection of bilateral breast cancer at screening mammography and the investigation of possibilities to improve its detection within the screening programme.

**Part two** (chapter 4 and chapter 5) comprises the evaluation of women who experienced a false positive referral, with focus on re-attendance after referral and the occurrence of repeated referral in the screening programme.

**Part three** (chapter 6) describes the current sensitivity of screening mammography, the rate of missed cancers and the experiences with related malpractice claims in our screening region.

**The last part** of this thesis concludes in chapter 7 with a general discussion of the main findings, their significance for the current and future breast screening programme at regional and national level and future perspectives.

## PATIENTS AND METHODS

The studies in this thesis are based on data of the women who underwent screening in a southern breast cancer screening region of the Netherlands, BOZ (Bevolkings Onderzoek Zuid/Cancer Screening South), one of the five regional screening organisations in the Netherlands. This organisation provides screening for both cervical cancer and breast cancer in the provinces of Brabant and Limburg, as well as colon cancer screening in the near future. In this region biennial screening mammography was started in 1995. The overall attendance rate has climbed to nearly 84%[69].

Screening mammography (until 2010) in this specific BOZ region was performed at one of two specialized screening units (one fixed unit in Eindhoven and one mobile unit travelling around). Prior to a screening examination women were asked permission to use their screening and follow-up data for evaluation purposes. Women were also asked to fill in a questionnaire comprising the following topics:

- date, type and reason of previous breast surgery
- family history of breast cancer
- hormonal replacement therapy.







### Follow-up procedure

Following standard procedures, the general practitioner informs the screening organisation (BOZ) to which hospital the women had been referred. About 3-6 months after referral the BOZ collects copies of the pathology reports from the regional pathology laboratories, and radiotherapy reports from the regional radiotherapy institute. One radiologist (LD) yearly visited the regional hospitals involved in the work-up of referred women, to collect data of each referred women on imaging procedures, breast biopsy (kind of biopsy and outcome), and breast surgery procedures.

For women diagnosed with breast cancer after referral, diagnostic and therapeutic data were collected from the time of referral through the moment of final therapy (e.g., breast conserving therapy, mastectomy or palliative treatment). Information on the vital status of women screened is obtained from linkage of our database to the national screening database and the municipal register of Death (Gemeentelijke Basisadministratie Persoonsgegevens, GBA). This enabled us to identify the referred women who had died and to identify the referred women who had attended the screening programme in another screening region[70]. Interval cancers were defined as breast cancers diagnosed in women, whose last screening examination yielded negative results (defined as no recommendation for referral) and before a subsequent biennial screen was performed. Most interval cancers were identified by linking the screening records to the regional cancer registry in the southern screening region, Eindhoven cancer registry (ECR). To trace interval cancers to the maximum further efforts were made including collecting data of all radiotherapy reports from regional radiotherapy institutes of women who underwent radiation treatment for breast malignancies and participated in the screening programme[54].

### Eindhoven cancer registry (ECR)

The ECR is part of the Comprehensive Cancer centre South (IKZ, founded in 1982), the data collection of the registry started in 1955 as part of a programme for nationwide cancer registration. The registry started in three hospitals in Eindhoven and gradually expanded, at the moment including the province of North Brabant and the Northern part of the province Limburg, an area with 2.4 million inhabitants (about 15% of the Dutch population), 10 general hospitals and 6 regional pathology laboratories and two radiotherapy institutes[71]. The cancer registry collects information of newly diagnosed malignancies from the national pathology archive (PALGA), national registry of hospital discharge and radiotherapy institutes. Additional data on diagnosis, stage and treatment are collected from hospital records. Also information on comorbidities and lifestyle factors are collected. The data from hospital medical records are actively collected by trained registration clerks. The completeness of the cancer registry is estimated to be at least 95%[72].

### Review of screening mammograms

Two experienced screening radiologists (LD and FJ) independently reviewed the screening mammograms of all screen detected cancers and interval cancers. For cancers detected at subsequent screening, they determined whether the cancer had been missed or whether it had shown a (non-specific) minimal sign at the previous screening mammogram. For interval cancers, they determined if the cancer was occult, had shown a minimal sign, or had been missed at the latest screen.

For all women who were referred and those who presented with an interval cancer, all data was recorded in a special database which was used for quality assurance of the screening programme in the BOZ region.







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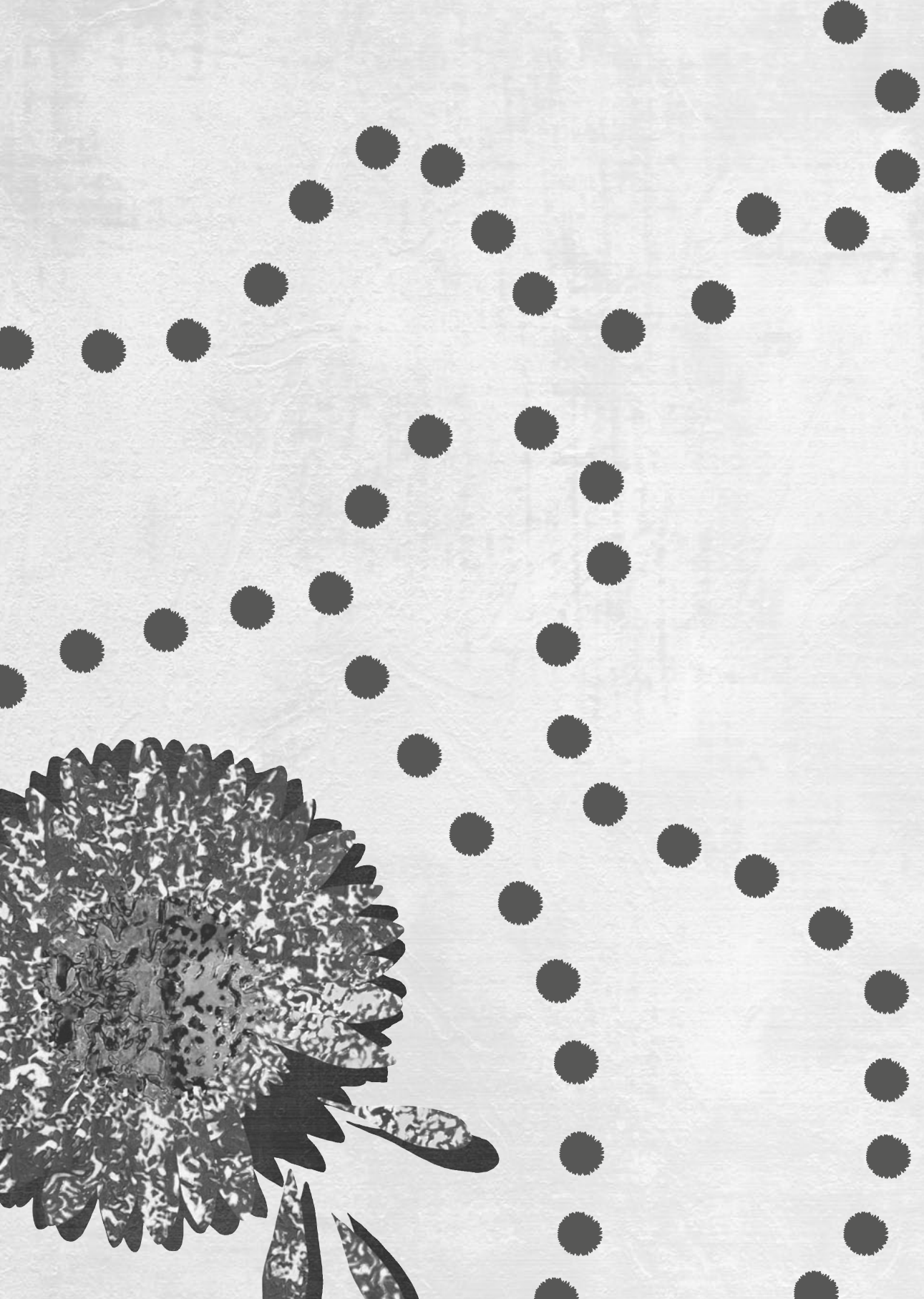
# PART I
## Bilateral breast cancer
at screening mammography



# Chapter 2

## Detection of bilateral breast cancer at biennial screening mammography in the Netherlands:

a population-based study

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## ABSTRACT

### Background

To determine the incidence of bilateral breast cancer at biennial screening mammography and to assess the sensitivity of screening for the detection of bilateral breast cancer.

### Methods

All women gave written informed consent, and the requirement to obtain review board approval was waived. The authors included all 302196 screening mammograms obtained in 80466 women aged 50-75 years in a southern breast screening region of the Netherlands between May 1998 and July 2008. During two-year follow-up, we collected clinical data, breast imaging reports, biopsy results and breast surgery reports from all screen-detected and interval cancers. Two screening radiologists reviewed the screening and clinical mammograms of all bilateral screening detected and interval cancers for mammographic abnormalities. The radiologists were initially blinded to each other's referral opinion, and discrepant assessments were followed by consensus reading.

### Results

Of all women with screen-detected cancer (n=1555) or interval cancer (n=585), 52 (2.4%) had bilateral breast cancer. The sensitivity of screening mammography in the detection of bilateral breast cancer was 19% (10 of 52 women, 95% confidence interval: 8.5%-29.9%). At blinded review, 18 of the 53 non-screen-detected tumors (34%) were considered to be missed, 11 (21%) showed non-specific minimal signs, and 24 (45%) had been mammographically occult at screening. Five women referred for further analysis experienced a 6-17 month delay of the second breast cancer; in four of those women, the delay resulted from an incorrect BI-RADS classification at clinical mammography.

### Conclusion

The sensitivity of screening mammography in the detection of bilateral breast cancer detection is disappointingly low. Both screening radiologists and clinical radiologists should pay vigorous attention to the contralateral breast in order to detect bilateral malignancies without diagnostic delay.






## INTRODUCTION

Mammography is widely used to screen asymptomatic women for breast cancer. Several studies have shown that screening mammography reduces breast cancer mortality by helping detect breast malignancies at an early stage[1,2]. It is estimated that about 20%-30% of breast cancers emerge as interval cancers (cancers diagnosed after a negative screening examination (defined as no recommendation for referral) and before the next scheduled screening round). Of these interval cancers, 18%-29% are considered to be missed at screening mammography[3-5].

Breast cancer may be diagnosed bilaterally. The overall frequency of bilateral breast cancer has been shown to range from 4%-10%. The frequency of bilateral synchronous breast cancer is more uncommon and has been reported in 1%-3%[6-9]. Radiologic improvements in breast cancer detection, such as the use of magnetic resonance imaging (MRI), have raised interest in bilateral breast cancer, because of an increase in detection of contralateral breast cancer. In women with newly diagnosed breast cancer, MR imaging has been reported to find contralateral cancer in 3%-5% of patients[10-12].

Studies about the sensitivity of breast radiology in the detection of bilateral breast cancers have mainly focused on symptomatic patients[12,13]. Although screening mammography programs are increasingly implemented throughout the world, to our knowledge no data have been published with regard to bilateral breast cancer detection at screening mammography. Therefore, the aim of the current study was to determine the incidence of bilateral breast cancer at biennial screening mammography and to assess the sensitivity of screening for the detection of bilateral breast cancers.

## MATERIALS AND METHODS

### Screening procedure and imaging technique

We included all 302196 screening examinations obtained in 80466 women aged 50-75 years at one fixed and one mobile unit in a southern breast cancer screening region of the Netherlands (Bevolkings Onderzoek Zuid, BOZ) between May 1, 1998 and July 1, 2008. Women participating in the Nationwide Dutch screening program are asked to give written informed consent for the use of their data for scientific purposes and all but three women included in our study had given this informed consent. According to the Dutch Central Committee on Research involving Human Subjects (CCMO), approval by our local Institutional Review Board was not required for this study.

Two-view mammography (medio-lateral-oblique view and cranio-caudal view) of each breast was performed at the initial examination (ie, the first time the women were screened). Subsequent screening examinations primarily consisted of one-view mammography (medio-lateral-oblique view) only. An additional cranio-caudal view was obtained in 43.7% of subsequent screening examinations (115399 of 264043 subsequent screening mammograms). Indications for this second view included any changes in mammographic findings at screening, a complicated judgment regarding interpretation owing to dense fibroglandular tissue, a history of previous breast surgery and an interval of more than 2 years since the previous screening examination.

All mammographic examinations were performed by specialized screening mammography technicians. The mammograms were obtained by using commercially available units (at fixed center: Performa, Oldelft, Tuusula, Finland; at mobile center: Alfa RT, Oldelft and from 2004: Performa, Oldelft). Dedicated mammography screens were used (at fixed center: Mamoray MR-R, Agfa, Schroenhausen, Germany; at mobile center: Mamoray MR-S, Agfa and from 2004: Mamoray MR-R). Both dedicated film (both centers: Mamoray HDR; Agfa, Mortsel, Belgium), as well as extended-cycle dedicated processing were used.

## Image interpretation and referral

During the study period, a total of 11 screening radiologists participated in the screening program. Each radiologist read more than 5000 mammograms annually. All screening mammograms were assessed independently by two certified screening radiologists. From May 1998 till January 2001, discrepant readings for which the two screening radiologist did not reach consensus about referral were presented to a panel of three radiologists. Women were referred for further analysis when at least one of the three panel radiologists recommended referral. Arbitration panel reading was abandoned in January 2001 as this reading strategy did not detect all lesions that subsequently proved to be malignant[14]. From 2001 to 2002, discrepant readings for which the two screening radiologists did not reach consensus were therefore routinely referred for further analysis. From 2003 on, the mammograms were independently read by two mammography screening technicians in addition to independent double reading performed by the radiologists[3,15]. A woman was referred for additional workup if both screening radiologists considered the mammogram to be positive or, in the case of discrepant readings, if at least one radiologist considered referral necessary after consensus meeting. In addition, mammograms that the technologists had considered to be positive but that had not been referred by the radiologists were reviewed by two screening radiologists. A woman was referred if, on review, at least one of the radiologists considered workup to be necessary. A woman was not referred for further diagnostic workup in case of normal findings,





benign mammographic findings (e.g., lymph nodes, calcified fibroadenoma, lipoma and vascular calcifications) or non-specific minimal signs (vague area of density with an incomplete sharp border and a diameter between 5 and 30 mm [density comparable to that of glandular tissue], fewer than 6 clustered nonspecific microcalcifications, and subtle architectural distortions that include asymmetric glandular tissue)[16]. Lesions determined to be suspicious or malignant at screening mammography were classified into one of the following categories: 1) suspicious high density (spiculated density or density with indistinct borders); 2) suspicious microcalcifications (pleiomorphic, branching or amorphous / indistinct microcalcifications); 3) high density in combination with microcalcifications; 4) architectural distortion, or 5) asymmetry.

## Diagnostic workup

In case of suspicious or malignant findings at screening mammography, the woman was referred by her general practitioner to a surgical oncologist. After physical examination by the surgeon, clinical two-view mammography of each breast was obtained; local compression or magnification mammograms are obtained at the radiologist's discretion. The radiologist then decided whether breast ultrasonography, MR imaging and/or biopsy should be performed. At diagnostic workup, radiologists classified the radiologic findings according to the American College of Radiology BI-RADS[17,18]. Patients with probably benign breast imaging results (BI-RADS III) or benign biopsy results at workup usually undergo a first follow-up mammography at 6 months. Depending on the findings at follow-up mammography, a repeated mammogram at a later stage may be obtained to exclude malignancy.

## Screening follow-up procedure and review of bilateral breast cancers

During a follow-up period of about 2 years (until the next biennial screening examination), we collected screening mammography findings, clinical data, additional breast imaging reports, biopsy results and breast surgery reports of all women with a positive screening result (i.e. those that required additional evaluation). Procedures for the detection of interval cancers have been described previously[14,19]; most interval cancers were identified by linking the screening records to the regional cancer registry (Eindhoven Cancer Registry) and regional pathology laboratories.

Two screening radiologists (L.E.M.D., F.H.J., with 13 and 15 years of screening experience, respectively) reviewed the screening and clinical mammograms of all women in whom bilateral breast cancer was diagnosed within 2 years after the latest screening examination. They retrospectively determined whether tumors that were not detected with screening mammography (first and/or second examinations) had been missed, had shown a

nonspecific, minimal sign or had been mammographically occult at screening. At review, the radiologists were informed about the bilateral nature of the malignancies, but they had no information whether the cancers had been detected at screening or had emerged as interval cancers. The radiologists also assessed the breast density of the most recent screening mammograms according to the American College of Radiology BI-RADS (Breast Imaging Reporting and Data System)[18] and classified the mammographic abnormality of each visible cancer into one of the five categories described previously. Finally, to determine the cause of a delay in breast cancer diagnosis after referral, the radiologists also reviewed the initial clinical mammogram of those women who had a diagnosis of the contralateral breast cancer more than 3 months after referral. These clinical mammograms were also classified in accordance with BI-RADS. At review, the radiologists were initially blinded to the referral opinion of each other and discrepant assessments were followed by consensus reading.

Synchronous and metachronous bilateral breast cancers were defined as bilateral cancers in which the cancer in the contralateral breast was diagnosed within 3 months or more than 3 months, respectively, after the diagnosis of the index cancer for which the woman had been referred.

### Statistical analysis

The primary outcome measures were the incidence of bilateral breast cancer at biennial screening mammography and the sensitivity of screening mammography for the detection of these cancers. Descriptive statistics were performed using Statistical Package for Social Sciences 17.0 (SPSS Inc. Chicago, IL). The chi-square test and Fisher's Exact test were used to test the differences in breast density and histologic tumor characteristics between referred women whose bilateral cancer had or had not been detected at screening. The significance level was set at p=0.05.

## RESULTS

### Overall screening outcome

A total of 302196 screens were obtained in 80466 women between May 1, 1998 and July 1, 2008. Altogether, 3801 (1.3%) screening mammograms were referred for further diagnostic assessment. Assessment of women with positive screening mammograms was performed at 18 hospitals; at least 500 women were evaluated at 4 of the hospitals. At follow-up, breast cancer was diagnosed in 1555 women, yielding an overall cancer detection rate of 5.1 per 1000 women screened and a true positive referral rate of 40.9%. At 2-year follow-up, interval cancers had been diagnosed in 585 women. The overall screening sensitivity for breast cancer detection, irrespective of the unilateral or bilateral presence of breast cancer,



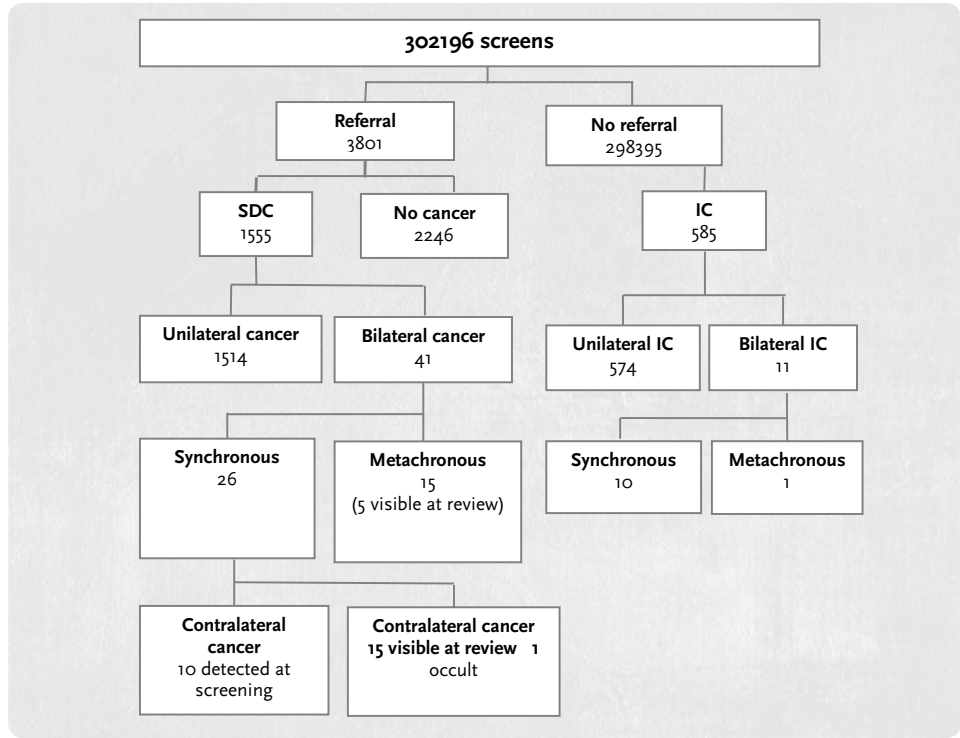


was 72.7% (1555 of 2140 women; 95% confidence interval [CI]: 70.9%-74.6%). Bilateral breast cancer was diagnosed in 41 of the 1555 women with screening-detected cancers and 11 of the 585 interval cancers (ie, 2.4% (52 of 2140 women) of all cases), resulting in a bilateral breast cancer detection rate of 0.17 per 1000 screening mammograms.

### Screening sensitivity for bilateral breast cancer detection

Ten of all 52 women with bilateral breast cancer (including the women with bilateral interval cancers) had been referred for the assessment of a bilateral mammographic abnormality noted at screening mammography, resulting in a screening sensitivity for bilateral breast cancer of 19% (10 of 52 women, 95% CI: 8.5%-29.9%). Another 31 women with bilateral breast cancer had been referred for a unilateral abnormality alone; the contralateral tumor was detected within 3 months following referral in 16 women (synchronous bilateral cancer) and more than 3 months following referral in 15 women (metachronous bilateral cancer). The remaining 11 bilateral breast cancers were interval cancers (Figure).

FIGURE. Outcome at biennial screening mammography




*SDC = screen detected cancer; IC = interval cancer; Synchronous: contralateral cancer diagnosed ≤ 3 months after index cancer. Metachronous: contralateral cancer diagnosed > 3 months after index cancer*

In the 52 women with bilateral breast cancer (104 cancers), 51 tumors were detected at screening mammography and 53 were not. At blinded review, 18 of the 53 tumors (34%) non detected at screening were considered to have been missed at screening mammography, 11 (21%) had shown a minimal sign and 24 (45%) had been mammographically occult.

## Characteristics of bilateral cancers in referred women

At review of the screening mammograms of the 16 synchronous contralateral cancers not detected at screening, the tumor was considered mammographically occult in 1 case (6.3%), to have shown a minimal sign in 4 cases (25%) and to have been missed in 11 cases (69%). Review of the screening mammograms and initial clinical mammograms (ie, the first mammogram obtained after referral) of the 15 metachronous contralateral cancers not detected at screening showed a suspect lesion in 4 cases, a minimal sign lesion in 1 case, and no mammographic abnormalities in 10 screens. The diagnostic delay of the 5 cancers that had been visible at screening was due to misclassification of BI-RADS categories (BI-RADS 3 instead of BI-RADS 4 or 5) at the initial clinical mammograms in 3 cases and to a false negative core biopsy of a BI-RADS 4 lesion in 1 case. In one patient, a cluster of microcalcifications, located at the periphery of the screening mammogram and defined as a minimal sign abnormality at review, was not depicted at initial clinical mammography. Biopsy was performed when the microcalcifications were properly visualized at follow-up mammography 6 months after breast conserving surgery. The diagnostic delay of these 5 contralateral cancers ranged from 6-17 months.

The 10 metachronous contralateral cancers not detected at screening, which were considered mammographically occult on both the latest screening mammogram and the initial clinical mammogram, were diagnosed 6-23 months after the first cancer (mean 14 months). These cancers were diagnosed after they manifested as a palpable mass (3 cases) or as a radiologic abnormality at follow-up of the first cancer (7 cases).

A BI-RADS breast density category of less than 2 was assigned in 38 of the 51 (75%) screening-detected cancers (51 tumors, of which 41 were index tumors and 10 were screening-detected contralateral tumors) and 20 of the 31 (65%) non-screening detected cancer (31 contralateral cancers); the difference was not significant (p=0,23).

The 41 bilateral breast cancers in referred women comprised 55 invasive ductal cancers (67%), 19 invasive lobular cancers (23%) and 8 in situ ductal cancers (9.7%). There was no significant difference in detection of invasive ductal cancers compared to invasive lobular cancers (71% [39 of 55 women] vs. 47% [9 of 19 women], respectively; p=0.06).





## Characteristics of bilateral interval cancers

All but one of the 11 bilateral interval cancers were detected synchronously, shortly after clinical presentation. The predominant, index lesion presented as a palpable abnormality (8 cases) or nipple retraction (3 cases). The mean time between the last screening mammogram and the clinical presentation of the interval cancers was 11 months (range 5-19 months). Nine index lesions were classified as BI-RADS 4 or 5 lesions at clinical mammography, whereas 2 index lesions with normal findings at clinical mammography were found at breast ultrasound of a palpable mass. The 10 synchronously diagnosed contralateral cancers were detected at clinical mammography (7 cancers), breast ultrasound of a palpable mass (2 cancers), or MR imaging (1 cancer). The single metachronously diagnosed contralateral cancer showed a BI-RADS 3 density at the initial clinical mammogram and the malignant nature of this lesion was confirmed by percutaneous biopsy at 12 months follow-up.

Review showed that 9 of the 22 interval cancers (41%) had either been missed at the latest screen (3 cases, of which 2 were densities and 1 was an architectural distortion) or demonstrated a minimal sign (6 cases, of which 4 were densities and 2 were clusters of nonspecific microcalcifications).

The 22 interval cancers comprised 16 invasive ductal cancers (72.7%) and 6 invasive lobular cancers (27.3%).

The total group of 52 bilateral breast cancers (104 tumors) comprised 71 invasive ductal cancers (68%), 25 invasive lobular cancers (24%), and 8 ductal cancers in situ (7.7%). There was no significant difference in detection of invasive ductal cancers compared with that of invasive lobular cancers (55% [39 of 71 cases] vs. 36% [9 of 25 cases], respectively; p=0.08).

# DISCUSSION

To our knowledge, this is the first study to address the detection of bilateral breast cancers at screening mammography. In our population bilateral breast cancer comprised 2.4% of all screening-detected cancers and interval cancers. Variations in cancer detection rates at screening programs may partly be explained by differences in characteristics of screened women and differences in screening protocols. Nevertheless, the overall 73% screening sensitivity in our study is in line with those reported in other series[20,21].

Although controversy exists as to the exact impact bilateral breast cancer has on survival, several studies have shown that the prognosis of women with bilateral breast cancer tend to

be worse compared to women with unilateral cancer[8,9,22] and a delay in the diagnosis of breast cancer will further worsen the prognosis[23]. It may therefore be even more important to timely detect bilateral breast cancer at screening. Unfortunately, the screening sensitivity of 19% for bilateral breast cancer detection in our study was frankly disappointing. Several factors may have attributed to this low sensitivity. First, some of the contralateral cancers could simply not be detected at screening because they were mammographically occult. However, more often they were missed as a result of perception error (mammographic abnormality not detected at screening) or interpretation error (mammographic abnormality misinterpreted at screening). Perception errors and interpretation errors both account for approximately half of missed breast cancers visible at screening[21]. Review showed that a majority of the contralateral breast cancers in women who had been referred for a unilateral lesion only (and in whom the contralateral tumor was detected within 3 months) had been missed at screening; only one contralateral cancer had been mammographically occult. An important cause for missing contralateral cancers may be the happy eye syndrome, or satisfaction of search[24]. The observation of a suspicious lesion may mislead a screening radiologist into not looking carefully for other, contralateral lesions. The sensitivity of mammography for breast cancer detection also depends on tumor histology. Invasive lobular breast cancer accounts for approximately 8-10% of breast cancers in the general population, but it is found more frequently in bilateral breast cancers[25]. Compared with invasive ductal cancers, invasive lobular cancers are more difficult to detect at mammography as these tumors more commonly present as subtle architectural distortions or focal asymmetric densities resembling that of normal breast parenchyma, or show no mammographic abnormalities at all[26]. We also observed a relatively high percentage of invasive lobular cancers (24%) in women with bilateral interval cancers or bilateral cancers diagnosed after referral owing to a unilateral or bilateral screening abnormality. The detection of invasive lobular cancer in our series, however, was not worse than that of invasive ductal cancer, which may be explained by the relatively small number of bilateral breast cancers in our study.

Five of the referred women experienced a 6 to 17-months delay in the diagnosis of the contralateral breast cancer, despite the fact that the mammographic abnormality was visible on the latest screening mammogram and/or initial clinical mammogram. Previous studies have shown that the workup of referred patients should be improved in order to prevent an unnecessary delay in cancer diagnosis[19,27,28]. These diagnostic delays may be due, especially, to misinterpretation of mammographic lesions as benign or probably benign at clinical mammography.

In women with bilateral interval cancers, one of the malignancies was found at contrast-enhanced MR imaging. Contrast-enhanced MR imaging has emerged as a highly sensitive





imaging modality for the detection of synchronous contralateral cancers or high-risk lesions in patients with newly diagnosed breast cancer[29]. Compared with conventional mammography, contrast-enhanced MR imaging has a higher sensitivity in detecting invasive lobular cancers and may be used for a more accurate determination of tumor size, tumor multifocality and assessment of pectoral muscle invasion by tumor growth[30,31]. Although randomized controlled trials are needed to establish the long-term effects of contrast-enhanced MR imaging in women newly affected by breast cancer[32], the use of this diagnostic modality could probably have led to an earlier diagnosis of the metachronous cancers in our study.

Our study has certain limitations. The referral rate in the Dutch nationwide screening program is much lower than that in other screening programs[33]. We are not able to quantify the impact of this lower referral rate on the sensitivity of detecting breast cancer, regardless whether it is unilateral or bilateral. Patients with nonspecific minimal signs, which are present in about 11% of screening mammograms, were not referred for further diagnostic assessment because these lesions have a low cancer risk of 0.5% and a favorable tumor stage if malignant[16]. After a critical reconsideration of non-specific minimal signs and the implementation of screening BI-RADS, an increased referral rate is currently observed in the Dutch breast screening program[34]. Screening outcome parameters will be influenced by the screening interval used at screening programs. Many European programs, including the Dutch one, offer biennial screening for women aged 50-75 years. In contrast, women in the United Kingdom are screened every 3 years and those in the United States are usually offer annual screening[33]. In contrast to programs where two-view mammography is routinely performed, the Dutch screening program offers single-view mammography (medio-lateral-oblique) at subsequent screening. An additional cranio-caudal view is obtained if indicated only and the detection of breast cancer, either unilateral or bilateral, may have been hampered by this limited use of two-view mammography at subsequent screening mammography in our study[35]. The applicability of our study may somewhat be limited by the fact that only mammograms obtained with analog screening units were included; most mammography units are now digital. In the Netherlands, the conversion from analog to digital screening has recently been completed for the nationwide breast screening program. Despite the similar of even higher cancer detection rate found at digital screening when compared to analog screening[36,37], we currently cannot predict the effect of digital screening on the detection of bilateral breast cancers. Finally, the knowledge of a high probability of bilateral breast cancer at review of the screening mammograms and clinical mammograms in our population is not a true reflection of daily screening practice, and may have introduced detection bias.

In summary, we found that screening mammography has a low sensitivity for the detection of bilateral breast cancer. Both screening radiologists and clinical radiologists should pay utmost attention to the contralateral breast in order to detect bilateral malignancies without diagnostic delay. Although bilateral breast cancers comprise a small proportion of all screen detected cancers and interval cancers, a timely diagnosis of the bilateral disease is important in order to prevent a worsening in survival prognosis.





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# Chapter 3

## Patient and tumour characteristics of bilateral breast cancer

a population-based study

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## ABSTRACT

Few data are available on bilateral breast cancer in the screening population. The aim of this study was to determine patient and tumor characteristics of women with bilateral breast cancer at screening mammography. We included all 350637 screening mammography examinations of women participating in a biennial screening program in a southern screening region of the Netherlands between May 1998 and January 2010. For referred women all breast imaging reports, biopsy results and surgery reports during one year after referral were collected. We compared patient and tumor characteristics of referred women with a diagnosis of bilateral breast cancer or unilateral breast cancer at workup. Bilateral or unilateral breast cancer had been diagnosed in respectively 40 (2.2%) and 1766 (97.8%) of 1806 referred women. Women with bilateral or unilateral breast cancer did not differ significantly in mean age, mammographic breast density, family history of breast cancer or use of hormone replacement therapy. Compared with index cancers, contralateral cancers comprised significantly more lobular cancers (p=0.02). Tumor size, mitotic activity and estrogen receptor status were comparable for both groups, but contralateral cancers had a significantly lower risk of lymph node metastases (p=0.03). Compared to unilateral breast cancer, contralateral malignancies in women with bilateral breast cancer comprised significantly more lobular cancers (p=0.004) and lymph node negative cancers (p=0.01). Contralateral breast cancers detected at screening comprise more lobular cancers and show less nodal involvement than index cancers or unilateral cancers. No differences are observed with respect to other patient and tumor characteristics.






## INTRODUCTION

In western countries, breast cancer is the most common malignancy diagnosed in women. Screening mammography aims to detect breast cancer at an early stage and several studies have shown that screening mammography reduces breast cancer mortality[1,2].
Breast cancer is infrequently diagnosed bilaterally. Of all breast cancers diagnosed in symptomatic women, only 0.3% to 12% comprises bilateral cancers[3-6]. This proportion is likely to increase as a result of implementation of screening mammography programs worldwide, and a more intensive use of Magnetic Resonance (MR)-mammography in the diagnostic workup of breast disease[7-11].

Risk factors for bilateral breast cancer in symptomatic patients are young age and a family history of breast cancer[10,12]. Several studies report more favorable tumor characteristics for bilateral breast cancer compared to unilateral breast cancer, including a smaller tumor size at the time of diagnosis and a larger proportion of receptor positive cancers[5,13]. Furthermore, invasive lobular cancer is more frequently diagnosed in bilateral than in unilateral breast cancer[4,13-15]. Although the impact of bilateral breast cancer on prognosis is still a question of debate, a majority of studies conclude that the survival of patients with bilateral disease is worse than that of patients with unilateral disease[3,6,13,16-18].

Despite the increased use of screening mammography programs worldwide, to our knowledge, few data are available on bilateral breast cancer characteristics in the screened population. We recently showed that the sensitivity for bilateral breast cancer detection at screening mammography is very low[19]. The purpose of the current study was to investigate patient and tumor characteristics of screened women with a diagnosis of bilateral breast cancer after referral and to compare these characteristics with referred women who had a diagnosis of unilateral breast cancer.

## MATERIALS AND METHODS

### Study population

We included 84160 women aged 50-75 years, who underwent biennial screening mammography in a southern breast cancer screening region of the Netherlands between May 1, 1998 and December 31, 2009. Women participating in the nation-wide Dutch screening program are asked to give written informed consent for the use of their data for scientific purposes and all but three women in the study period had given this informed consent. According to the Dutch Central Committee on Research involving Human Subjects (CCMO), approval by our local Institutional Review Board was not required for this study.

## Screening procedure and referral

Screening mammography was performed at one of two specialized screening units (one fixed and one mobile unit). In May 2009, the two analogue screening units were replaced by two digital screening units. Details of the nation-wide breast screening program have been described previously[20]. In brief, women fill in a basic questionnaire before screening mammography is performed. This questionnaire relates to issues such as previous breast surgery or breast malignancy, family history of breast cancer (defined as at least one first-degree relative with a diagnosis of breast cancer before the age of 50 years or at least two second-degree relatives with breast cancer) and hormonal replacement therapy. All examinations were independently read by two certified screening radiologists and discordant assessments between the two radiologists were solved by consensus reading. Women with normal, benign, or non-specific minimal signs, were not referred for further work-up. Women with suspicious or malignant findings at screening mammography were referred to a surgical oncologist for further analysis. Suspicious or malignant findings were classified into one of the following five categories: suspicious high density (spiculated or irregular borders), suspicious microcalcifications (pleomorphic, branching or amorphous/indistinct), high density in combination with microcalcification, architectural distortion or breast parenchyma asymmetry. Work-up consisted of physical examination by the surgeon and clinical two-view breast imaging. Additional mammographic views, breast ultrasonography or magnetic resonance (MR)-imaging was performed at the radiologist's discretion. Breast imaging was followed by percutaneous biopsy (fine needle aspiration cytology or core biopsy) or surgical biopsy if indicated.

## Follow-up procedure

For all women with a positive screening mammogram, we recorded the information of the basic questionnaire in our database. We collected data on any diagnostic procedures, breast cancer diagnosis, histopathology and tumor-node-metastasis (TNM) classification during the first year after referral to identify screen-detected cancers. Breast malignancies other than primary breast cancers were excluded from the analysis and we considered lobular carcinoma in situ to be a benign lesion. Detailed information about the follow-up procedures is described elsewhere[8,20].

Bilateral cancer was considered synchronous if both cancers were diagnosed within 3 months from each other, whereas metachronous bilateral breast cancers constituted those cases where the contralateral malignancy was detected more than 3 months after diagnosis of the index cancer for which the woman had been referred. For women who had been referred for bilateral screening abnormalities, the cancer with the highest T stage was defined as index tumor. If a woman had been referred for a unilateral mammographic





abnormality, the index tumor comprised the malignancy for which she had been referred and we defined the contralateral tumor as the second primary that had been detected in the other breast, either synchronously or metachronously.

## Review of screening mammograms

Two screening radiologists (L.D., F.J.) reviewed the screening mammograms of all women with bilateral breast cancer diagnosed within one year after referral. For those women with bilateral breast cancer who had been referred for a one sided abnormality only, they classified the mammographic abnormality of the contralateral malignancy at the latest screening examination. The radiologists also assessed the breast density of the most recent screening mammograms, according to the American College of Radiology BI-RADS (Breast Imaging Reporting and Data System), of all referred women with a diagnosis of breast cancer at workup[21]. At review, the two radiologists were initially blinded to information from each other and discrepancies were followed by consensus reading.

## Statistical analysis

The main outcome measures were patient and tumor characteristics in referred women with a diagnosis of unilateral or bilateral breast cancer. We compared patient characteristics of all bilateral cancers with those of unilateral cancers and compared tumor characteristics of index cancers and contralateral cancers with each other and with unilateral cancers. Descriptive statistics were performed using Statistical Package for Social Sciences 17.0 (SPSS Inc. Chicago, IL). The *t*-test, chi-square or Fisher exact test was used to test differences in characteristics. The significance level was set at p=0.05.

# RESULTS

## Cohort characteristics

A total of 350637 screens in 84160 women were obtained between May 1, 1998 and December 31, 2009. Altogether, 4841 screens (1.4%) were referred for further diagnostic examination. Breast cancer was diagnosed in 1806 referred women, yielding an overall cancer detection rate of 5.2 per 1000 screening examinations and a true positive referral rate of 37.3%. The 1806 true positive referrals constituted 40 bilateral breast cancer patients (2.2%) and 1766 unilateral breast cancers (97.8%). Bilateral breast cancer was diagnosed, either synchronously or metachronously, in respectively 32 (80%) and 8 (20%) women.

## Patient characteristics

There was neither a difference in mean age between bilateral breast cancer cases compared to unilateral breast cancer cases (mean age 62.8 years vs. 62.5 years, p=0.74),

nor a difference in the presence of a family history of breast cancer (27.5%) [11/40] vs. 19.6% [346/1766], p=0.21) or use of hormone replacement therapy (7.5% [3/40] vs. 8.4% [149/1766], p=0.83). The fibroglandular tissue density at the latest screening mammogram was also comparable between the two groups (breast density category 3 or 4: 30.0% [12/40] vs. 31.3% [553/1766], p=0.85).

## Tumor characteristics

**Bilateral breast cancers;**

**Index cancer (n=40) versus contralateral cancer (n=40)**

Eleven women had been referred for a two-sided abnormality. In these women all index cancers and all but one of the contralateral cancers were invasive. Invasive index cancers and invasive contralateral cancers comprised comparable proportions of T1 cancers (<20 mm) (index cancers: T1, 81.8% [9/11]; contralateral cancers: T1, 90.0% [9/10], p=0.5). At clinical workup, bilateral breast cancer was diagnosed in another 29 women who had been referred for an abnormality in one breast. At review, the contralateral cancer was considered radiologically occult at screening in 6 women and these cancers were diagnosed at evaluation of a palpable breast lesion (3 women) or detected at MR-imaging (3 women).

The lesion characteristics at the latest screening mammogram were comparable for index cancers and contralateral cancers (Table 1). For invasive breast cancer, contralateral cancers comprised significantly more malignancies of the lobular type (36.4% [12/33] vs. 13.5% [5/37], p=0.02). Tumor size of invasive cancers was comparable for index cancers and contralateral cancers, but women with invasive contralateral cancers were significantly less likely to have lymph node metastases (90.9% [30/33] vs. 70.3% [26/37], p=0.03). We observed no significant differences in the mitotic activity index score or receptor status between invasive index or contralateral cancers.

**Bilateral and unilateral breast cancers;**

**Index cancer of bilateral breast cancer (n=40) versus unilateral breast cancer (n=1766)**

There were no significant differences between the two groups with respect to mammographic presentation of breast cancer at screening mammography or tumor characteristics (further data not shown).





TABLE 1. Screening mammography and tumor characteristics of index cancers and contralateral cancers in bilateral breast cancer patients

| | Index cancer N=40 | Contralateral cancer N=40 | P-value |
|---|---|---|---|
| Mammographic abnormality, No (%) [a] | | | 0.53 |
| High density | 29 (72.5) | 21 (61.8) | |
| Microcalcifications | 7 (17.5) | 9 (26.5) | |
| High density with microcalcifications | 3 (7.5) | 4 (11.8) | |
| Architectural distortion | 1 (2.5) | 0 (0.0) | |
| Tumor type, No (%) | | | 0.17 |
| Ductal cancer in situ | 3 (7.5) | 7 (17.5) | |
| Invasive cancer | 37 (92.5) | 33 (82.5) | |
| Invasive cancer histology, No (%) | | | 0.02 |
| Ductal | 32 (86.5) | 21 (63.6) | |
| Lobular | 5 (13.5) | 12 (36.4) | |
| Size of invasive cancers, No (%) | | | 0.66 |
| T1a-c | 31 (83.8) | 28 (87.5) | |
| T2+ | 6 (16.2) | 4 (12.5) | |
| Unknown[b] | 0 | 1 | |
| Lymph-node status of invasive cancers, No (%) | | | 0.03 |
| Negative | 26 (70.3) | 30 (90.9) | |
| Positive | 11 (29.7) | 3 (9.1) | |
| Estrogen-receptor status, No (%)[c] | | | 0.51 |
| Positive | 32 (86.5) | 25 (80.6) | |
| Negative | 5 (13.5) | 6 (19.4) | |
| Unknown[b] | 0 | 2 | |
| Mitotic activity (No. of mitoses per 2 mm2), No (%)[c] | | | 0.92 |
| <10 | 31 (88.6) | 25 (89.3) | |
| >10 | 4 (11.4) | 3 (10.7) | |
| Unknown[b] | 2 | 5 | |

[a] *Six contralateral cancers were mammographically occult at screening;*

[b] *Unknown cases were excluded from statistical analysis;*

[c] *Invasive cancers only*

**Contralateral cancer of bilateral breast cancer (n=40) versus unilateral breast cancer (n=1766)**

Compared to unilateral breast cancer patients, invasive contralateral malignancies of bilateral breast cancer patients comprised significantly more lobular cancers (36.4% [12/33] vs. 17.1% [249/1454], p=0.004) and significantly more lymph-node negative cancers (90.9% [30/33] vs. 72.2% [1028/1424], p=0.01; Table 2). There were no significant differences in cancer presentation at screening mammography, tumor size, receptor status or mitotic activity (Table 2).

TABLE 2. Screening mammography and tumor characteristics of unilateral breast cancer patients and contralateral cancers of bilateral breast cancer patients

| | Unilateral cancer N=1766 | Contralateral cancer N=40 | P-value |
|---|---|---|---|
| Mammographic abnormality, No (%) [a] | | | 0.67 |
| High density | 1170 (66.3) | 21 (61.8) | |
| Microcalcifications | 341 (19.3) | 9 (26.5) | |
| High density with microcalcifications | 187 (10.6) | 4 (11.8) | |
| Architectural distortion | 14 (0.8) | 0 (0.0) | |
| Asymmetry | 54 (3.1) | 0 (0.0) | |
| Tumor type, No (%) | | | 0.99 |
| Ductal cancer in situ | 309 (17.5) | 7 (17.5) | |
| Invasive cancer | 1454 (82.5) | 33 (82.5) | |
| Unknown[b] | 3 | 0 | |
| Invasive cancer histology, No (%) | | | 0.004 |
| Ductal | 1205 (82.9) | 21 (63.6) | |
| Lobular | 249 (17.1) | 12 (36.4) | |
| Size of invasive cancers, No (%) | | | 0.20 |
| T1a-c | 1135 (78.3) | 28 (87.5) | |
| T2+ | 315 (21.7) | 4 (12.5) | |
| Unknown[b] | 4 | 1 | |
| Lymph-node status of invasive cancers, No (%) | | | 0.01 |
| Negative | 1028 (72.2) | 30 (90.9) | |
| Positive | 396 (27.8) | 3 (9.1) | |
| Unknown[b] | 30 | 0 | |
| Estrogen-receptor status, No (%)[c] | | | 0.17 |
| Positive | 1245 (88.6) | 25 (80.6) | |
| Negative | 160 (11.4) | 6 (19.4) | |
| Unknown[b] | 49 | 2 | |
| Mitotic activity (No. of mitoses per 2 mm2), No (%)[c] | | | 0.71 |
| ≤10 | 1167 (86.9) | 25 (89.3) | |
| >10 | 176 (13.1) | 3 (10.7) | |
| Unknown[b] | 111 | 5 | |





Table 2: [a] *Six contralateral cancers were mammographically occult at screening*
[b] *Unknown cases were excluded from statistical analysis;* [c] *Invasive cancers only*

**All bilateral breast cancers (index cancers + contralateral cancers, n=80) versus unilateral breast cancer (n=1766)**

There were no significant differences in lesion characteristics at screening mammography or tumor characteristics (further data not shown).

## DISCUSSION

To our knowledge, this is the first study describing patient and tumor characteristics of bilateral breast cancer cases in a screened population. We observed no differences in patient characteristics between women with a diagnosis of bilateral versus unilateral breast cancer. The mean age at the time of cancer diagnosis was 63 years in both groups, whereas other studies report a lower mean age (below 60 years) for women with bilateral breast cancer[4,5,18,22]. This difference can be explained by the fact that our series was restricted to asymptomatic women aged 50-75 years, while other studies generally comprised women of all ages in the symptomatic population. In symptomatic patients, a positive family history of breast cancer is more frequently present in bilateral breast cancer than in unilateral breast cancer cases[16,17,22]. This was not the case in our study. Again, this observation can be explained by differences in study population characteristics. In a routine mammography screening program, the proportion of women with a family history of breast cancer, especially if genetically predisposed, will be small as many of these women will attend strict surveillance programs in a clinical setting. Furthermore, a majority (80%) of the contralateral malignancies in our series of bilateral cancers had been diagnosed within 3 months after the index cancer, whereas in other studies a family history of breast was more prevalent in metachronous than in synchronous bilateral breast cancer[16]. Presentation at screening mammography was similar for bilateral cancers and unilateral cancers. Of the six contralateral cancers that had been mammographically occult at screening, three were detected at MR-imaging. MR-imaging has as higher sensitivity than mammography and/or breast ultrasonography for the detection of synchronous contralateral cancer in patients with newly diagnosed breast cancer and studies have shown that the rate of mammographically and clinically occult contralateral cancers detected at MR-imaging ranges from 3-18%[11,23,24].

Certain tumor characteristics differed significantly, both when comparing the index cancer with the contralateral cancer and when comparing the contralateral cancer in women with bilateral breast cancer with the cancer in women with unilateral breast cancer. Comparison

with other studies is complicated due to variations in the definition of synchronous and metachronous breast cancer. Authors usually classify bilateral cancer as synchronous if the contralateral malignancy is diagnosed within three months[4,10,14,16] after the index cancer, although others use a time span of 6 to 12 months[5,15,18,22]. Moreover, the definition of index lesion and contralateral lesion in bilateral breast cancer is crucial. In one series, where the index tumor, or first tumor, was defined as the tumor with the highest TNM classification, significantly more invasive lobular cancers were found in bilateral than in unilateral breast cancer[16]. In another study, bilateral cancers were divided into left sided and right sided cancers, with the underlying idea that a routine definition of the tumor with the highest stage as index tumor introduces statistical bias[4]. Although the authors did not observe a difference between index tumors and contralateral tumors, they also found significantly more lobular cancers in the total group of these tumors when compared to unilateral breast cancers. In the 11 women with a diagnosis of bilateral breast cancer after bilateral referral, we defined the index tumor as the malignancy with the largest tumor size. It is unlikely that this definition has introduced statistical bias, as the proportion of T1 cancers among invasive index cancers was comparable to that of contralateral cancers.

The fact that we observed a higher, but not statistically significant, proportion of lobular cancers in the total group of invasive bilateral cancers, when compared to unilateral cancers, may be due to the relatively small number of bilateral breast cancers in our study. However, contralateral cancers comprised significantly more lobular cancers compared with both index and unilateral cancers. No specific data have previously been reported concerning the frequency of ductal cancer in situ (DCIS) at bilateral breast cancer. Although one might expect a larger proportion of DCIS in contralateral cancers than in index cancers, comparable proportions of DCIS were found in our study. The number of DCIS in both groups was small, however.

We observed no differences in invasive tumor size between index cancers and contralateral cancers, although several bilateral breast cancer studies report a smaller tumor size for contralateral cancers[5,13,25-27]. In our asymptomatic population, more than 80% of index cancers were small invasive cancers (<20 mm), whereas up to 50% of index cancers in symptomatic women will be larger than 20 mm[17]. Our observation of a more favorable lymph node stage in contralateral cancers than in index cancers is in line with those reported in studies concerning symptomatic bilateral breast cancer patients[5,26]. We did not find significant differences in estrogen receptor status or mitotic activity between invasive contralateral cancers and index cancers, in women with bilateral breast cancer or between invasive contralateral cancers in bilateral breast cancer patients and patients with unilateral breast cancer. Studies on symptomatic synchronous bilateral breast cancer report that 50-





60% of cancers are estrogen receptor positive and contralateral bilateral breast cancers are more likely to show this positive status than index tumors or unilateral cancers[4,13]. Also, screen detected cancers are smaller, show less nodal involvement and are more often hormone receptor positive compared to interval cancers and breast cancers diagnosed in women unexposed to screening[28]. The fact that we did not observe significant differences in estrogen receptor status among the various groups may be explained by the fact that more than 80% of index cancers, contralateral cancers and unilateral cancers in our study were estrogen receptor positive.

In the current study we did not investigate the survival of bilateral breast cancer patients. Although controversy exists on the impact of bilateral breast cancer on survival, several studies have shown that the prognosis of women with bilateral breast cancer tends to be worse compared to women with unilateral cancer[3,10,29,30]. A delay in the diagnosis of bilateral disease, due to the low sensitivity of screening mammography for bilateral breast cancer detection, may worsen the prognosis[19,31].

## CONCLUSION

We found that patient characteristics are similar for bilateral and unilateral breast cancer cases diagnosed at workup of mammographic screening abnormalities. Presentation at screening mammography, tumor size and tumor biology are comparable for index cancers, contralateral cancers and unilateral cancers. Compared with index cancers and unilateral cancers, contralateral malignancies show a significantly higher proportion of invasive cancers of the lobular type and less lymph node involvement.

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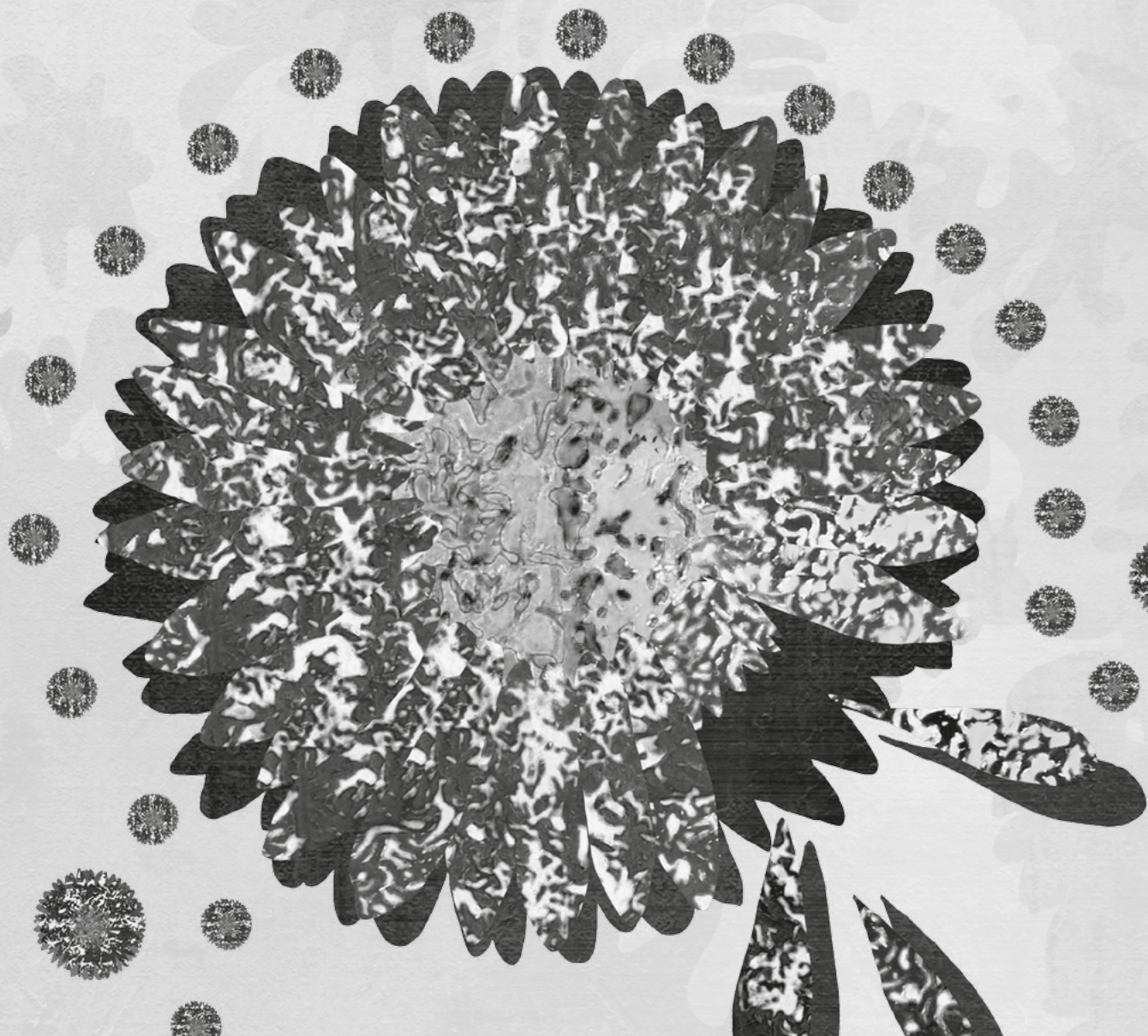
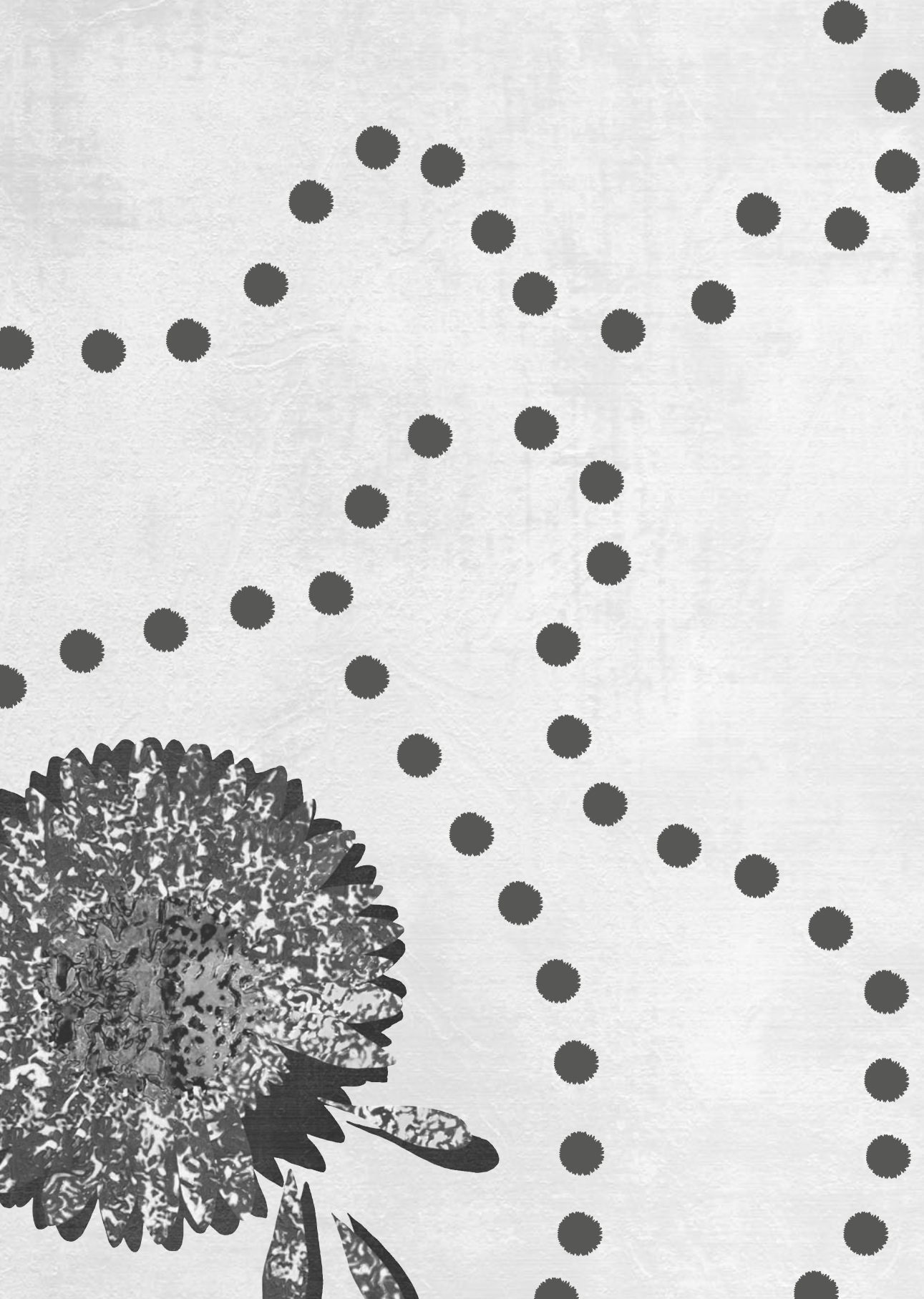
# PART II
## False positive screening mammography;
a different point of view





# Chapter 4

## Re-attendance after false positive screening mammography,

with emphasis on the occurrence of surveillance mammography outside the national screening programme

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## ABSTRACT

### Background

In the current study mammography adherence of women who had experienced a false referral is evaluated, with emphasis on the probability of receiving surveillance mammography outside the national screening programme.

### Methods

We included 424703 consecutive screens and collected imaging, biopsy and surgery reports of 3463 women who experienced a false positive referral. Adherence to screening, both in and outside the screening programme, was evaluated.

### Results

Two years after the false positive referral, overall screening adherence was 94.6%, with 64.7% of women returning to the national screening programme, compared to 94.9% of women re-attending the screening programme after a negative screen (p<0,0001). Four years after the false positive screen the overall adherence had decreased to 85.2% (p<0.0001) with a similar proportion of the women re-attending the screening programme (64.4%) and a lower proportion (20.8%) having clinical surveillance mammography. Women who had experienced a false positive screen at their first screening round were less likely to adhere to mammography than women with an abnormal finding at one of the following screening rounds (92.4% vs. 95.5% p<0.0001).

### Conclusion

Overall screening adherence after previous false positive referral was comparable to the re-attendance rate of women with a negative screen at 2 year follow-up. Overall adherence decreased 4 years after previous false positive referral from 94.6% to 85.2%, with a relatively high estimate of women who continue with clinical surveillance mammography (20.8%). Women with false positive screens should be made aware of the importance to re-attend future screening rounds, as a way to improve the effectiveness of the screening programme.






## INTRODUCTION

Many Western countries have implemented screening mammography programmes with the aim to reduce breast cancer mortality. However the extent of the mortality reduction through screening alone remains subject to discussion worldwide[1]. Moreover, the unintended negative consequences of screening mammography, including overdiagnosis and subsequent overtreatment[2] and false positive referrals[3, 4] are of particular concern in the debate concerning the effectiveness of screening mammography. Women with false positive screening results undergo additional imaging and biopsy procedures and many of them experience anxiety and distress[5-7], particularly in the first month post-screening. At 12 months, concerns that seem to prevail are intrusive thinking and a higher perceived risk of breast cancer[5]. In some women breast cancer specific distress is reported to last for up to 3 years after a false positive screen[4]. Whether or not receiving a false-positive mammogram undermines attendance at subsequent scheduled screening mammography is controversial. A meta-analysis of 12 studies reported no significant relationship between false-positive screening mammograms and return for routine screening among European women. On the other hand a decreased likelihood of re-attendance among Canadian women and even an increased re-attendance among women who experienced a false-positive mammogram in the United States was demonstrated[3].

Because the effectiveness of screening is closely related to adequate adherence among the target population, it is important to know whether women who experience a false-positive referral do return for routine testing. To our knowledge screening behaviour after false positive referral has only been evaluated with regard to re-attendance in the screening programme. In the current study we evaluated whether women who did not re-attend the national screening programme after a false positive referral, underwent surveillance mammography outside the screening programme, or refrained from repeated mammography at all.

## MATERIALS AND METHODS

### Study population

We used the information of a consecutive series of 91,570 women who underwent screening mammography in a southern breast cancer screening region of the Netherlands (BOZ, Bevolkings Onderzoek Zuid) between January 1st 1995 and January 1st 2010. Biennial screening was started in this region in 1995. Initially it included women aged 50-69 years, but from 1998 onwards women aged 70-75 years were invited as well. The overall attendance rate was around 84% and varied a little over time[8].

Prior to screening examination women were asked whether their screening and follow-up data can be used for evaluation purposes. Three women refused this and they were excluded from the study. Ethical approval by our local Institutional Review Board was not required for this study, according to the Dutch Central Committee on Research involving Human Subjects (CCMO).

## Screening procedure and referral

Screening mammography in the BOZ region was performed at one of two specialized screening units (one fixed and one mobile unit). The two analogue (screen film) units were replaced by digital screening units in May 2009. Details of the nation-wide breast cancer screening programme in the Netherlands have been described in detail previously[9]. All examinations were performed by specialized screening mammography radiographers. At analogue screening, two-view mammography (medio-lateral-oblique and cranio-caudal view) of each breast was performed at the first screening round. At subsequent analogue screening rounds, one view mammography (medio-lateral-oblique) was obtained routinely and additional views (cranio-caudal) were obtained in 45% of cases. Indications for this two-view mammography included any changes in mammographic findings at screening, complicated judgement due to dense fibroglandular tissue, a more than two-year interval since the previous screen and previous breast surgery. Digital screening mammography always consisted of two-view mammography.

All screens were independently double read by 16 certified screening radiologists and each radiologists evaluated at least 3,000 screening mammograms per year. Mammograms of previous screening round were always available for comparison. Women with normal, benign or non-specific findings[10] at screening mammography were not referred. For each referred woman the screening radiologists classified the abnormal mammographic findings according to one of five categories: (1) suspicious high density (spiculated density or density with irregular borders); (2) suspicious microcalcifications (pleiomorphic, branching or amorphous/indistinct microcalcifications; (3) high density in combination with microcalcifications; (4) architectural distortion or (5) asymmetry. Women with suspicious or malignant findings at screening mammography were referred to their general practitioner and subsequently to a regional hospital of their choice for further diagnostic assessment. A total of 16 hospitals were involved in the work-up of referred women. This work-up consisted of physical examination by a surgical oncologist and additional mammographic views. Breast ultrasonography, magnetic resonance (MR) mammography and/or biopsy were performed at the radiologist's discretion.





## Follow-up procedure and re-attendance after a false positive referral

One radiologist (LD) yearly visited the regional hospitals involved in the work-up of referred women, to collect data on any imaging procedures, breast biopsy outcomes and breast surgery procedures of each referred woman. For women diagnosed with breast cancer after referral, diagnostic and therapeutic data were collected from the time of referral through the moment of final therapy (e.g., breast conserving therapy, mastectomy or palliative treatment). For all women not diagnosed with breast cancer (i.e., those with a false positive referral), the radiologist collected outcome data for two years (until the next scheduled biennial screening examination) at the hospitals the women had been referred to. Furthermore, for those women who did not re-attend the screening programme after a false positive screen, the radiologist checked each year if they had undergone any breast imaging procedure, breast biopsy or breast surgery at one of the regional hospitals. This information enabled us to determine whether or not these women had undergone clinical mammographic surveillance outside the screening programme. Moreover, the radiologist obtained information on the reasons for not being under clinical mammographic surveillance outside the screening programme, such as having undergone preventive mastectomy or suffering from serious other illness. Information was also retrieved on how long a woman underwent clinical follow-up after a false positive referral. Linkage of the our database to the national screening database and the regional register of Death (Gemeentelijke Basisadministratie Persoonsgegevens) enabled us to identify the referred women who had died and to identify the referred women who had attended the screening programme in another screening region[11]. Strategies used to identify interval cancers have been described previously[12].

## Follow-up and re-attendance after a negative screen

Data on women who had received a negative screen (i.e. no referral) during the study period were collected from the BOZ screening database. The women who were not eligible for re–screening were identified (i.e. women who had died, who had moved to another screening region, as well as women who informed the screening organization that they did not appreciate a re-invitation for screening). The screening adherence at the subsequent screening round was determined.

In the current study, surveillance mammography is defined as a mammogram performed in the clinical setting, in one of the adherent hospitals in the BOZ region, in the 2 year or 4 year period after actual referral, in women who experienced a false positive screen. This mammogram could have been performed on the woman's request, or at the surgeon's or radiologist's discretion

We defined re-attendance in the screening programme as participation at the next routine screening round following a screening invitation. For the current study, we used a follow-up period of at least 2 years (until the next biennial screening) for women screened between April 2008-April 2010 and of at least 4 years for women screened between January 1995-April 2008 (until the second round after the index mammography).

To determine which women were no longer eligible for screening after a previous screen, we identified the ones who had died from other causes than breast cancer, the women who had been diagnosed with an interval cancer, and those who had moved to another screening region or had turned 76 years before the next screening round. These women constitute the 'non-target' group. An interval cancer was defined as a breast cancer diagnosed before the next (biennial) screening round after a previous negative screen.

### Statistical analysis

Descriptive statistics were performed using Statistical Package for Social Sciences 17.0 (SPSS, Chicago, IL). The chi-square test was used to test the differences for a statistical significance. The significance level was set at p=0.05. The main outcome measure was the adherence to screening, which was defined as the proportion of women returning to the screening programme or having surveillance mammography 2 and 4 years following a false positive screening result. Differences in the proportion of women re-attending the screening programme were tested between women who experienced a false positive referral and those with a negative screen. The proportion of women re-attending the screening programme was also studied over time, looking at three time intervals (1995-1999, 2000-2004 and 2005-2009), and according to screening history (first screening round versus subsequent screening rounds).

## RESULTS

### Overall screening results

A total of 424,703 screens (406,856 analogue and 17,847 digital screens) were obtained in 91,570 women between January 1st, 1995 and January 1st, 2010. Of these, 85,099 were initial screens and 339,604 were subsequent screens. The screening programme in our region started in 1995. Several women had already been screened in another region before this date and were then added to our screening region, explaining why the number of women with a first screen is lower than the number of women screened in the study period 1995-2009. In the whole study period 512,262 invitations were sent and the overall attendance therefore was 82.9%. The mean age of all women screened women was 62.5 years. Altogether 5,529 women (5,676 screens) were referred for further diagnostic testing

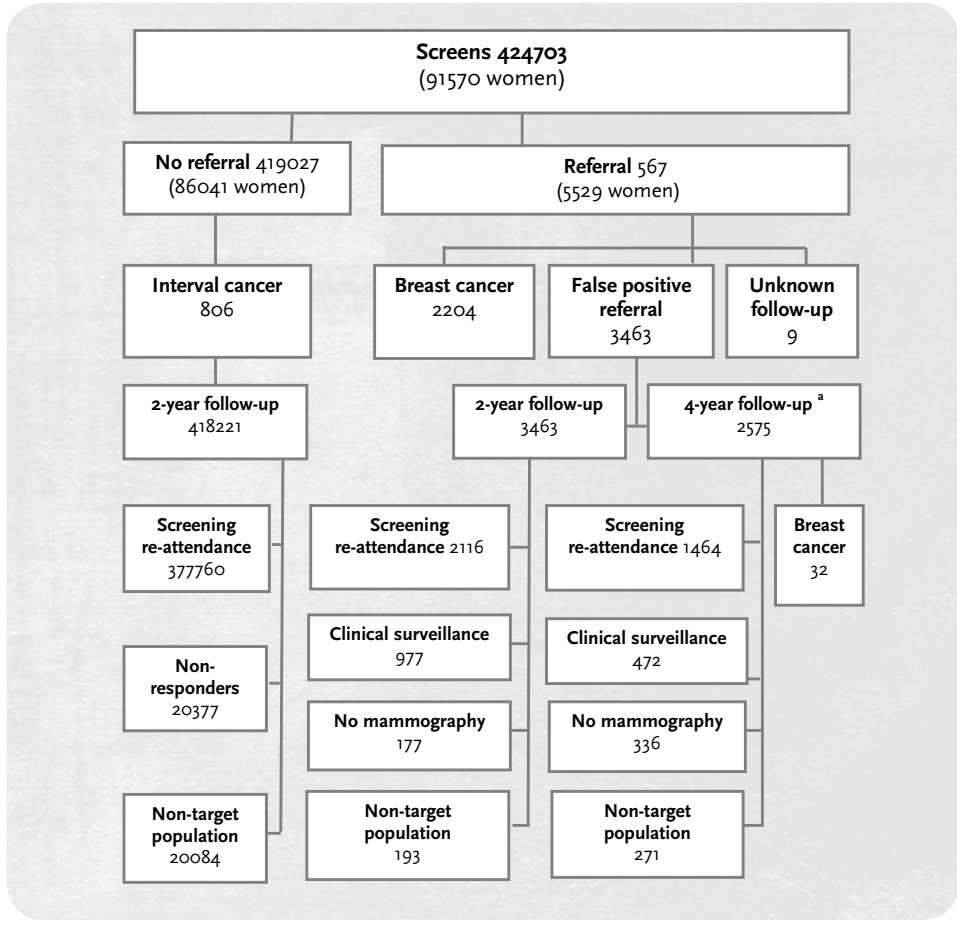




(1,528 referrals at initial screen and 4,148 referrals at subsequent screens). The overall referral rate was 1.3%. Altogether 2,204 of the referred women were diagnosed with breast cancer (including 372 ductal carcinomas in situ), yielding an overall detection rate of 5.2 per 1,000 women screened and a positive predictive value of referral of 38.8%. A total of 3,463 women experienced a false positive referral resulting in an overall false-positive referral rate of 8.2 per 1,000 women screened. The follow-up of the remaining 9 referred women was unknown and these women were excluded from analysis (Figure 1).

In addition to the 2,204 women diagnosed with a screen detected cancer, 806 women were diagnosed with an interval cancer (including 33 ductal carcinomas in situ), resulting

FIGURE 1. Mammography screening outcome, 1995-2009




[a] *4-year follow-up complete for women screened until March 2008*

TABLE 1A. Screening behaviour following a false positive screen

| Baseline population [a] | False positive screen, No 3,463 | | Negative screen, No 419,027 | p-value |
|---|---|---|---|---|
| | 2-year [b] | 4-year [c] | | |
| **Non-target population, No** (not eligible for re-screening at follow-up | 194 | 303 | 20,890 | |
| Deceased<br>Moved<br>Not appreciating re-invitation [d] | 38 | 58 | 9,491 | |
| ≥ 76 years before next screening round | 149 | 207 | 10,593 | |
| Diagnosis of serious disease | 5 | 4 | | |
| Preventive ablation | 1 | | | |
| Unknown follow-up | 1 | 2 | | |
| Interval cancer | | | 806 | |
| Breast cancer diagnosis [e] | | 32 | | |
| **Target population, No** (eligible for re-screening at 2-year follow-up) | 3,269 | 2272 | 398,137 | |
| **Re-attendance at subsequent screen, No (%)** | | | | |
| Yes | 2,116 (64.7) | 1464 (64.4) | 377,760 (94.9) | <0.0001 |
| No | 1,153 (35.3) | 808 (35.5) | 20,377 (5.1) | |

[a] *Baseline population: 424,703 screens, 2,204 breast cancers, 9 unknown follow-up*

[b] *2-year: follow-up 2 years after previous false positive referral*

[c] *4-year: follow-up 4 years after previous false positive referral*

[d] *not appreciating re-invitation: those women who had made a written statement that they did not want to attend the screening programme in the future (reason not specified)*

[e] *breast cancer diagnosis after a repeated referral for a contralateral of ipsilateral screening abnormality*





TABLE 1B. Screening behaviour following a false positive screen in time

| | 2 years after FP referral | 4 years after FP referral | p-value |
|---|---|---|---|
| Screening adherencea after FP referral, No (%) | 3,092 (94.6) | 1,936 (85.2) | <0.0001 |
| No rescreening after FP referral, No (%) | 177 (5.4) | 336 (14.8) | |
| | First screening round | Subsequent screening | |
| Screening adherence [a] after FP referral, No (%) | 896 (92.4) | 2,196 (95.5) | <0.0001 |
| No rescreening after FP referral, No (%) | 74 (7.6) | 103 (4.5) | |

*Abbreviation: FP referral= false positive referral;*

[a] *Screening adherence: mammography within screening pro-gramme or clinical surveillance mammography*

in a 73.2% (2,204/3,010) sensitivity and 99.2% (418,221/421,693) specificity of breast cancer screening (based on 418,221 true negative screens and 3,472 false positive screens, including 9 referrals with unknown follow-up). Of the 3,463 false positive referrals, diagnostic work-up was limited to additional breast imaging in 2,117 (61.1%) women, whereas 1,035 (29.9%) also underwent percutaneous biopsy (fine needle aspiration cytology (FNAC) and/or core needle biopsy (CNB)). Excisional biopsy (with or without preceding percutaneous biopsy) had been performed in 305 (8.8%) women who experienced a false positive screen. Six women refused any kind of workup and were not referred to a hospital for further assessment.

## Re-attendance 2 years after a negative screening result

The screening radiologists found no indication for referral in 419,027 screens. A total of 20,890 women were not eligible for re-attendance (non-target group, Table 1a). There were 20,377 women who did not re-attend the subsequent screening round (non-responders). Therefore the re-attendance rate after a negative screen was 94.9% (377,760 out of 398,137) (Figure 1, Table 1a)

## Re-attendance 2 years after a false positive referral

After 2 year follow-up 3,269 women were still eligible for screening mammography. At that time, 194 (5.6%) of the 3,463 women who had experienced a false positive referral were no longer available for screening (non-target group, Table 1a). After 2 years 2,116 (64.7%) of the 3,269 women still eligible for screening returned for their screening mammogram, which

was significantly lower than for the women with a true negative screen (94.9%, p<0.0001). A group of 976 women (29.9%) had undergone surveillance mammography in the clinical setting. Of all women in the target population 94.6% (3,092 out of 3,269) therefore underwent mammography after a previous false positive referral, either being a scheduled screening examination or a clinical surveillance mammogram outside the screening programme. A total of 177 (5.4%) women had no mammography performed in or outside the screening programme within 2 years after their false positive referral (Figure 1, Table 1a and b).

## Re-attendance after 4-year follow-up

The 4-year follow-up could be determined for 2,575 of the 3,463 women who experienced a false positive referral in the study period. For the other 888 women screened after March 2008, 4-year follow-up was not reached yet. A total of 303 (11.7%) women were not eligible for re-screening (non-target group, Table 1a). Four years after a false positive referral 64.4% (1,464 out of 2,272) of the women in the target population had re-attended the screening programme. A total of 472 women (20.8%) had a surveillance mammogram performed in the clinical setting. Therefore, after 4 years 85.2% (1,936 out of 2,272) of the women underwent mammography after a previous false positive screen in or outside the screening programme, which was significantly lower compared to the adherence of 95.6% after 2 years (p<0.0001). (Table 1b). A total of 336 women (14.8%) did not attend screening 4 years after their false positive referral, although 207 (61.6%) of these women did participate in the screening programme at 2 year follow-up (Figure 1, Table 1a and b).

## Re-attendance in time and according to screening history

When comparing the re-attendance rate two years after false positive referral in the national screening programme for three different screening periods (1995-1999, 2000-2004 and 2005-2009), we found a statistically significant increase from 59.8% in 1995-1999 to 67.9% in 2005-2009 (p<0.0001). The proportion of women who underwent clinical surveillance mammography decreased from 33.2% in 2000-2004 to 26.8% in 2005-2009 (p<0.0001) (Table 2).

The proportion of women who re-attended after a false positive referral in their first screening round remained stable over the years (Table 2). Of the 3,269 women with a false-positive screen eligible for re-screening, 970 experienced their false positive screen at initial screening and 2,299 women at subsequent screening. Women who had experienced a false positive screen at their first screening round were significantly less likely to return for screening or clinical surveillance mammography than those with a false positive referral at subsequent screening rounds (92.4% (896 out of 970) vs. 95.5% (2,196 out of 2,299) p<0.0001) (Table 1b)





TABLE 2. Screening re-attendance and clinical surveillance mammography after a previous false positive screening mammography during three screening periods

| | Total 3,463 | 1995-1999 654 | 2000-2004 1,066 | 2005-2009 1,743 | p-value |
|---|---|---|---|---|---|
| Non-target population, No (not eligible for re-screening at 2-year follow-up) | 194 | 39 | 55 | 100 | |
| Target population, No | 3,269 | 615 | 1,011 | 1,643 | <0.0001 |
| Screening re-attendance, No (%) | 2,116 (64.7) | 368 (59.8) | 632 (62.5) | 1,116 (67.9) | |
| Clinical surveillance, No (%) | 976 (29.9) | 201 (32.7) | 336 (33.2) | 439 (26.7) | |
| No mammography, No (%) | 177 (5.4) | 46 (7.5) | 43 (4.3) | 88 (5.4) | |
| **First (initial) screening round** | | | | | |
| No mammography after a false positive referral, No (%) | 74 (7.4) | 34 (10.4) | 16 (8.7) | 24 (5.2) | 0.023 |
| Screening adherence[a] after a false positive referral, No (%) | 896 (92.4) | 294 (89.6) | 167 (91.3) | 435 (94.8) | |
| **Subsequent screening round** | | | | | |
| No mammography after a false positive referral No (%) | 103 (4.5) | 12 (4.2) | 27 (3.3) | 64 (5.4) | 0.07 |
| Screening adherence[a] after a false positive referral No (%) | 2,196 (95.5) | 275 (95.8) | 801 (96.7) | 1,120 (94.6) | |

[a] *Screening adherence: mammography within screening programme or clinical surveillance mammography*

# DISCUSSION

To our knowledge, the current population-based study is the first that is able to determine to what extend women not returning to the screening programme after a previous false positive screen, were undergoing surveillance mammography outside the screening programme. The study gives a virtually complete picture of screening behaviour after false positive referral in a southern screening region of the Netherlands, in which we were able to determine almost all causes related to nonattendance at subsequent screening. We found that two years after a previous false positive screen 64.7% of women had re-attended the screening programme.

This percentage was significantly lower compared to women with a negative screen (94.9%) in the same period. Almost one third (29.9%) of women with a previous false positive screen had a clinical surveillance mammography performed, resulting in an overall mammography adherence of 94.6%, which is comparable to the adherence among women with a true negative screen. After 4-years we found a significant decrease in the overall adherence to 85.2% for women who experienced a false positive referral. The compliance to the screening programme, in women who experienced an abnormal mammogram, increased significantly in time and overall adherence in women with an abnormal initial screen was significantly lower compared to women who received a subsequent false positive screen.

Published estimates of re-attendance after experiencing a false-positive screen range between 27 and 52% in Canada[13, 14], with a lower likelihood of re-attendance in this group as compared to the women without a previous false positive screening result. In the US the reported re-attendance rates vary between 63% and 87%[15, 16], but with a higher re-attendance among those with a false positive exam. Estimates of re-attendance in European studies range between 71% and 95%, two of which have reported comparable re-attendance between women with a false-positive screen or negative screen[17, 18], whereas two others reported lower re-attendance after previous false positive referral[19, 20]. The study by Seigneurin et al[19] reported estimates of 72.9% vs. 80.6% respectively, for women with and without a previous false positive screening mammogram, and in the study by Roman et al[20] the re-attendance rate was 79% for women with and 85% for those without a false positive screening result.

It is difficult to compare the reported differences in adherence after a false positive screen, because of the known differences in the organisation of screening procedures between countries worldwide. There is an important difference in the diagnostic work-up after referral between the Netherlands and other countries with regard to intermediate mammograms. In the Netherlands diagnostic work-up after referral is not an integrated part of the screening programme. Such intermediate follow-up mammograms are performed in the clinical setting at the radiologist's discretion.

In our study the re-attendance rate to the national screening programme was 64.7%, which seems relatively low compared to the rates reported in other European countries. However, we now know that a substantial part of the Dutch women continues to undergo a surveillance mammography in the clinical setting, and taking these women into account the overall attendance for mammography after a previous false positive screen is well above the attendance of 84% for the screening programme as a whole[8] and comparable to women with a negative previous screen. We presume that in our population there is a tendency to





keep referred women with a non-malignant diagnosis at additional work-up under clinical surveillance, instead of advising them to return to the screening programme. A major part of our study population was referred before the introduction and gradual implementation of the BI-RADS lexicon[21] in the Netherlands, but it is likely that the policy was to keep these women for clinical routine follow-up, like a BI-RADS 3 lesion nowadays. After the implementation of the BI-RADS criteria, probably more lesions are pathology proven, since both radiologists and patients prefer a definite diagnosis instead of a wait and see policy. Therefore more lesions will be classified as BI-RADS 1 or 2 and these women with a normal or benign screening result are directly advised to return to the screening programme. This hypothesis is supported by our data, which showed a significant decrease in the proportion of women undergoing clinical surveillance after false positive referral after 2004. The recommendation within the Dutch health system is that women should return to the screening programme if the suspicion of breast cancer has been ruled out by additional imaging or invasive procedures (mammographic abnormality classified BI-RADS 1 or 2). For women with a BI-RADS 3 lesion, meaning that the presence of breast cancer is unlikely, a standardized follow-up can be advised (at 6 months, 18 months, and 30 months after referral) or the lesion can be biopsied. Those women who end up in follow-up for a BI-RADS 3 lesion are therefore not expected to return in the screening programme 2 years after a false positive referral. However at 4 years, these women should have returned in the screening programme. We determined that at 4 years still 20% of women with a previous false positive referral undergo a clinical surveillance mammography. Unfortunately, for this group of women, we do not know the reasons for not re-attending screening.

The effect of false positive referral on screening behaviour might also depend on the general attitude of women towards screening and higher participations rates may reflect greater confidence in the benefit of screening. Before 2000 the adherence rate in the Netherlands was around 78%, and between 2000 and 2008 it showed a continuous increase up to 82.0% (84% in the southern breast cancer screening region, BOZ)[8, 22]. This increase is thought to be the result of information campaigns aimed at promoting screening. Parallel to the increase in overall adherence, we found a significant increase over time in re-attendance among women with a previous false positive referral (from 59.8% to 67.9%). From these observations we may conclude that the attitude towards breast cancer screening and behavioural intent have evolved in a similar way among women with normal and false positive mammograms. However, our study showed that even after 2004 more than 20% of women who were referred with a false positive screening result, continued with clinical surveillance mammography, at least until 4 years after referral. This prolonged clinical surveillance results in additional costs compared to mammography performed within the national screening programme.

Previous research in our screening population showed that a prolonged screening interval within the screening programme is associated with the detection of breast cancer in a more advanced stage[23]. For women with a previous false positive referral von Euler-Chelpin et al[24] found an excess breast cancer risk, not only in the period 2-4 years after a false positive referral, but even up to 12 years after it. For effective screening, both high re-attendance rates as well as repeated sequential screening with adequate intervals are essential to reduce breast cancer mortality. In order to prevent a possible delay in cancer diagnosis with the risk of more advanced disease, additional information and advice with regard to re-attendance, specifically for women experiencing a false positive screen, is of great importance. General practitioners as well as surgical oncologists should emphasize the importance of re-attendance to these women.

The false positive risk has been shown to be higher at first screening[25]. We found that women with an abnormal screening mammogram at their first screening round were somewhat less likely to return for screening (in or outside the screening programme) than women with a false positive subsequent screen (92.4% vs. 95.5%). This in line with previous investigations[26, 27]. Moreover McCann et al[27] reported that the risk of an interval cancer is increased in these women. It is therefore important to provide women who attend screening for the first time, with information on the risk of a false positive screening result and to make them more aware of the significance of their future attendance, to reduce the risk of an interval cancer.

Our study has certain limitations. We were not able to elucidate the reasons for non-attendance of women in the target group at subsequent screening after a false positive referral. Previous studies have looked at the impact of the type of work-up after false positive referral on adherence and they nearly all concluded that re-attendance after a false positive screen is not influenced by the level of diagnostic workup, whether being additional imaging evaluation only, imaging followed by percutaneous biopsy or surgical excision biopsy after referral[18, 28]. Furthermore, our study is mainly based on the results with screen film mammography. From May 2009 analogue screening was replaced by digital screening units and Nederend et al[29] showed that the introduction of digital screening mammography significantly increased the referral rate and cancer detection rate, at the expense of a lower positive predictive value. We have not yet evaluated the effect of the increase in the number of false positive screening referrals by digital mammography on the re-attendance rates. No information on patient characteristics, such as family history or use of hormone replacement therapy, was available for the women with a negative screen (i.e., those who were not referred for further diagnostic assessment). For that reason multivariate analyses to adjust for differences between women who experienced a false positive screen and women who received a negative screen could not be performed





In conclusion, we found that overall mammography adherence after a previous false positive screen was 94.6%, which was comparable to the 94.9% re-attendance rate of women who had not been referred. Almost one third of women in the first group received a surveillance mammogram at the time they were scheduled for subsequent screening mammography. At 4 year follow up we found a significant decrease in overall adherence to 85.2% and a relatively high estimate of women who continue with clinical surveillance mammography (20.8%). Our findings stress the significance to inform women with a previous false positive screen and those who are invited for their first screening round, of the importance to re-attend to future screening rounds to increase their opportunities of early breast cancer detection and improve the cost-effectiveness of the screening programme.

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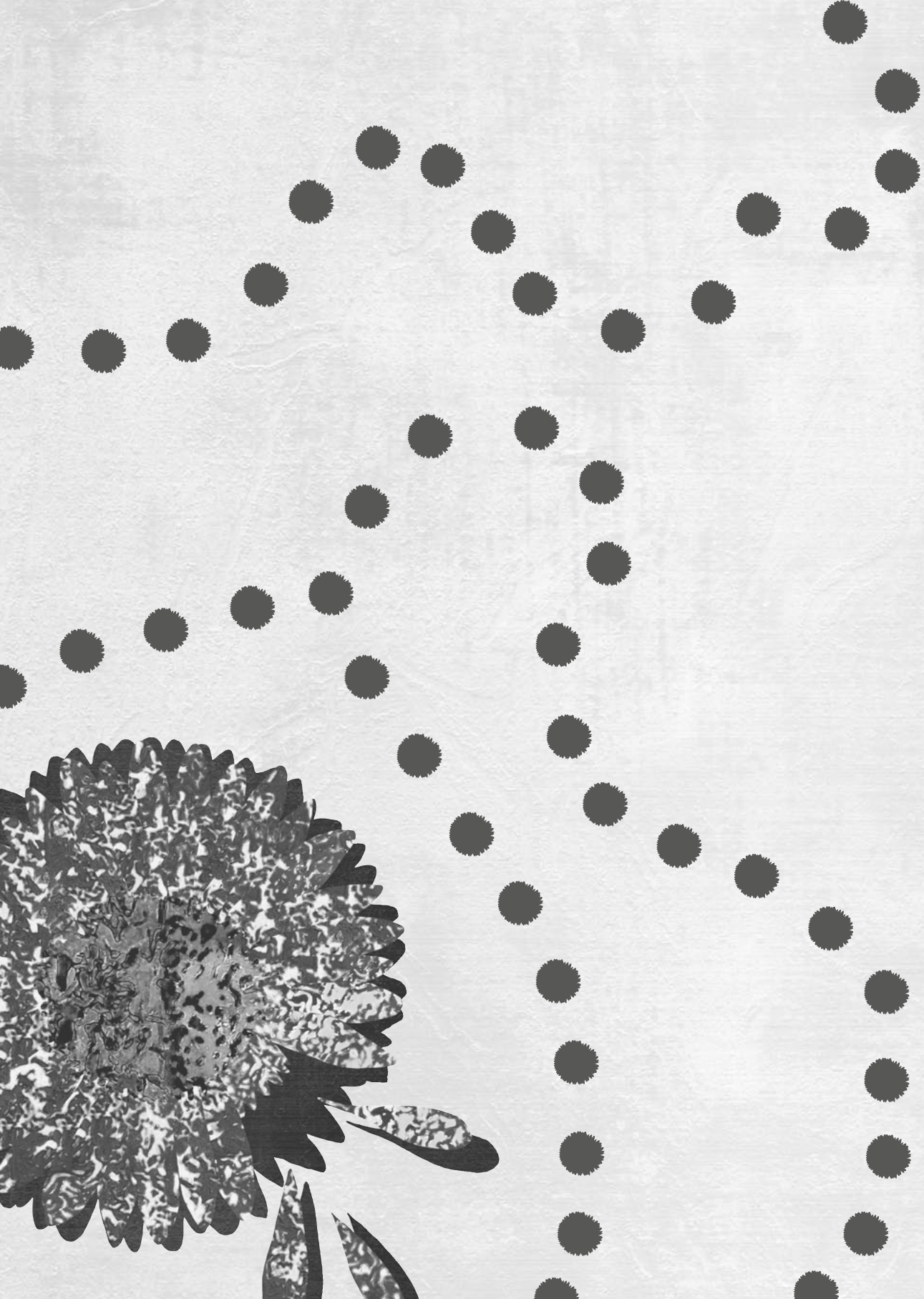

# Chapter 5

## Characteristics and screening outcome of women referred twice at screening mammography

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## ABSTRACT

### Objectives

To determine the characteristics and screening outcome of women referred twice at screening mammography

### Methods

We included 424,703 consecutive screening mammograms and collected imaging-, biopsy-, and surgery reports of women with screen-detected breast cancer. Review of screening mammograms was performed to determine whether or not an initial and second referral comprised the same lesion.

### Results

The overall positive predictive value of referral for cancer was 38.6% (95% CI 37.3%-39.8%). Of 147 (2.6%) women referred twice, 86 had been referred for a different lesion at second referral and 32 of these proved malignant (37.2%, 95% CI 27.0%-47.4%). Sixty-one women had been referred twice for the same lesion, of which 22 proved malignant (36.1%, 95% CI 24.1%-48.0%). Characteristics of these women were comparable to women with cancer diagnosed after first referral. Compared to women without cancer at second referral for the same lesion, women with cancer more frequently showed suspicious densities at screening mammography (86.4% vs. 53.8%, P=0.02) and work-up at first referral had less frequently included biopsy (22.7% vs. 61.5%, p=0.004).

### Conclusions

Cancer risk in women referred twice for the same lesion is similar to that observed in women referred once, or referred for a second time but for a different lesion.






## INTRODUCTION

Many Western countries have implemented breast cancer screening programmes in the last two decades in order to detect breast cancer at an early stage[1]. Screening programmes seek to find an optimal balance between the number of women who are referred for further examination, but ultimately do not receive a diagnosis of breast cancer (i.e., false-positive cases) and the number of cancers detected (i.e., true-positive cases). This balance, however, varies widely between countries, as reflected by considerable differences between screening programmes in referral rates (ranging from less than 2% to more than 10%) and positive predictive value rates (ranging from 10-43%)[2,3]. Moreover, there is an ongoing debate concerning possible disadvantages of screening, especially the consequences of experiencing a false positive referral[4]. The chance of experiencing a false positive screen varies widely, and is reported to be 20-50% during a screening period of one to two decades[5,6]. Previous studies have reported that such a referral negatively affects women's well-being, with increased levels of anxiety and cancer related concerns[5,7]. In addition, a false positive referral generates diagnostic work-up costs, such as additional breast imaging examinations and biopsy procedures[8]. Furthermore it may reduce the re-attendance rate for screening mammography[9].

Taking into account the negative effects of a false positive screening result, it is especially important to minimize the number of women who experience a recurrent false positive referral for the same lesion. To our knowledge, no studies have been performed among these women. Therefore, the aim of the current study was to determine the characteristics and screening outcome of women who have been referred twice for the same lesion at screening mammography.

## MATERIALS AND METHODS

### Study population

Our study population comprised 424,703 consecutive screening mammograms (85,099 initial screens and 339,604 subsequent screens) obtained in 91,570 women aged 50-75 years, who underwent biennial screening mammography in a southern breast cancer screening region of the Netherlands (BOZ, Bevolkings Onderzoek Zuid) between January 1995 and January 2010. Biennial screening in this region was started in 1995 and initially included women aged 50-69 years; from 1998, women aged 70-75 years are invited as well. The overall attendance rate is nearly 84%[10]. Women participating in the Dutch screening programme are asked to give written informed consent regarding the use of their data for scientific purposes. All but three women included in our study had given this informed consent. The three women, who did not approve, were excluded. Approval by our local

Institutional Review Board was not required for this study, according to the Dutch Central Committee on Research involving Human Subjects (CCMO).

## Screening procedure, referral and diagnostic work-up

Details of the Dutch Nationwide Breast Cancer Screening Programme have been described in detail elsewhere[11]. In summary, screening mammography was performed at one of two specialized screening units (one fixed and one mobile unit). In May 2009, the two analogue screening units were replaced by digital screening units. Before screening mammography was performed, women were asked to complete a short questionnaire concerning family history of breast cancer (defined as at least one first-degree relative with a diagnosis of breast cancer before the age of 50 years, or at least two second-degree relatives with breast cancer), the use of hormone replacement therapy, as well as issues related to previous breast malignancy or previous benign breast surgery. Screening mammograms were obtained by specialized screening mammography radiographers. At analogue screening, two-view mammography (medio-lateral-oblique and cranio-caudal view) of each breast was performed in initial screens. In subsequent screens, generally one-view mammography mammography (medio-lateral-oblique) was carried out. Additional cranio-caudal views of each breast were obtained in 45.6% (154,829/339,604) of subsequent screens and indications for this two-view mammography included any changes in mammographic findings at screening, complicated judgment due to dense fibroglandular tissue, a more than two-year interval since the previous screen and previous breast. Digital screening mammography routinely consisted of two-view mammography. A total of 16 radiologists participated in the screening programme and each radiologist evaluated at least 3,000 screening mammograms yearly. Prior screening mammograms were always available for comparison at the time of subsequent screening. To facilitate comparison of subsequent digital screens with prior analogue screens, the most recent analogue screening mammograms were digitized by using a film scanner and archiver designed for mammography (DigitalNow; R2/Hologic). The original analogue screening mammograms were also available for viewing. Women were not referred in case of normal findings, benign mammographic findings (e.g., lymph nodes, calcified fibroadenoma, lipoma and vascular calcifications) or non-specific findings / minimal signs (e.g., a vague area of density with an incomplete sharp border and a diameter between 5 and 30 mm [density comparable to that of glandular tissue], less than 6 clustered non-specific microcalcifications, and subtle architectural distortions that include asymmetric glandular tissue)[12]. Lesions that were considered suspicious or malignant at screening mammography were classified into one of the following categories by the screening radiologists:





1) suspicious high density (spiculated density or density with indistinct borders);
2) suspicious microcalcification (pleiomorphic, branching or amorphous / indistinct microcalcification);
3) high density in combination with microcalcification;
4) architectural distortion, or
5) asymmetry.

Women with suspicious or malignant findings were referred to a hospital for further assessment. After physical examination by the surgeon, additional mammographic views were performed at the discretion of the radiologist. Further diagnostic evaluation included breast ultrasonography, Magnetic Resonance Mammography, percutaneous fine needle aspiration cytology (FNAC) or core needle biopsy (CNB) (usually image-guided) or open surgical biopsy, dependent on the findings at physical examination and mammography.

## Follow-up procedure and identification of women with a repeated referral

During a follow-up period of at least 2 years (until the next biennial screening), we routinely collected screening mammography findings, clinical data, additional breast imaging reports, biopsy results and breast surgery reports from all women with a positive screening result (i.e., those that required additional evaluation). Data on TNM (tumour-node-metastasis) classification[13], estrogen-receptor and progesterone-receptor status (data available from 1998), Her2/Neu over-expression (data available from 2004) and Nottingham grade (available from 2001) were collected. Of those women with a diagnosis of breast cancer at work-up, two screening radiologists (LD and FJ) retrospectively assessed the breast density on the most recent screening mammograms according to BI-RADS (Breast imaging-reporting and data system)[14] for women screened since 1997. At review, the radiologists were initially blinded to each other's classification and discrepant assessments were followed by consensus reading[15]. These data, as well as the information of the basic questionnaire, were stored in an Excel database. The database was used to identify women who had been referred twice between January 1995 and January 2010 and one radiologist (LD) then determined whether or not the second referral concerned the same lesion for which a woman had been referred previously. Finally, to determine whether a delay in breast cancer diagnosis could be attributed to the radiological assessment, the two screening radiologists independently and retrospectively reviewed the diagnostic breast images of all women with a diagnostic delay and classified the lesions according to the American College of Radiology BI-RADS[3,14].

### Statistical analysis

Descriptive statistics were performed using Statistical Package for Social Sciences 17.0 (SPSS Inc. Chicago, IL). A double sided t-test, or chi-square test was used to test differences in patient or disease characteristics between patients with breast cancer diagnosed after a second referral for the same lesion and those with breast cancer diagnosed without delay. Among those patients who had been referred twice for the same lesion at screening, comparisons were also made between those with and without a diagnosis of breast cancer at second referral. The significance level was set at P=0.05.

## RESULTS

### Cohort characteristics

A total of 424,703 screens were obtained between January 1, 1995 and December 31, 2009. Altogether, 5,676 women were referred for further diagnostic assessment. At follow-up, breast cancer was diagnosed in 2,192 referred women, yielding an overall cancer detection rate of 5.2 per 1,000 women screened and a true positive referral rate of 38.6% (95% CI 37.3%-39.8%). There were 3,484 false-positive referrals (including 10 cases with unknown follow-up), resulting in an overall false-positive referral rate of 8.2 per 1,000 women screened.

### Women referred for a second time

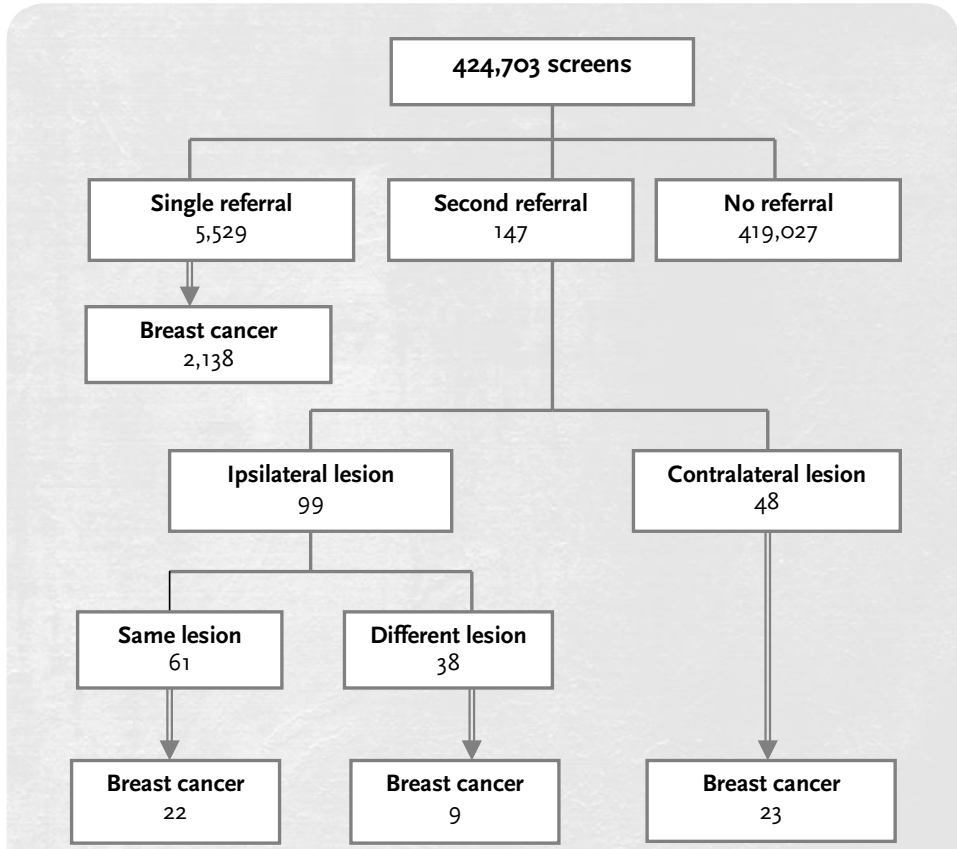
Out of 5,676 referred women, 147 (2.6%) had been referred for a second time after a previous, false positive screen. Of these 147 women, 86 had been referred for a different screening abnormality (48 contralateral lesions and 38 ipsilateral lesions), of which 32 proved malignant (37.2%, 95% CI 27.0%-47.4%). A total of 61 women (41.5%) had been referred for the same lesion that had been considered benign at work-up following previous referral and cancer was diagnosed in 22 cases (36.1%, 95% CI 24.1%-48.0%) (Figure 1). These 22 women with a diagnostic delay comprised 1.0% (22/2191) of breast cancers detected at screening mammography. Breast cancer in the 22 women was confirmed one or several screening rounds after the initial referral and the median delay in cancer diagnosis was 43 months (range 21-92) months.

When comparing patient characteristics of these 22 women with the 2,170 women diagnosed with breast cancer at first referral, we observed no statistically significant differences in age, use or hormone replacement therapy, previous (benign) breast surgery, family history of breast cancer, breast density at screening mammography, or lesion characteristics at screening mammography (Table 1). Also, no statistically significant differences were observed in proportion of invasive breast cancers, tumour histology, or tumour diameter between the two groups (Table 2). The proportion of women diagnosed with advanced





FIGURE 1 Mammography screening outcome, 1995-2009




breast cancer (defined as invasive cancer >20 mm or invasive cancer with positive lymph nodes) after second referral was not significantly different compared to women diagnosed with breast cancer after first referral (4/22, 18.2% vs. 705/1465, 32.5%, P=0.15). Receptor status and Nottingham grade were also similar (Table 3).

Among the 61 women who had been referred twice for the same lesion, suspicious high densities at screening mammography, with or without microcalcifications, were significantly more often present in the 22 women diagnosed with cancer than in the 39 women without cancer (86.4% vs. 53.8%, P=0.02). The mammographic abnormalities between women diagnosed with breast cancer at first referral and women who experienced a false positive referral only once, were comparable (80.8% vs. 79.8%, P=0.36). However, women who presented with a suspicious high density at first referral experienced statistically significant

less frequently work-up with pathological confirmation, than did women who presented with suspicious foci of microcalcifications (2,099/3,869 54.3% vs. 1,124/1,401 80.2% P=0.001).

In a majority of women (17/22, 77.3%) subsequently diagnosed with breast cancer at second referral for the same lesion, work-up at first referral only consisted of additional breast imaging. In contrast, most women with benign findings at second referral had received a combination of breast imaging and biopsy (FNAC, 4 cases; CNB, 16 cases, excision biopsy, 4 cases) at first referral (24/39, 61.5%, P=0.004). Five women diagnosed with breast cancer at second referral experienced a false negative biopsy outcome of their BI-RADS 4 lesion at previous referral (Table 4). One had undergone FNAC (Figure 2), one had received CNB, and a combination of FNAC and CNB had been performed in three women (Figure 3). In the 17 women who only received additional imaging at previous referral and were diagnosed with cancer at second referral, the mammographic abnormality at first referral was classified normal (BI-RADS 1) in two, benign (BI-RADS 2) in eight and probably benign (BI-RADS 3) in seven of the 17 women. At review, the two screening radiologists concluded that the BI-RADS classification after first referral should have been at least BI-RADS 4 in 14 of these 17 women.

The proportion of initial screens at first referral among the 61 women who had been referred twice for the same lesion was similar for women diagnosed with breast cancer at second referral and women without cancer (6/22, 27.3% vs. 9/39, 23.1%), P=0.7). Eight of the 22 women (36.4%) diagnosed with breast cancer had participated in at least one screening round between the first and second referral.

Of the 2192 women with breast cancer after first referral, 2170 were correctly diagnosed, whereas the remaining 22 women (22/2192, 1.0%) experienced a delay in cancer diagnosis. Breast cancer in these 22 women was diagnosed one or several screening rounds after the initial referral and the median delay in breast cancer diagnosis was 43 months (range 21-92 months).





TABLE 1. Characteristics of women with screen detected breast cancer

| | Cancer diagnosed with delay[a] (n=22) | Cancer diagnosed without delay (n=2,170) | P-value |
|---|---|---|---|
| **Characteristics** | | | |
| Mean age, years | 61.2 | 62.0 | 0.5 |
| Hormone replacement therapy, No (%)[b] | | | |
| Yes | 1 (4.5) | 168 (8.7) | 0.49 |
| No | 21 (95.5) | 1,764 (91.3) | |
| Family history of breast cancer, No (%)[b] | | | |
| Yes | 6 (27.3) | 376 (19.5) | 0.36 |
| No | 16 (72.7) | 1,556 (80.5) | |
| Previous breast surgery, No (%)[b] | | | |
| Yes | 3 (13.6) | 211 (10.9) | 0.69 |
| No | 19 (86.4) | 1,721 (89.1) | |
| Breast density at screening mammography, No | | | |
| 0-50% | 18 (81.8) | 1,320 (68.3) | 0.18 |
| >50% | 4 (18.2) | 612 (31.7) | |
| Mammographic abnormality, No (%) | | | |
| High density | 17 (77.3) | 1,423 (65.5) | |
| Microcalcifications | 3 (13.6) | 420 (19.4) | 0.41 |
| High density with microcalcifications | 2 (9.1) | 238 (11.0) | |
| Other | 0 (0.0) | 89 (4.1) | |

*Unknown cases were excluded from statistical analysis*

[a] *Diagnosis of breast cancer after a 2nd referral for the same lesion*

[b] *Data only available of women screened since 1997*

TABLE 2. Tumour characteristics of women with screen detected breast cancer

| | Cancer diagnosed with delay[a] (N=22) | Cancer diagnosed without delay (N=2,170) | P-value |
|---|---|---|---|
| Characteristics | | | |
| Tumour type, No (%) | | | |
| Ductal cancer in situ | 3 (13.6) | 371 (17.1) | 0.67 |
| Invasive cancer | 19 (86.4) | 1,799 (82.9) | |
| Invasive cancer histology, No (%) | | | |
| Ductal | 14 (73.7) | 1,482 (82.4) | 0.29 |
| Lobular | 5 (26.3) | 305 (17.0) | |
| Lymph-node status invasive cancers, No (%) | | | |
| Negative | 17 (89.5) | 1,271 (70.7) | 0.09 |
| Positive | 2 (10.5) | 484 (26.9) | |
| Size of invasive cancers, No (%) | | | |
| T1a-c | 16 (84.2) | 1,393 (77.4) | 0.51 |
| T2+ | 3 (15.8) | 394 (21.9) | |
| Size of invasive cancers, No (%) | | | |
| T1a | 1 (5.3) | 79 (4.4) | 0.88 |
| T1b | 3 (15.8) | 433 (24.2) | |
| T1c | 12 (63.0) | 881 (49.9) | |
| T2 | 3 (15.8) | 369 (20.6) | |
| T3 | 0 (0.0) | 15 (0.8) | |
| T4 | 0 (0.0) | 10 (0.6) | |
| Mean size of invasive cancers in mm | | | |
| T1a | 3 | 3.5 | 0.77 |
| T1b | 8 | 8.2 | 0.73 |
| T1c | 13.7 | 14.6 | 0.24 |
| T2 | 32.3 | 27.5 | 0.2 |
| T3 | NA | 57.6 | NA |
| T4 | NA | 29.7 | NA |

*Unknown cases were excluded from statistical analysis*

[a] *Diagnosis of breast cancer after a 2nd referral for the same lesion*

*NA= not applicable*





TABLE 3. Tumour receptor status and Nottingham grade of women with screen-detected invasive breast cancer

| | Cancer diagnosed with delay[a] (N=22) | Cancer diagnosed without delay (N=2,170) | P-value |
|---|---|---|---|
| Characteristics | | | |
| Estrogen receptor No (%)[b] | | | |
| Positive | 18 (100) | 1290 (88.6) | 0.13 |
| Negative | 0 (0) | 166 (11.4) | |
| Progesterone receptor No (%)[b] | | | |
| Positive | 14 (82.4) | 1128 (75.8) | 0.53 |
| Negative | 3 (17.6) | 361 (24.2) | |
| Her2Neu over expression No (%)[c] | | | |
| No | 7 (100) | 635 (89.3) | 0.36 |
| Yes | 0 (0) | 76 (10.7) | |
| Triple negative No (%)[c] | | | |
| No | 7 (100) | 711 (93.1) | 0.47 |
| Yes | 0 (0) | 53 (6.9) | |
| Nottingham grade No (%)[d] | | | |
| I | 8 (44.4) | 529 (45.1) | 0.59 |
| II | 9 (50.0) | 491 (41.8) | |
| III | 1 (5.6) | 154 (13.1) | |

*Unknown cases were excluded from statistical analysis;*

[a] *Diagnosis of breast cancer after a 2nd referral for the same lesion;*

[b] *Data only available of women screened since 1998;*

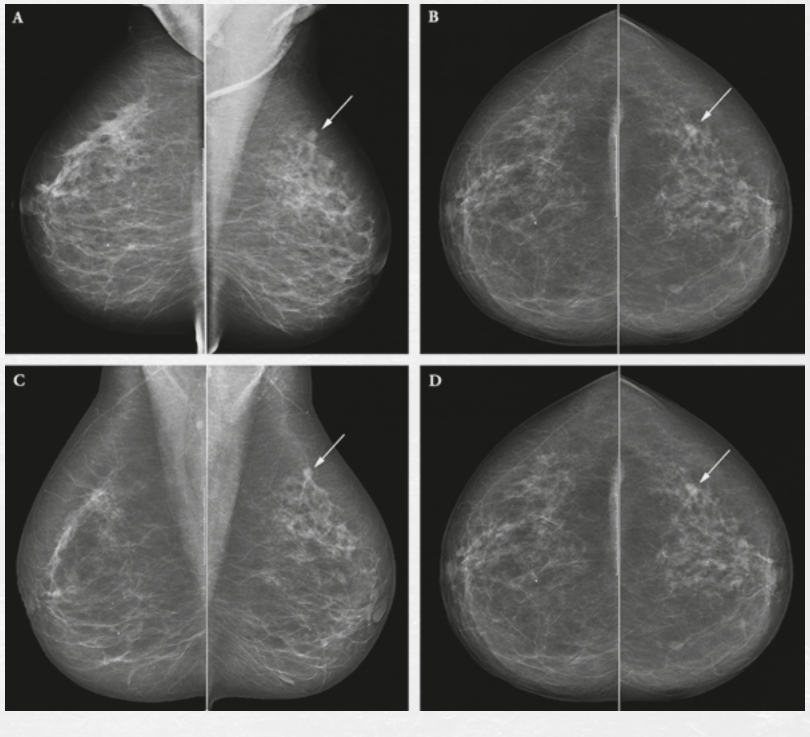
[c] *Data only available of women screened since 2001;*

[d] *Data only available of women screened since 2004*

TABLE 4. Screening characteristics of women who have been referred twice for the same lesion at screening mammography

| | Cancer at 2nd referral (N=22) | No cancer at 2nd referral (N=39) | P-value |
|---|---|---|---|
| Mammographic abnormality, No (%) | | | |
| High density | 16 (72.7) | 17 (43.6) | |
| Microcalcifications | 2 (9.1) | 17 (43.6) | 0.02 |
| High density with microcalcifications | 3 (13.6) | 4 (10.3) | |
| Other | 1 (4.5) | 1 (2.6) | |
| Work-up at 1st referral, No (%) | | | |
| Breast imaging | 17 (77.3) | 15 (38.5) | 0.004 |
| Breast imaging + FNAC/CNB | 5 (22.7) | 24 (61.5) | |

FIGURE 2. Patient example, previous false negative FNAC

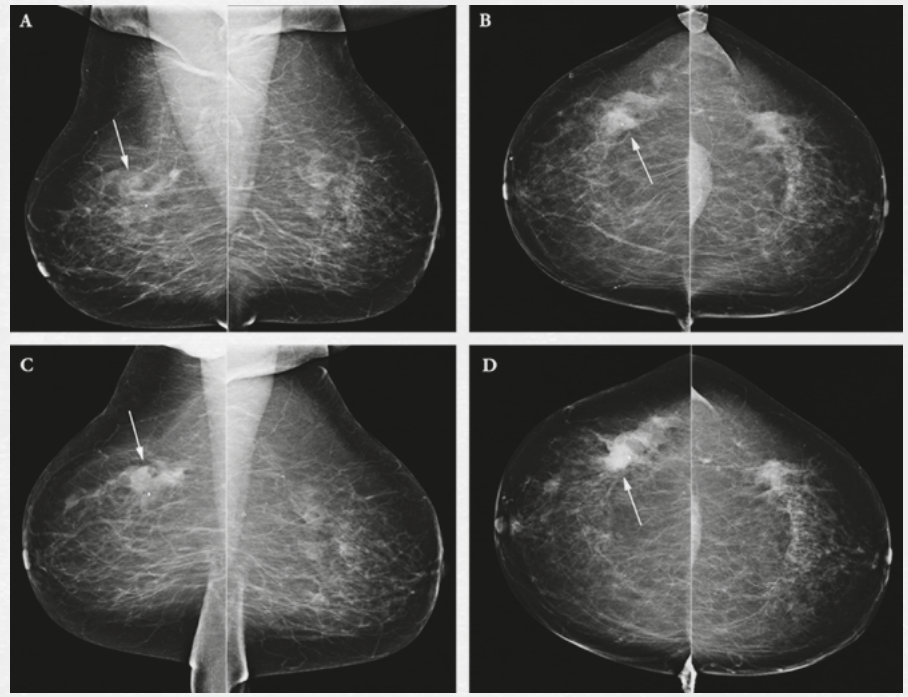



*Two-view screening mammogram (A, medio-lateral oblique (MLO) view and B, cranio-caudal (CC) view) at first referral in 2003 shows an ill-defined high density in the cranio-lateral quadrant of the left breast (arrow). Additional ultrasound guided FNAC revealed atypia. CNBCore biopsy was cancelled as no lesion could be visualized anymore at ultrasound. The lesion was downgraded to BI-RADS II (benign) at follow-up mammography in 2004. The woman was referred again in 2009 (after 2 consecutive screening rounds) because of a subtle increase in size and more spiculated margins of the same lesion. Assessment after second referral revealed an 8 mm invasive ductal carcinoma without lymph node metastasis (T1bN0).*





FIGURE 3. Patient example, previous false negative biopsy




*Two-view screening mammogram (A, medio-lateral oblique (MLO) view and B, cranio-caudal (CC) view) at first referral in 2007 shows an ill-defined high density in the cranio-lateral quadrant of the right breast (arrow). No breast cancer was diagnosed after additional ultrasound guided FNAC and CNB. The woman was referred again at subsequent screening mammography in 2009 (C, MLO-view and D, CC-view) because of an increase in size and density of the breast lesion, with architectural distortion. Assessment after second referral revealed a 40 mm (and 4 mm focus) multicentric, mixed invasive ductal/lobular cancer without lymph node metastasis (T2N0).*

## DISCUSSION

To our knowledge, the current population based study is the first that addresses the screening results of women who have been referred twice at screening mammography for the same lesion. We found that 36.1% (95% CI 24.1%-48.0%) of these lesions proved to be cancer and this percentage was similar to the positive predictive value of 38.6% (95% CI 37.3%-39.8%) for the overall screened population and 37.2% (95% CI 27.0%-47.4%) for women referred a second time, but for a different lesion. A suspicious density at screening mammography and having received only additional breast imaging and no biopsy at first

referral were associated with an increased risk of breast cancer at second referral for the same lesion. We found no differences in patient or tumour characteristics between women with breast cancer diagnosed with or without delay and these characteristics will therefore be of no value in an attempt to decrease the proportion of women who will experience a delay in cancer diagnosis.

Essential in the concept of screening mammography is the early detection of breast cancer. A delay in the diagnosis can diminish treatment options and will probably worsen the prognosis as a result of a more advanced stage of the disease[16]. Unfortunately, a delay in the diagnosis of breast cancer is frequently encountered and it is the most common clinical scenario resulting in malpractice claims in the United States[17]. In a Dutch screening study, Duijm et al reported that 6.5% of referred women experienced a delay in breast cancer diagnosis[3]. We found that women diagnosed with breast cancer after second referral for the same lesion experienced a mean delay of 43 months in breast cancer diagnosis, whereas the proportion of advanced cancers was comparable among women with a diagnostic delay and women with a diagnosis of breast cancer after first referral. Other patient and tumour characteristics were also comparable between these groups.

Breast cancer was significantly more likely to be diagnosed at second referral if work-up had only consisted of additional imaging at first referral to rule out breast cancer. In our study, 7 lesions classified as probably benign at first referral subsequently proved to be malignant at second referral. Mammographic follow-up, rather than biopsy, is usually advocated for lesions categorized as probably benign (BI-RADS 3) as only 1-2% of these lesions ultimately turn out to be cancerous[18,19]. However, considerable inter-observer variation exists in the use of BI-RADS 3 classification and several studies report that many of these lesions that turn out to be malignant retrospectively do not fulfil the BI-RADS 3 criteria[3,20,21]. Therefore, a careful use of the BI-RADS 3 category is recommended and pathologic confirmation of a lesion should be considered if there is the least of doubt whether or not a lesion should be classified as BI-RADS 3. Another five women with breast cancer diagnosed at second referral had received a false negative biopsy of the same lesion at previous referral. Although the malignancy miss rate on FNAC and core biopsy is rare, biopsy should be repeated if discrepancy persists between radiologic abnormalities and biopsy findings[22,23]. Youk et al[24] provide recommendations in order to reduce diagnostic delay after CNB. An annual mammography is suggested if the histological diagnosis is specific, and a short interval follow up (at 6, 12 and 24 months) is recommended if a non-specific diagnosis is given. These recommendations, however, are not yet implemented in the Netherlands.





An increased risk of breast cancer at second referral was also present if screening mammography showed a suspicious high density rather than suspicious microcalcifications, which is in line with our previous observation of a disproportionate number of suspicious densities in women experiencing a diagnostic delay[3,21]. For the timely detection of breast cancer at screening mammography, a prompt confirmation of the malignancy after recall is required in addition to correct detection of suspicious mammographic findings at screening. As fewer women with suspicious high density received histological confirmation than did women who presented with suspicious microcalcifications, our study shows that there is room for improvement, especially in the work-up for suspicious densities.

There is a delicate balance between referral rate, cancer detection rate and false positive referral rate[25]. The 1-2% referral rate of the Dutch screening program is much lower than the 5-10% referral rates observed in UK and US programs[2]. Otten et al calculated that a referral rate of 2-4% would still be cost-effective for the Dutch nation-wide breast screening programme[25] and a US study showed that cancer detection rate increased only marginally above a referral rate of 4.8%[26].

Extensive research has been done on the negative consequences of false positive results at screening mammography. A false positive result may cause short term anxiety and psychological distress, as well as long–term breast cancer related concerns[7,9]. Moreover, high false positive referral rates increase the financial burden of screening as a result of increased work-up costs related to breast imaging and biopsy procedures. Although studies unanimously conclude that re-attendance after a false positive screen is not influenced by the type of diagnostic procedure at recall[27,28], there are conflicting reports whether or not a false positive test changes a women's future screening adherence[9,27-30].

In the Dutch breast screening programme, coordinating screening radiologists complete a short checklist of each referred woman concerning the specific diagnostic procedures performed at work-up (i.e., breast imaging only, or additional FNAC, CNB or surgical biopsy at work-up). In order to reduce the risk of a second false positive referral for the same lesion, placing this information at the screening radiologist's disposal may be helpful to determine whether or not a lesion should be referred for the second time at a future screening.

Our study has certain limitations. Although breast cancer screening in the Netherlands must be performed by certified screening radiographers and certified screening radiologists who are subject to quality assurance procedures, work-up of referred women can take place at any hospital. Considerable variations in work-up performance may exist among these hospitals[3], but the number of women in our study with breast cancer at

second referral was too small to take this factor into consideration. The type of diagnostic procedures has changed significantly over the years with gradual replacement of surgical biopsy and FNAC by CNB and by introduction of magnetic resonance mammography[31]. Some authors indicate that FNAC offers reliable and simple alternative to open biopsy of non-palpable breast lesions[32,33]. On the other hand, a large multicentre trial demonstrated that FNAC of non-palpable abnormalities had limited value given the high insufficient sample rate and greater diagnostic accuracy of other interventions such as CNB and needle-localized open surgical biopsy[34]. Although one can argue that the rate of false negative assessments may be affected by diagnostic alterations, we did not observe a significant change in the proportion of women with a diagnostic delay during an eleven year screening period[3]. Finally, it would be of interest to gain insight in the impact of a second false positive referral on future screening adherence. This topic, however, was beyond the scope of the current study.

In conclusion, we found that an important subset of women referred twice for the same lesion at screening mammography had breast cancer and the breast cancer risk was similar to the one observed in women referred only once, or referred for a second time but for a different lesion. Suspicious high density at screening mammography or the absence of biopsy at first referral increased the risk of breast cancer being diagnosed at second referral. Mean diagnostic delay in these women was 43 months, with the risk of worsened prognosis.





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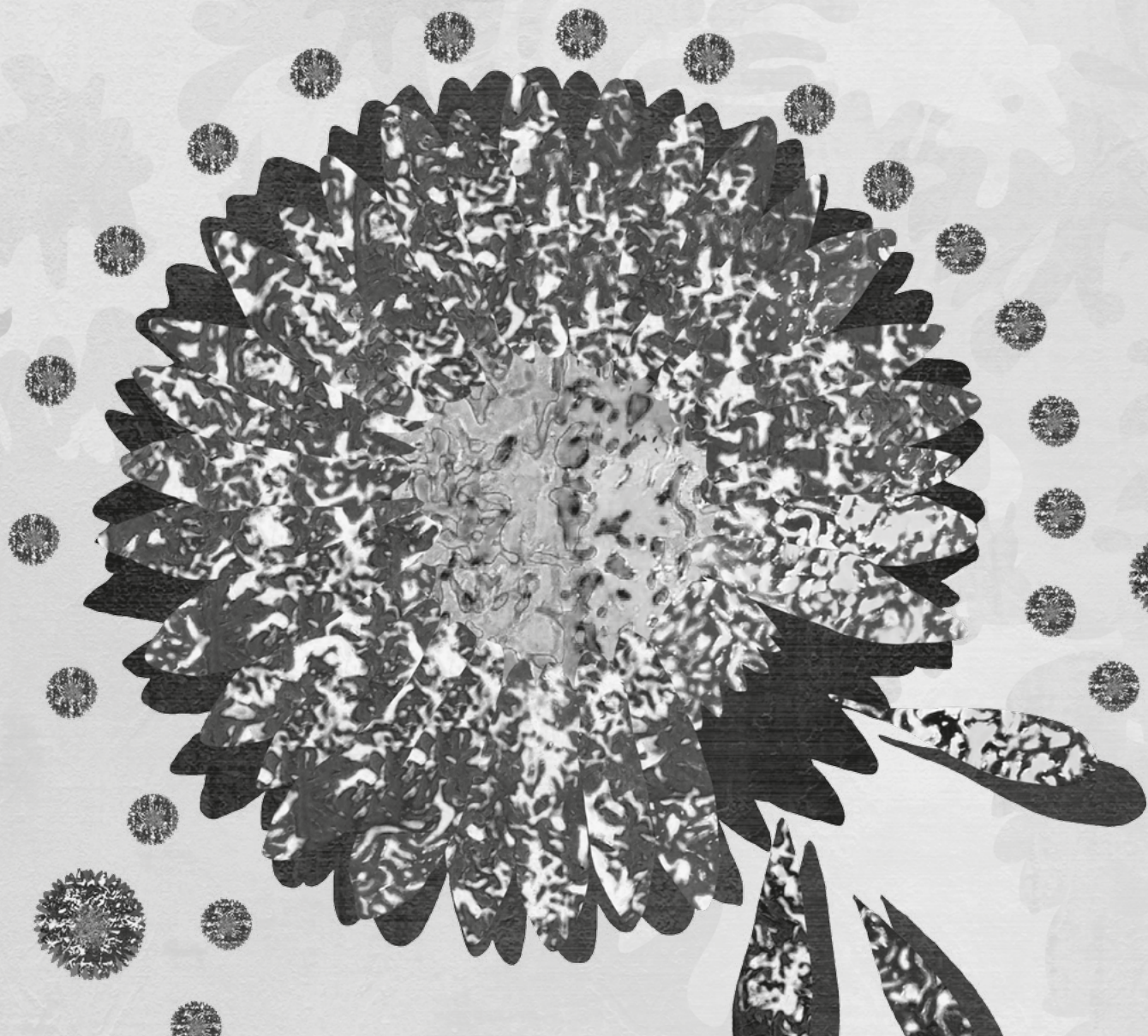
# PART III
## Experiences with malpractice claims
at screening mammography



# Chapter 6

## Malpractice claims following screening mammography in the Netherlands;

missed breast cancers and related delay in diagnosis after referral

**Published as:** van Breest Smallenburg V, **Setz-Pels W**, Groenewoud, Voogd AC, Jansen FH, Louwman MW, Tielbeek AV, Duijm LE. Malpractice claims following screening mammography in The Netherlands. **Int J Cancer 2012; 131: 1360-1366.**

## ABSTRACT

Although malpractice lawsuits are frequently related to a delayed breast cancer diagnosis in symptomatic patients, information on claims at European screening mammography programmes is lacking. We determined the type and frequency of malpractice claims at a Dutch breast cancer screening region. We included all 85,274 women (351,009 screens) who underwent biennial screening mammography at a southern breast screening region in the Netherlands between 1997-2009. Two screening radiologists reviewed the screening mammograms of all screen detected cancers and interval cancers and determined whether the cancer had been missed at the previous screen or at the latest screen, respectively. We analysed all correspondence between the screening organization, clinicians and screened women, and collected complaints and claims until September 2011. At review, 20.9% (308/1,475) of screen detected cancers and 24.3% (163/670) of interval cancers were considered to be missed at a previous screen. A total of 19 women (of which 2, 6 and 11 women had been screened between 1997-2001 (102,439 screens), 2001-2005 (114,740 screens) and 2005-2009 (133,830 screens), respectively) had contacted the screening organization for additional information about their screen detected cancer or interval cancer, but filed no claim. Three other women directly initiated an insurance claim for financial compensation of their interval cancer without previously having contacted the screening organization.

We conclude that screening related claims were rarely encountered, although many screen detected cancers and interval cancers had been missed at a previous screen. A small, but increasing proportion of women sought additional information about their breast cancer from the screening organization.








## INTRODUCTION

Many countries have introduced screening mammography programmes with the aim to reduce breast cancer mortality[1]. Essential for reducing morbidity and mortality is the early detection of breast cancers, as a diagnostic delay lowers breast-conserving treatment options and worsens prognosis[2,3]. Unfortunately, a delayed diagnosis resulting from a missed cancer at screening is not rare. Certain cancers are just not visible at screening mammography, whereas others are misinterpreted or overlooked[4,5].

Interpretation of mammograms is one of most difficult tasks in radiology and the sensitivity of screening mammography for breast cancer detection ranges from 70 to 80%[6,7]. Nevertheless, the public's expectations of the efficacy of screening mammography are high and diagnostic errors can have major legal consequences for the screening radiologist. An Italian study observed, over a period of twelve years, a marked rise in malpractice claims related to diagnostic mammography in symptomatic women[8]. In the United States, a delay in breast cancer diagnosis is nowadays the most prevalent and the second most expensive condition resulting in malpractice lawsuits[9,10]. The most common defendant in these lawsuits is the interpreting radiologist and as a consequence the number of radiologists willing to read mammograms in the US is decreasing[11-13]. Recall rates in most European screening programmes vary from 3-6%[1], which is in line with the recommended recall rate in the European guidelines for quality assurance in breast cancer screening and diagnosis[14]. In contrast, recall rates in the US frequently exceed 10%[15] and these higher recall rates may be the result of the fear for lawsuits[16]. The combination of manpower shortage and the high risk of lawsuits may thus have a detrimental effect on breast cancer screening and health care in general.

A majority of claims are related to mammographic misinterpretation and failure to communicate openly with patients about these errors[10,11]. Discussing errors with patients could enhance their satisfaction and may reduce the number of malpractice claims. However, fear of lawsuits makes disclosure of medical errors to patients difficult and recent studies suggest that communicating openly about errors is the exception rather than the rule[17,18].

To our knowledge, no data have been published about malpractice claims involving screening mammography in Europe. In the current study we determined the type and frequency of malpractice claims at a Dutch breast cancer screening region over a 12-year screening period.

# MATERIALS AND METHODS

## Study population

We included all 351,009 screening examination of 85,274 women who underwent screening mammography at two specialized analogue screening units in a southern breast cancer screening region of the Netherlands between January 1, 1997 and January 1, 2009. All women in our study had given written informed consent to use their data for evaluation purposes before participating in the screening programme. Approval by our local Institutional Review Board was not required for this study, according to the Dutch Central Committee on Research involving Human subjects (CCMO).

## Screening procedure and referral

Details of our breast cancer screening programme have been described previously[19-21]. In summary, five regional breast-screening organizations offer the Dutch screening programme, providing biennial screening mammography to all Dutch women aged 50-75 years. All mammograms are performed by specialized screening mammography radiographers. In our screening region, the screening examinations are independently double read by a group of 12 certified screening radiologists. From 2003, in addition to radiologist double reading, the radiographers also actively participate in the assessment of the screening mammograms. Each of the screening radiologists evaluates at least 5,000 screening mammograms yearly. In case of subsequent screening, prior screening mammograms are always available for comparison. Women with normal or benign mammographic findings or with a non-specific minimal sign are not referred. Minimal sign lesions are present in about 10% of screening mammograms and have a less than 1% chance of malignancy[22]. If screening mammography shows a suspicious or malignant lesion, women are referred by their general practitioner to a surgical oncologist or breast clinic for further analysis of the mammographic abnormality.

## Follow-up procedure

For each referred woman, we collected data on radiology, pathology and surgical procedures at the hospitals where the mammographic screening abnormalities of referred women were evaluated, with two-year follow-up. A majority of interval cancers (interval cancers are breast cancers that are diagnosed in women after a negative screening examination, defined as no recommendation for referral) were identified by linking the records of screened women to those of the regional cancer registry and radiotherapy laboratory. Some interval cancers were traced by the occasional reports on interval cancers provided by general practitioners or medical specialists to the screening centre, whereas other interval cancers were identified by inquiry about pathology specimens at the various regional pathology laboratories, some months after a hospital had requested the screening





mammograms of a screening participant who had not been referred. Communications between the screening organization and screened women that were related to screening procedures, screening outcome or diagnostic procedures after referral were routinely recorded by the organization.

## Review of screen detected cancers, interval cancers and delayed cancer diagnosis after referral

Two experienced screening radiologists (LD and FJ) reviewed the screening mammograms of all screen detected cancers and interval cancers. For cancers detected at subsequent screening, they determined whether the cancer had been missed or whether it had shown a non-specific minimal sign at the previous screening mammogram. For interval cancers, the two radiologists determined whether the cancer had been missed or had been present as a minimal sign lesion at the latest screening mammogram. To determine the main reasons for diagnostic delay after referral, the two radiologists reviewed the diagnostic breast images of all women who had breast cancer pathologically confirmed more than three months following a positive screen[23,24]. Each reviewer classified the lesions according to the American College of Radiology BI-RADS[25]. The radiologists were blinded to each other's review and discrepant assessments were followed by consensus reading. To determine whether the delay was due to a false negative pathology report, a pathologist reviewed the specimen of those women who had undergone more than one breast biopsy procedure needed for breast cancer confirmation.

## Communication between the coordinating screening radiologist and screened women

Our screening organization routinely asked the coordinating screening radiologist to contact women with a request for additional information about her screen detected cancer or interval cancer. Contact between the radiologist and the woman was established first by telephone, and then, if desired, by personal contact. In all cases, the radiologist specifically informed the woman whether or not her screen detected cancer had been visible at the previous screen, or in the case of interval cancer, whether the malignancy had been missed at the latest screen. The conclusions of these communications were routinely documented and were also recorded at a database that had been developed for this study. For the current study, we included all communications regarding the screening period 1997-2009, that had been recorded until September 1, 2011.

# RESULTS

## Overall screening results

A total of 351,009 analogue screens in 85,274 women were acquired between January 1, 1997 and December 31, 2008 (Figure 1). Altogether, 4,450 screens (1.3%) required further evaluation because of a mammographic screening abnormality. Six of these women (0.2%) had either not been referred by their general practitioner or their type of diagnostic procedures was unknown. Breast cancer was diagnosed in 1,773 referred women, yielding an overall cancer detection rate of 5.1 per 1,000 screening examinations and a true positive referral rate of 39.8%. Within two year of follow-up, interval cancers had been diagnosed in 670 women who had been screened negative, resulting in a 72.6% (1,773/2,443) screening sensitivity for breast cancer detection.

In 1,586 (59.4%) of 2,671 referred women with benign follow-up, evaluation of the abnormality detected at screening mammography merely consisted of one or several radiologic examinations (i.e., additional mammographic views, breast ultrasonography and/or magnetic resonance mammography). Evaluation also included percutaneous biopsy in 830 (31.1%) women, invasive surgical biopsy in 133 (5.0%) women or a combination of percutaneous and surgical biopsy in 122 (4.5%) women (Figure 1).

Of the 1,773 referred women with a diagnosis of breast cancer at follow-up, the mammographic abnormality had been detected at initial screening in 298 women and at subsequent screening in 1,475 women (Figure 1). Review of the latter group showed that 308 (20.9%) cancers had been missed 2 years earlier, at the previous screening mammogram, and 322 (21.8%) had been visible as a minimal sign. The remaining 845 (57.3%) cancers detected at subsequent screening were either mammographically occult or not yet present at the previous screening examination.

A total of 670 interval cancers had been diagnosed among the screened population (Figure 1). The reviewers reported that 163 (24.3%) of these cancers had been missed at the latest screening mammogram, 164 (24.5%) had been visible as a minimal sign and 343 (51.2%) were not visible at the latest screen.

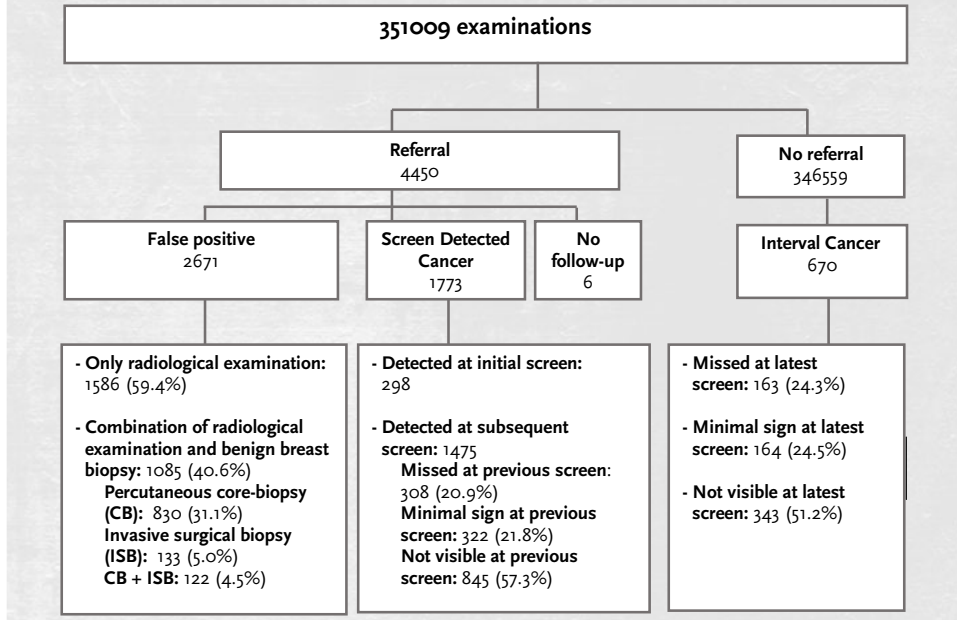
## Requests for additional information and malpractice claims

Between January 1997 and September 2011, a total of 19 screened women had contacted the screening organization for questions related to their cancer detected at screening (8 women) or interval cancer (11 women) (Figure 2). Of these 19 women, 2 had been screened between 1997-2001 (102,439 screens, including 498 screen detected cancers and 169 interval cancers), 6 between 2001-2005 (114,740 screens, including 599 screen detected





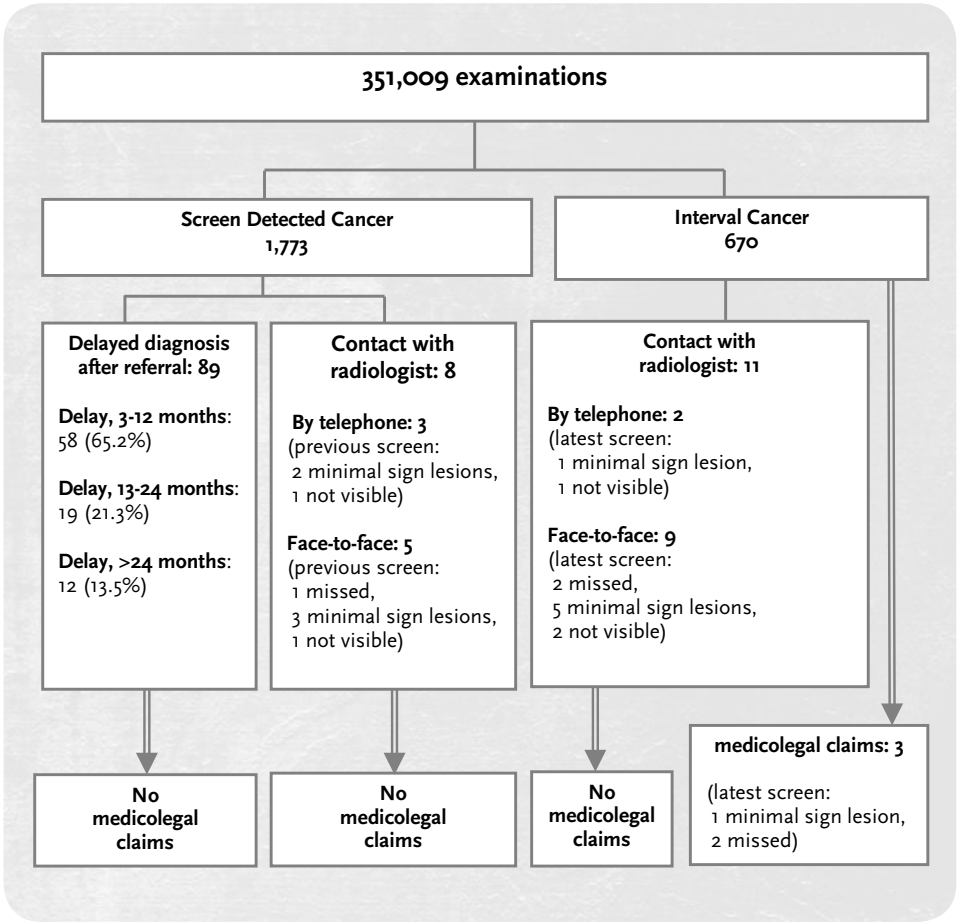
FIGURE 1. Mammography screening outcome January 1997- January 2009




cancers and 244 interval cancers) and 11 between 2005-2009 (133,830 screens, including 676 screen detected cancers and 257 interval cancers). The resulting contact between the women and the coordinating radiologist was limited to conversation by telephone in 5 cases and comprised 3 screen detected cancers (previous screen: 2 minimal sign lesions, 1 not visible) and 2 interval cancers (latest screen: 1 minimal lesion, 1 not visible). Additional face to face contact occurred in 14 women, of whom 5 had advanced cancer detected at subsequent screening (previous screen: 1 missed, 3 minimal sign lesions, 1 not visible) and 9 had a diagnosis of advanced interval cancer (latest screen: 2 missed, 5 minimal sign lesions, 2 not visible). In these patients advanced cancer was defined as invasive cancer >20 mm. and/or lymph node positive cancer. None of the 19 women started a malpractice lawsuit or insurance claim for financial compensation.

Apart from the 19 women mentioned above, another 3 women directly initiated an insurance claim for financial compensation of their interval cancer without previously having contacted the screening organization (Figure 2). The time span between the latest screen and the start of the claim in these 3 cases was 14, 25 and 40 months, respectively.

FIGURE 2. Malpractice claims at screening mammography




One claim was rejected (latest screen: minimal sign lesion), whereas the verdicts of the other 2 claims (two interval cancers that had been missed at the latest screen) still have to be finalized.

There was one special case of a referred woman who initially demanded from the screening organization to be compensated for the €155 expenses made for additional clinical mammography and breast ultrasonography. She refrained from further steps after being informed by the coordinating radiologist that only the actual costs for screening mammography are covered by the nation-wide breast screening programme.





## Delayed cancer diagnosis after referral

Of the 1,773 referred women with breast cancer, 89 (5.0%) experienced a more than 3 months delay in cancer diagnosis (Figure 2). An incorrect BI-RADS classification at clinical mammography, especially categorization of suspicious lesions (BI-RADS 4) or malignant lesion (BI-RADS 5) as probably benign lesions (BI-RADS 3), comprised 57.3% (51/89) of diagnostic delays. The pathologist did not encounter any incorrectly classified biopsy reports. However, false negative percutaneous biopsy results, i.e. retrieval of non-suspicious cells from a malignant lesion, accounted for 20.2% (18/89) of diagnostic delays. The remaining 21 (23.6%) diagnostic delays were due to a variety of reasons, including false negative open (surgical) biopsy or non-compliance of a surgical oncologist with the pathologist's advise to excise a lesion with suspicious cytology or histology at percutaneous biopsy. There were no women-based reasons of delay (e.g., refusal to undergo additional evaluation after referral). The delay was 3-12 months, 13-24 months or more than 24 months in respectively 58 (65.2%), 19 (21.3%) and 12 (13.5%) women. An advanced tumour stage at the time of definitive surgery was diagnosed in 27.0% (24/89) of women with a delayed diagnosis, compared to 19.3% (325/1,684) in women who experienced no diagnostic delay after referral. None of the 89 women with diagnostic delay filed a malpractice claim.

# DISCUSSION

To our knowledge, no previous data have been published with respect to screening mammography claims in Europe. We found that, although more than one-fifth of screen detected cancers and interval cancers had been missed at a previous screen, only 3 insurance claims for financial compensation had been filed following a diagnosis of interval cancer. Moreover, none of the women who experienced a delay in cancer diagnosis after referral filed a claim against any of the involved hospital physicians.

A delay in breast cancer diagnosis is the most common reason for medical malpractice claims in the United States and the radiologist is the most frequently litigated physician in these cases (9). Similar observations were made in Italy[8]. Consequently, the number of qualified screening radiologists, especially in the US, is decreasing and this may seriously impede access to breast cancer screening in the future. Besides a reduction in the number of breast radiologists and screening mammography radiologists, malpractice lawsuits may also result in a lower quality of mammographic interpretation. Lawsuits may cause uncertainty of the interpreting radiologist, which is associated with high recall rates at screening and lower positive predictive value rates[15,16]. Higher recall and false positive rates also increase anxiety among referred women and increase workup costs[26].

Several authors have focused on the issue of increasing medical malpractice claims regarding mammography in the United States[10,11]. One explanation for the high number of claims seems to be the public's high expectations of mammography performance. The limitations of screening are often poorly understood, which is probably due to campaigns encouraging women to undergo screening mammography and the media, which tend to emphasize only the benefits of screening. Berlin suggested that improving public education about shortcomings of mammography may reduce the number of lawsuits[10]. Moreover, jury verdicts are influenced by the public's perception and a better public understanding of the limitations of screening mammography may not only reduce the number of lawsuits, but may also lower the costs of medical malpractice claims by reducing the awards paid to patients following a jury verdict.

In our study, only 19 women had contacted the screening organization for additional information about their cancer detected at screening or interval cancer. This is a remarkably low number, especially when taking into account the fact that a large proportion of screen detected cancers and interval cancers could have been diagnosed at a previous screening round and showed an unfavorable, advanced tumor stage at surgery. None of these women filed a claim, even if they had been informed by the coordinating screening radiologist that the cancer had been missed (3 cases) or had shown a minimal sign abnormality (11 cases) at a previous screen. The open communication between the coordinating radiologist and these women may probably have prevented them to initiate a litigation procedure. A majority of the 19 women (11/19; 58%) had been screened between 2005-2009 and this finding suggests that the proportion of women who contact a screening organization after a diagnosis of breast cancer will probably increase in the future.

So far, only 3 women have filed a claim for financial compensation of their interval cancer and they did so without first contacting the coordinating screening radiologist. Apart from the open communication, several other factors may also partly explain the very low number of contacts between the screening organization and screening participants and sporadic claims in our study. With each invitation, women receive written information that breast cancer may be missed at screening mammography and they should always seek medical attention in case of breast complaints following a negative screen. Although data about payouts for missed and delayed breast cancer diagnoses in the Netherlands are lacking, these payouts may probably be much lower when compared to the United States. Moreover, Dutch lawyers are not allowed to practice a no-win no-fee policy. Finally, women may have refrained from contacting the coordinating screening radiologist and starting malpractice claims after having received satisfactory information from their physicians in the hospitals to which they had been referred.





False positive referral negatively affects quality of life[26] and almost 1 out of every 10 referred women in our study (9.5%, 255/2,671) with benign follow-up underwent invasive surgical biopsy. Surgical biopsy harbors the risk of infection, cosmetic drawbacks and may decrease the accuracy of future screening mammography (20). Nevertheless, only one referred woman complained about her false positive referral and she wanted the screening organization to compensate her for the costs of clinical mammography and breast ultrasonography. The Dutch nation-wide screening mammography programme provides free screening mammography, but it does not cover any costs related to additional diagnostic procedures. An addition of this information to the screening invitation letter probably prevents invited women to be confronted with unexpected financial expenses in case not all hospital related costs are covered by their medical insurance.
Although the screening organization is not responsible for the quality of clinical assessment of referred women, we also determined whether any of the referred women with a delay in breast cancer diagnosis filed a claim. About 5% of women in our screened population experienced a diagnostic delay of more than 3 months after their referral and we previously found that this delay is most frequently due to erroneous interpretation or classification of breast lesions at clinical breast imaging[23,24]. To our surprise, none of the women filed a malpractice claim, not even when they were diagnosed with advanced cancer 2 years after referral.

In our screening programme, several measures have been taken in the past to minimize the risk of delayed cancer diagnosis. First, our team of screening radiologists routinely reviews newly diagnosed interval cancers with the aim to reduce the proportion of interval cancers at future screening. Second, as part of the nation-wide quality assurance of screening mammography, the National Expert and Training Centre for Breast cancer screening (NETCB) evaluates our screening results every 3 years. This evaluation not only includes feedback on screening outcome parameters such as referral rate and cancer detection rate, but also a comprehensive review of interval cancers and advanced breast cancers detected at subsequent screening. Finally, our radiographers have been encouraged to interpret screening mammograms. During quality assurance sessions, they bring mammographic abnormalities that may require additional work-up to the attention of a supervising breast radiologist[6].

Our study has certain limitations. We realize that the eagerness of patients to start a lawsuit will be influenced by national legislation and the beforehand probability and height of insurance payouts. The Dutch nation-wide breast screening programme differs in several aspects from other European programmes and US programmes. For example, the referral rate in the Netherlands is very low when compared to a 3-6% referral rate in other

European countries and a 10% referral rate in the United States[1,15]. In the Netherlands, all mammograms are routinely double read by two screening radiologists, which may not be standard practice in other screening programmes[7,27]. Also, many European programmes, including the Dutch one, offer biennial screening for women aged 50-75 years. In contrast, women are screened every 3 years in the UK and US programmes usually offer annual screening from the age of 45. Screening interval length may influence screening outcome parameters such as screening sensitivity and tumour size of screen detected cancers and interval cancers[28,29]. Furthermore it was not possible to compare the low number of claims in our screening region with a nation-wide number of claims following breast cancer screening. Details of claims are not routinely registered by screening organizations in the Netherlands. We found, however, one published claim, regarding a woman with interval cancer[30]. Her claim was rejected after concluding that both screening radiologists had made the right decision by not referring the woman for her minimal sign lesion. Despite the absence of a national registry of claims, we have no reason to believe that the frequency of claims in our region differs from those in other parts of the Netherlands.

Two interval cancer claims in our study are still under discussion. In 1991, the screening organization of the Southern Netherlands (Bevolkingonderzoek Zuid, BOZ) started with the implementation of biennial screening mammography. More than 2,500,000 screens have been performed since then and it is estimated that about 220,000 women will attend screening mammography in the Southern Netherlands in 2011. So far, the screening organization had to compensate for a claim only once; € 5,000 was paid in advance for temporary compensation of an interval cancer diagnosed in a woman who had been screened at another unit than ours. The general practitioner and clinical radiologist were also held responsible for the delay in cancer diagnosis in this particular case and the final decision of the claim has not yet been set. The insurance policy of the screening organization covers a maximum payout of € 5,000,000 per claim and a maximum annual payout of € 10,000,000. Acceptance of our two claims will probably have no impact on the communication and referral strategy as the insurance policy sufficiently covers payouts for missed and delayed cancer diagnosis and screening radiologists are not personally liable for any financial compensation of claims. Moreover, insufficient communication is a leading factor in a majority of radiologic lawsuits and an open and clear communication with screened women may thus potentially prevent a litigation procedure[31].

Finally, only mammograms obtained with analogue units were included in the current study, whereas most mammography units are now digital. Digitization of the breast cancer screening programme in the Netherlands has recently been completed and the proportion of cancers missed at a previous screen may hopefully decrease in the future as digital screening





tends to yield higher cancer detection rates when compared to analogue screening[32,33].
In summary, we conclude that women rarely filed a malpractice claim, although a substantial proportion of screen detected cancers and interval cancers had been missed at a previous screen and 5% of women experienced a delay in breast cancer diagnosis after referral. An open communication between the screening organization and women who seek additional information after having been diagnosed with breast cancer may help to refrain women from starting a litigation procedure.

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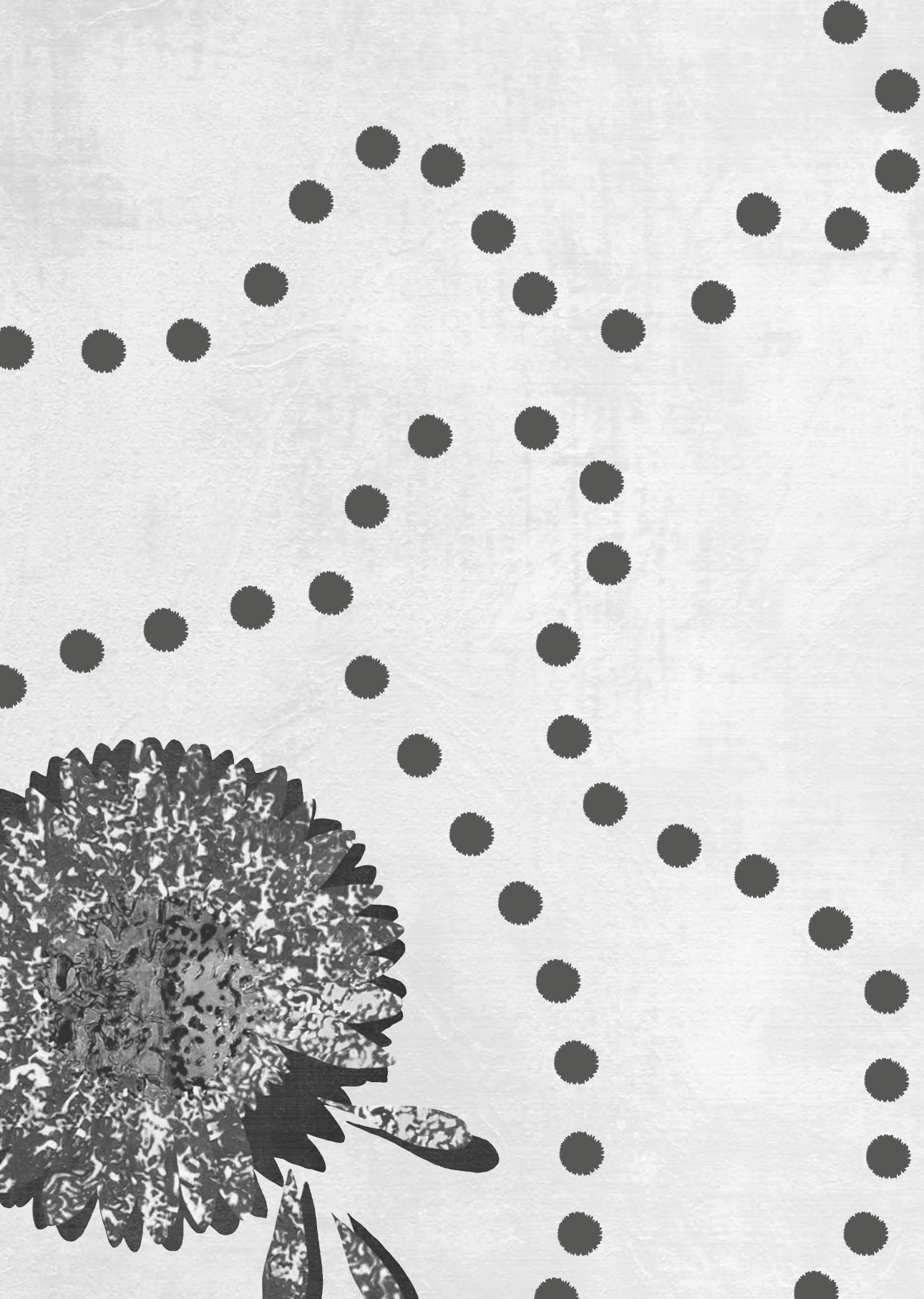

# Chapter 7

## General Discussion

## WHY STILL SCREENING?

No other type of screening than breast cancer screening has been the object of so many randomized studies and evaluations[1]. Despite a continuous flow of research papers trying to quantify the impact of breast cancer screening on breast cancer mortality[2-4] consensus is still lacking whether its benefits outweigh the harms. Together with the growing awareness of the complexity of setting up and running a breast cancer screening programme, it is reasonable to ask if there still is a rationale for breast cancer screening. Before we discuss the findings of this thesis, we describe why screening can still be valued in the Netherlands. Already in 1963 the World Health Organisation[5] defined general criteria that should be met to perform effective screening, better known as the criteria of Wilson and Jungner. They were further elaborated by Cole in 1980[6] and later by Obuchowski in 2001[7]. These criteria are listed and clarified in the following text:

### The problem

1. The disease should be an important health problem:
   Worldwide breast cancer is now the most common cancer diagnosed in women and one of the leading causes of cancer death in women[8], with around 14,000 new patients being diagnosed[9] and more than 3,000 women dying from breast cancer each year in the Netherlands[10]. Besides, breast cancer incidence is still increasing and its nature may be changing as well[11,12].

2. There should be a detectable preclinical or latent phase of the disease:
   The preclinical phase is the duration of time that an occult tumour can be detected before the onset of symptoms, and usually ends when a patient seeks medical care[6], which depends on the populations awareness of the disease and the patient's access to health care. Breast cancer awareness among Dutch women is substantial and the access to screening mammography is guaranteed for the whole female population aged 50-75 years. Screening mammography can detect cancer before the critical point when the primary breast tumour metastasizes to lymph nodes or distant sites in the body (bones, liver, lung). Mammography can detect ductal carcinoma in situ (DCIS), which usually presents as microcalcifications, and DCIS can be a precursor of invasive breast cancer. Mammography is also able to detect small cancers below the clinical detection size (5 mm)[13,14].

3. Screening detects little pseudo-disease:
   Pseudo-disease appears at the screening test, but does not and will never negatively affect the patient's life. Pseudo-disease never progresses, may regress naturally or progresses so slowly that the patients never develops symptoms and dies from another

cause[7]. Although DCIS is a precursor of invasive breast cancer, not all DCIS lesions will progress to invasive carcinoma[15]. However, which part of these lesions really represent clinically insignificant DCIS, and therefore the true proportion of overdiagnosis, currently remains unknown. Thus for breast cancer the natural development from preclinical phase to invasive cancer, is not yet adequately understood

## The screening test

4. Screening has high accuracy for detecting the preclinical phase of the disease:
   Ideally, a screening test should have both a high sensitivity and specificity. In screening we usually have to deal with tests that are less invasive and cheaper than the gold standard and thus have less discriminative power. The challenge is to find the delicate balance between sensitivity and specificity of the screening test, realizing that increasing the sensitivity will result in a decrease of the specificity. When screening an asymptomatic population, the disease prevalence is relatively low (<1%) and even a high specificity of screening mammography (e.g. >95%) will result in a considerable number of false positive screening results[16]. Mammography is still the most optimal diagnostic screening tool for the detection of breast cancer, with a sensitivity of around 70% (both in the initial and subsequent screening round) and a specificity of around 98% and 99% for respectively initial and subsequent screens[17], depending on the skills and experience of screening radiologists, as well as patient related factors, such as breast density.

5. The screening test should be acceptable to the population:
   The screening test must not inflict significant morbidity on those screened. For breast cancer screening, the short term side-effect is patient discomfort, i.e. pain during mammography. The radiation dose as a result of biennial screening mammography is low and does not significantly increase the risk of (breast) cancer[18]. However mass screening has unintended harmful effects, primarily caused by the psychological consequences of false positive referrals, and related (unnecessary) additional work-up, especially if these potential harms are poorly related to the women invited to screening[19].

6. The screening test is affordable and available:
   Mammography is affordable and available to the target population. In comparison to other screening programmes such as cervical cancer, the national screening programme for breast cancer is relatively cheap. For breast cancer, 2,200 euro per QALY (Quality-adjusted life year) is calculated[20](cost-utility analyses performed in 2007), which is equal to the expected cost effectiveness of screening for colorectal cancer and low compared to 15,000 euro per QALY for cervical cancer[21].





## The treatment

7. There should be an accepted treatment for patients diagnosed with the disease:
   Surgery combined with radiotherapy and/or (neo) adjuvant systemic therapy is the standard of care for most patients with breast cancer. Continuous improvements in these treatment modalities have also resulted in a significant decrease in breast cancer mortality in the last decades. However, the extent of mortality decrease through screening, besides mortality reduction as a result of improved therapy, is yet unclear[22]. For screening to be cost-effective, treatment should be more effective or less toxic when applied during the detectable preclinical phase, as compared with treatment applied after symptoms begin. Screening cannot be cost effective if the disease can be treated successfully after symptoms appear. It is, however, surprisingly difficult to demonstrate the benefit of early treatments in the current situation where almost all patients are receiving adjuvant systemic treatment.

8. Treatment should be acceptable to the population.
   Treatment cannot be so risky or toxic that it offsets its long-term benefits. This is particularly important when patients with pseudo-disease will undergo treatment. The immediate risks related to surgery, radiation therapy and chemotherapy seem reasonable and the mortality rate of these treatment modalities is virtually 0%[7]. Although long term side effects of breast cancer treatment, treatment related morbidity, should not be ignored, the risks are much lower now than they used to be in the past. The introduction of lumpectomy in the 70's reduced postoperative morbidity compared to a (modified) radical mastectomy. Treatment related morbidity further decreased with the introduction of sentinel node biopsy (SNB), instead of axillary dissection as standard of care. Axillary lymph node dissection is still associated with significant upper limb morbidity[23]. In the 80's adjuvant radiotherapy improved local disease control[24], however radiotherapy related harms like pain[25], cardiac morbidity, such as myocardial infarction or congestive heart failure[26], and lung toxicity[27] are relevant signs in long-term morbidity of breast cancer treatment[25]. Rapid developments within the field of radiotherapy, including a better understanding of possible interactions with other treatments, have diminished the risk of side-effects for patients treated more recently[28]. Chemotherapy can result in more serious long term adverse effects such as heart failure[29], second cancers (leukaemia), neurotoxicity and premature menopause[30]. Hormonal therapy leads to an increased risk of thromboembolic events and endometrial cancer, although these side effects are not that frequently encountered and dependant of dose and certain risk profiles[31]. Immunotherapy can lead to cardiac adverse events, however the cardiac dysfunction seems to be reversible[32].

### The population

9. There should be an agreed policy on whom to screen and whom to treat as patients: The screening population consists of middle aged women whose breast cancer risk is average at group level. Those women diagnosed with invasive breast cancer and ductal carcinoma in situ are treated according to reference guidelines. However both the age to start screening as well as the screening interval show variation in between countries.

Above mentioned criteria allow us to identify strengths and weaknesses of breast cancer screening. Taking into account the WHO criteria there appears to be a strong case for breast cancer screening; Breast cancer is an important health problem, with a sufficient prevalence of preclinical disease. Screening mammography has adequate sensitivity, which still can be improved as a result of the ongoing evolution of this technique, and good specificity. Screening mammography can detect cancer before it metastasizes. The affordability and availability of screening mammography is good, especially compared to other screening modalities for breast cancer. Effective treatment regimens are available, with acceptable toxicity in relation to disease severity.

## WHY DOUBT THE USEFULNESS OF SCREENING?

Although breast cancer screening may seem justifiable when looking at the WHO criteria, there are 3 important criteria which are not fulfilled and may challenge this viewpoint.

#### Criterion 7.

#### Is there still a substantial benefit of early breast cancer treatment?

The (mortality) benefit of early diagnosis and treatment of breast cancer remains difficult to demonstrate, despite the availability of results from several randomized studies. Results of these trials have been questioned for various reasons. Four difficulties exist when comparing survival of screened patients with that of unscreened patients: lead time bias, length time bias, overdiagnosis-, and stage migration bias[16]. Because of these potential biases disease specific survival is not a useful measure to study the effectiveness of early treatment. Better but neither ideal, is to compare disease specific mortality, although this measure is not sensitive to some types of treatment benefits, i.e. prolonged survival instead of death prevention. Because of this screening specific bias, the different characteristics of screening programmes worldwide (with differences in screening interval, targeted screening ages and attendance), and especially the strong developments in treatment regimens, an objective measurement of increase in survival or decrease in mortality may not be possible anymore. We do know that in the Netherlands mortality has decreased since the early 1990's[9], but we do not know which proportion can





be contributed to only breast cancer screening. Statistical models (using data from the population-based registry programme of the National Cancer Institute (United States)) have shown that both screening mammography and adjuvant therapy have helped to reduce the rate of death from breast cancer, with estimations that screening leads to a 15% (range of 8%-23%) and adjuvant therapy to a 19% (range of 12%-21%) mortality reduction[33]. Remarkable, however, is the finding that the stage migration, with an expected decrease of advanced cancers detected at screening, has not been demonstrated after 2 decades of screening[34,35]. At present a new randomized trial would be the best way to end the debate on screening, although it would take at least 10 years to show such effects and it would probably be considered unethical to withhold screening mammography to women who currently have access to it. Observational studies have become the main contributors of new information on the impact of screening, with incidence-based mortality (IBM) approach, or case control design. The European Screening Network working group (Euroscreen) recently indicated that most of the current controversy on the effectiveness of breast cancer screening is due to the use of inappropriate data and study designs. They concluded that valid observational designs are those where sufficient longitudinal individual data are available so direct linking of a woman's screening history to her cause of death is possible. From such studies the estimate of breast cancer mortality reduction for European women invited for screening is 25-31%, which is consistent with the mortality reduction of the previous, older randomized controlled trials[4]

#### Criterion 3.

#### Does screening detects too much clinically insignificant lesions?

The frequency at which pseudo-disease (overdiagnosis) occurs, has recently become the topic of fierce debate, with the growing concern of extensive treatment for premalignant or indolent lesions that are unlikely to ever cause harm. The estimates of overdiagnosis differ significantly, ranging from 1 to 50%[36,37], and discrepancies are probably related to methodological differences and lack of sufficient follow-up[38]. The Euroscreen group concluded from a literature review that the benefits of screening in terms of lives saved, outweigh the harm that may be caused by overdiagnosis, with a highest estimate of overdiagnosis of 10[39]. However an excessive increase in the incidence of DCIS has been observed since screening became available[40]. Currently, we still lack detailed knowledge on tumour behaviour, especially for DCIS, and therefore we are not yet able to establish the true extent of overdiagnosis. Concerns of overdiagnosis are focussing mainly on low-grade DCIS, the most benign end of the histological range of breast cancers. Present treatment of patients with screen-detected DCIS consists of breast conserving surgery (followed by radiotherapy) in about 70% of cases and of mastectomy in up to 30%, irrespective of tumour grade (high, intermediate, low). This proportion compares unfavourably with

the 26% of women with screen-detected invasive cancer who undergo mastectomy[41]. Women's perceptions about the risks of recurrence, metastasis, and death are comparable to women diagnosed with early invasive breast cancer[42,43,44]. Studies concerning less extensive treatment regimens in case of low grade DCIS are proposed, although elaborate education towards women diagnosed with DCIS will be necessary[41].

Screening did result in more early stage disease[45,46], with a survival benefit for screen detected cancers compared to clinically detected cancers partly being explained by lead time bias[47]. It has been suggested that screening does mainly detect slow growing and more favourable cancer subtypes, indicating overdiagnosis or length time bias, and that screening has not led to a noticeable decrease in number of more aggressive cancers (detected at an advanced stage). Screen-detected cancers also have been shown to be frequently low risk biology tumour**s**. Tumours can be distinguished by histological subtype, grade, receptor status, as well as molecular subtype (combination receptor status and DNA profile). Tumour biology status plays an important role in predicting prognosis and is already considered when choosing treatment modalities. Molecular subtypes may further specify treatment in the future[48,49]. Further improvements in treatment efficacy may be achieved by a more adequate, selective use of existing therapies. The moment that we would be able to select those patients who are most likely to benefit from either chemotherapy, endocrine therapy and/or radiotherapy, 'tailor made treatment' will be able to decrease the impact of overdiagnosis with related overtreatment, and a part of invasive and non-invasive screen detected cancers might perhaps be treated with surgery alone in the future.

### Criterion 5.

### Is the screening test acceptable to the population?

The last criterion in breast cancer screening giving rise to much debate is the associated morbidity of screening mammography. Especially the negative effects of false positive referrals are critical and appear to be larger and lasting longer than initially thought. Women with false positive screening results undergo additional imaging with or without biopsy procedures and may experience important negative (long lasting) psychological effects[50, 51]. In addition a false positive referral generates diagnostic work-up costs, such as additional breast imaging examinations and biopsy procedures, with a concomitant increase in the financial burden of screening[52]. Follow up testing after false positive referral has been estimated to increase the cost of breast cancer screening by more than 33 %[53]. Whether or not receiving a false-positive mammogram undermines screening attendance at subsequent screening rounds is controversial[54]. The risk of a false-positive screening result shows a strong positive correlation with the recall rate. The recently risen (from 1%) recall rate of 2% in the Netherlands is still among the lowest (2%) in the world,





and the positive predictive value of screening of approximately 30-40% is among the highest[55,56]. It is also important to realize that not all women with a false positive referral will need to undergo invasive procedures. In the Netherlands approximately two third of women with a false positive screening result have an assessment which is limited to non-invasive (imaging) investigations and one third of women actually undergo invasive investigations[17]. The review by the EUROSCREEN group determined an average cumulative risk of false positive referral, over a period of two decades, of 20%, with a cumulative risk of an invasive procedure of 3%[57].

## HOW TO MAKE FURTHER IMPROVEMENTS?

Exactly the aforementioned weak points in breast cancer screening are often used as arguments against screening. However, they could also serve as a starting point for discussions on how to improve breast cancer screening as a valuable health service. Though very urgent, it is not very likely that questions about the benefit of early treatment and the true amount of overdiagnosis in the detection of DCIS will be answered in the near future. In this manuscript we described several aspects of the breast cancer screening process in the Netherlands that could be improved. Using a virtually complete database of systematically collected data of all women screened in a southern part of the Netherlands also covered by the Eindhoven cancer Registry in the last 15 years, we were able to give more detailed information on the results of screening in specific subgroups with the focus on bilateral cancers at screening mammography and women who experience a false positive referral. We describe possibilities on how to improve cancer detection, screening related morbidity and screening re-attendance.

### Bilateral breast cancer at screening mammography

In **chapter 2** we concluded that screening mammography has a surprisingly low sensitivity for the detection of bilateral breast cancer and that there is room for improvement in the timely detection of bilateral breast cancer in screening mammography. We found that the sensitivity for the contralateral cancer was 19% compared to an overall screening sensitivity of 73% for unilateral breast cancer in our population. Several reasons for this low sensitivity have been mentioned, but probably the most important reason for missing synchronous contralateral abnormalities we found was 'satisfaction of search', as most (34% missed cancers and 21% minimal sign lesions) contralateral lesions appeared as missed lesions at review. One could argue that when a women is referred for one lesion, additional findings do not matter that much at screening as women will be evaluated in hospital again. However, it appeared important to carefully evaluate the contralateral breast at screening as well, because at clinical evaluation an important part (33%) of

contralateral abnormalities are not recognised either, which can lead to an unnecessary delay (>3 months) in diagnosis of the contralateral breast cancer.

The contralateral cancer may be either synchronous, i.e. developing simultaneously, or metachronous, meaning that tumour manifestation occurs later than the primary one[58,59]. Although the definition of synchronous vs. metachronous bilateral breast cancer is variable, the most common classification is that synchronous contralateral cancers are diagnosed within three months after the diagnosis of the first tumour, and metachronous tumours are defined as those diagnosed more than three months since the diagnosis of the first. Women with a personal history of breast cancer have a cumulative incidence rate of 3-20% of developing contralateral breast cancer[60]. So far, it remains unclear how many of the metachronous carcinomas could have been diagnosed at an earlier stage and were therefore not characterized as a synchronously developing cancer manifestation[61], but an increased detection (by magnetic resonance imaging) of synchronous contralateral breast cancers is associated with a decreased number of diagnosed metachronous contralateral cancers within 4 years[62]. If the contralateral malignancy is detected with a delay after the initial treatment, this means that these patients have to undergo two separate treatment courses rather than a single one, with a substantial psychological and physical burden for these women as well as high additional medical costs. Early detection would therefore provide a major benefit. The evidence of the impact of bilateral breast cancer on survival has been conflicting[63]. The significant increase in adjuvant therapy after first tumours has complicated risk analysis[64].

MRI has been proven to represent an accurate method in pre-therapeutic cancer staging for determining exact tumour size, depicting multi-focality and multi-centricity[65,66]. Moreover MRI has the potential to visualize contralateral cancers in women diagnosed with primary breast cancer, with published detection rates for otherwise missed contralateral carcinomas reaching 24%[67,68]. Although MRI has high potential in detecting (contralateral) breast cancers, the high sensitivity will increase the rate of false positives. Moreover, additional costs and limited MRI availability are reasons that a preoperative MR mammography for primary breast cancer is only considered on specific indication, such as diagnosis of invasive lobular cancer, discrepancies in tumour size between mammography and ultrasound or clinical investigation, increased family risk. Though not recommended yet by the EUSOMA guidelines, MRI may probably also be of value in the pre-surgical work-up for patients with dense breast tissue[69].

Although two-view mammography is now the standard in the Netherlands, before digital mammography was introduced a craniocaudal view at subsequent screening





mammography was only obtained if indicated. Digital screening mammography creates the possibility to add computer-aided-detection (CAD). This technique may increase the sensitivity to 90% for the detection of both invasive ductal cancers (IDC) and invasive lobular cancer (ILC) in an early stage[70,71]. ILC is the second most common histological type of breast cancer and occurs in about 10-15% of patients with invasive breast cancer[72]. The contralateral cancers in our study population comprised a relatively high percentage, 24%, of ILC's. At mammography and particularly on the mediolateral oblique (MLO) view, invasive lobular carcinomas are usually difficult to identify. We expect that the routine use of two-view digital mammography and the possible future application of CAD in screening mammography may contribute to an increased detection of (both lobular and ductal) bilateral breast cancer.

Recently Skaane et al concluded that the addition of tomosynthesis (3D) to digital mammography (2D) in the screening population resulted in a significant increase in cancer detection rate (>27%) and a simultaneous significant decrease in false positive rate (<15%). These findings were observed across all breast density categories[73]. Furthermore breast tomosynthesis technology is further improving, with an upcoming ability to create synthesized 2D images from the 3D digital breast tomosynthesis data sets. This "C-view" option makes it possible to reduce both patient compression time as well as radiation dose[74]. Furthermore the developments in 3D ultrasound[75] could perhaps play a role in the near future in the timely detection of bilateral breast cancer at clinical work-up, or even at screening.

The increase in incidence of breast cancer, the improvements in diagnosis as well as treatment[76], together with a growing life expectancy have brought about an increase in the number of women at risk for (both synchronous and metachronous) bilateral breast cancer. We feel that knowing the contralateral cancer is easily missed at screening mammography, both screening and clinical radiologists, should pay explicit attention to the contralateral breast to detect bilateral malignancies without a delay.

**Chapter three** describes the patient and tumour characteristics of bilateral breast cancer at screening mammography. As we found that the detection of bilateral breast cancers at screening mammography could be improved, we presumed that the identification of specific patient or tumour characteristics might help in the detection of bilateral cancers. Unfortunately we did not observe any differences in patient characteristics like age, family history, use of hormone replacement therapy, or breast density between women diagnosed with unilateral or bilateral breast cancer at screening mammography, in our population. No differences in mammographic presentation were found and bilateral cancers presented as

densities, micro-calcifications or a combination of both. Tumour sizes were similar, with around 80% of cancers diagnosed as T1 tumours (<2cm), for both unilateral and bilateral carcinomas. With regard to tumour characteristics, contralateral cancers comprised significantly more invasive lobular cancers (ILC) compared to both index cancers as well as women diagnosed with unilateral breast cancer at screening mammography (36% vs. 14-17%) and contralateral cancers showed less lymph node involvement.

Studies on imaging findings of ILC report that these cancers are more difficult to visualize with mammography, because they tend to manifest as lesions with opacity less or equal to normal fibroglandular tissue. The most commonly manifestations at mammography are an ill-defined or spiculated mass, architectural distortion and asymmetries, more frequently presenting as asymmetry on the CC view[72]. ILC's more frequently tend to be larger, multicentric, and bilateral at detection[77,78]. All these factors may contribute to the limited sensitivity of screening mammography for the detection of a lobular cancer. Although conflicting data are reported in the literature on the outcome of women with ILC, recent data[79] determined the clinical usefulness of several traditional clinico-pathologic features of ILC as prognostic parameters and, in particular, highlight the role of tumour size, the occurrence of axillary lymph node metastases, and the absence of estrogen receptors (ER) as predictors of worse outcome. The prognostic role of the histopathologic subtyping of these tumours was also emphasized, with a more favourable outcome noted for patients with the classic subtype of ILC, and less favourable outcome of the pleiomorphic subtype, which could have implications for future treatment[79]. The histopathologic features and the failure to elicit a desmoplastic response relate to the tendency of invasive lobular cancers to have atypical imaging and clinical appearances, since these cancers fail to form a palpable lesion[72]. Lobular histology is associated with a significant increase in the risk of re-operation after breast conserving therapy in patients with screen detected breast cancer[80]. Distinctive patterns of metastatic spread have been reported for lobular breast cancer, with a tendency to metastasize to the (retro) peritoneum, gastrointestinal tract and myocardium, which is unusual for invasive ductal cancer.

In our study it was not possible to identify women at high risk for bilateral breast cancer, on the basis of patient characteristics, lesion characteristics, or tumour biology. However the knowledge that in women with bilateral breast cancer the contralateral cancer is almost two times more likely to comprise invasive lobular carcinoma, could make us more aware of the possible subtle mammographic signs of lobular cancers in the contralateral breast. This might increase the chance of diagnosing the contralateral cancer without delay.





## False positive screening mammography; a different point of view

In **Chapter four** we evaluated screening behaviour following a false positive referral. We determined to what extent women who did not participate in the screening programme after a false positive screen, underwent surveillance mammography outside the screening programme. We found that overall mammography adherence after a previous false positive screen was 94.6%, which was comparable to the 94.9% re-attendance rate of women who had not been referred. Almost one third of women in the first group received a surveillance mammogram at the time they were scheduled for subsequent screening mammography. A significant decrease in overall adherence to 85% was noticed after 4-year follow-up, with a relatively high (20%) percentage of women who continued their clinical surveillance, instead of being referred to the screening programme again. Clinical surveillance mammography is justifiable until 2.5 years after false positive referral for women with a BI-RADS III lesion[81], with a recommended clinical follow-up at 6, 12 and 30 months after actual referral. Usually, these women will return to the national screening programme within 4 years. Therefore, the remaining 20% of women who continued with clinical follow-up 4 years after previous false positive referral, would preferably have returned to the national screening programme for repeated sequential screening. This prolonged clinical surveillance of women with a previous false positive screen results in additional costs compared to mammography performed within the national screening programme.

Previous research in our screening population showed that a prolonged screening interval within the screening programme is associated with the detection of breast cancer in a more advanced stage[34]. For effective screening, both high re-attendance rates as well as repeated sequential screening with adequate intervals are essential to reduce breast cancer mortality. Our study showed that the overall attendance for repeated mammography in and outside the screening programme after previous false positive referral is satisfactory, although there is room for improvement with regard to re-attendance in the screening programme, which is important for effective screening. The improvement could be achieved by better communication and education about the screening process and the risk of false positive screens, which might be more explicitly mentioned in the leaflet, which is enrolled in the screening invitation. For women experiencing a false positive referral, additional information and advice with regard to re-attendance, is of great importance. Both general practitioners as well as members of the multidisciplinary teams involved should emphasize the importance of re-attendance and repeated screening to these women.

To make a well-founded decision whether or not to (re)attend screening mammography, access to information that is easy to understand, practical and unbiased, is essential.

Compliance with screening is associated with a woman's awareness of screening recommendations, knowledge of risk factors for breast cancer, and perceptions of survivability if they are diagnosed with breast cancer[82]. People tend to simplify information, remember especially what they see as opposed to what they hear, and to pay more attention to risk communications when the issue is perceived to have personal relevance. Positive framing (chances of survival) is more effective than negative framing (chances of mortality), as well as stressing the benefits of screening, also known as gain framing[83]. This does not mean however that only the positive effects of screening should be communicated. It is important to more explicitly inform women about the possible negative aspects of screening too, in order to let them make a truly informed decision.

If women are familiar with the risks and potential morbidity of false positive screens, they might experience less anxiety and distress at time of referral or at the time of experiencing a false positive screening result. There are, however, only a few studies that evaluate approaches aiming to decrease women's anxieties related to an abnormal mammogram reading[84]. Decrease of stress after referral has been reported when women completed follow-up evaluations the same day they had an abnormal mammogram[85]. The MASS trial in the Netherlands investigates whether a customized referral strategy, related to the individual breast cancer risk, BI-RADS classification dependent, will be appreciated, and will be able to decrease referral related stress and the costs. Results of this trial are awaited[86]. Although the impact of educational interventions on anxiety reduction could not be determined by Barton et al[84], previous research has shown that the understanding of the screening process was improved by education[87]. Therefore it seems that while educational interventions may perhaps not diminish stress or anxiety, the knowledge that positive and negative test results are not always correct, could make it easier for women to cope with the negative side effects of (false positive) referral or a cancer diagnosed between screening rounds (interval cancer). Increasing knowledge concerning the screening process and specifically about the possible impact of a false positive referral, may therefore be a way to improve re-attendance after a false positive screen.

In **chapter five** the characteristics and screening outcome of women who were referred twice at screening mammography in the national programme were described. Taking into account the negative psychological effects of a false positive screening result, it is important to minimise the number of women who experience a repeated false positive referral, especially for the same lesion. In our study population nearly 3% of referred women had been referred for a second time, after a previous false positive screen, and 42% of these women were referred twice for the same lesion. The cancer risk for lesions referred twice at screening mammography was 36%, which is similar for all lesions referred at





screening. Women who are diagnosed with breast cancer at second referral for the same lesion thus experience a significant delay in cancer diagnosis of at least 2 years. We did not find specific patient or tumour characteristics that could differentiate between women with breast cancer diagnosed with or without delay. Therefore these characteristics were of no value in the attempt to decrease the proportion of women who will experience a delay in cancer diagnosis. However, we found that the cancer risk at second referral was increased for women who had been referred for a suspicious density at first referral, as well as for women who had received only additional imaging without biopsy at first referral. This finding can be of value in diminishing screening related morbidity associated with repeated referral and delay in diagnosis.

Detection of breast cancer, before symptoms appear, is essential in the concept of screening. A delay in breast cancer diagnosis, however, is frequently encountered in women attending breast cancer screening, and is an important reason for malpractice claims[88,89]. The BI-RADS classification plays an essential role in causes of delay. There is a distinct discrepancy in the assignment of BI-RADS classifications in between radiologists[90], especially for the BI-RADS 3 category. The BI-RADS classification is used worldwide to describe breast lesions and micro-calcifications in order to quantify and communicate the breast cancer risk. In our screening region a considerable variation in the work-up performance across different hospitals of recalled women was found previously, with an improper use of BI-RADS 3 category at diagnostic mammography being the most important cause of diagnostic delay[88]. Therefore, one should aim for more uniformity in the assignment of BI-RADS classification, which may be obtained with a more uniform and standardized description of mammographic abnormalities and additional training[91]. This could be achieved in the near future by the introduction of a set of multidisciplinary quality indicators, including the BI-RADS category and quality of the mammographic reports as is now proposed by the NABON (Nationaal Borstkanker Overleg Nederland (NABON Breast Cancer Audit)[92]. Moreover, continuous training of (screening) radiologists is important to increase inter-observer agreement in classification of mammographic abnormalities. An update of the current BI-RADS classification is recently available, with an obligatory subdivision in BI-RADS 4 (4a,b,c), which could diminish erroneous BI-RADS 3 assignment[93] in the future.

To prevent a possible delay in breast cancer diagnosis after referral it is important to correlate the pathology results with imaging characteristics as well as clinical examination. Triple assessment has a reported overall diagnostic accuracy of 99% for symptomatic patients[94]. For the non-symptomatic screening population especially discrepancies between radiological abnormalities and biopsy findings should be noticed and followed by

additional imaging, repeated imaging, or repeated biopsy[95], to make sure breast cancer is ruled out. In order to prevent a delay in breast cancer diagnosis and to decrease repeated false positive referrals, it could be of help for the screening radiologist when information about previous mammographic abnormalities and clinical work-up at previous referral is available at the time of mammography reading.

Although our study provided no evidence for a worse tumour stage in patients with cancers missed after first referral compared to patients diagnosed with cancer at first referral, the length of the delay in diagnosis was substantial and may affect the long-term outcome[89]. Since these delays occur in only a small proportion of all cancers, their reduction will only result in a slight increase in detection rate at the population level. From the perspective of the individual patient, however, efforts should be made to ensure a timely diagnosis in all women participating in breast screening.

## Experiences with malpractice claims at screening mammography

In **chapter 6** the experiences with malpractice claims in the Dutch screening programme were described. Malpractice lawsuits are frequently related to a delayed breast cancer diagnosis in symptomatic patients. In a screening setting we found that at review over 20% of screen detected cancers and 24% of interval cancers were considered to be missed at previous screen. Nevertheless, only three out of more than 85,000 screened women, directly initiated an insurance claim for financial compensation of their interval cancer, without contacting the screening organization. A total of 19 women had contacted the screening organization for additional information about their screen detected or interval cancer, but filed no claim, although 14 of these women were diagnosed with advanced cancer. Over time, an increasing proportion of screened women undertook action after a presumed missed cancer, from 2 women seeking advice, screened between 1997-2001 (102,439 screens), to 11 women seeking advice, who were screened between 2005-2009 (133,830 screens). One may argue that this finding predicts an increase in claims in the Netherlands, parallel to the US, where nowadays a delay in breast cancer detection is the most prevalent and second most expensive condition resulting in malpractice lawsuits[96]. In the US the number of radiologists willing to read mammograms is decreasing, since the defendant in these lawsuits most commonly is the interpreting radiologist. Lawsuits concerning delays in breast cancer diagnosis are based on the fact that this may have reduced breast-conserving treatment options and prognosis. Previous research showed that women with a delay of 3 months or more have a 12% lower 5-year survival compared to women with a delay of less than 3 months[97], but these results are based on women treated before earlier mentioned changes in especially adjuvant treatment regimens. However the risk of advanced or metastatic disease was reported to increase with 22% for women with





a delay of 3 months or more, compared to delays of less than 3 months[98]. Important to realize is that cancer behaviour is dependent of tumour biology and women with DCIS or a slow growing invasive tumour will not necessarily suffer from a delayed diagnosis. We investigated the occurrence of delay in cancer diagnosis in our population and found that 5% of women who were actually diagnosed with breast cancer after referral experienced a more than 3-month delay in cancer diagnosis. Nearly 60% of diagnostic delays were due to an incorrect BI-RADS classification, 20% due to false negative percutaneous biopsy results and over 20% due to a variety of reasons, with none of them being women-based. The delay varied between 3 and over 24 months, with advanced tumour stage at time of surgery in 27% of women, compared to 19% of women who did not experience a diagnostic delay. However none of the women who experienced an actual delay in cancer diagnosis after referral filed a claim. Besides missed cancers (21%), a substantial proportion of the cancers in our study were at retrospect visible as a minimal sign (22%) on the previous mammogram. Minimal signs are defined as small vague densities, indefinable micro-calcifications and subtle architectural distortions. These signs are non-specific appearances of breast cancer with a risk of malignancy referred to as less than 1%[99] and a favourable stage at diagnosis compared to women with no minimal signs at previous screening mammogram[100]. Therefore women with a nonspecific minimal sign at screening mammography in the Netherlands are not referred. Referral of all minimal signs would result in a substantial (minimal signs are present in about 10% of all screening mammograms) increase of (false positive) referrals. The impact of minimal signs at digital mammography on screening outcome has not yet been established. Further research is needed to decide whether it would be useful to refer certain subsets of minimal signs in the current digital screening setting.

Authors[101,102] who have focused on the issue of an increasing number of claims regarding mammography in the US, explained this increase by the fact that the limitations of screening are poorly understood, and that the public's expectations of mammography performance are too high. Screening campaigns in the US tend to emphasize only the benefits of screening and mainstream media may give a distorted image of the benefits. In the Netherlands women do receive written information with each invitation that breast cancers may be missed at screening mammography and that they should always seek medical attention in case of breast complaints following a negative screen. De Gelder et al also concluded that false negative reassurance after a negative screen is not a paramount problem in the Netherlands, unlike the situation reported in the US[18]. A majority of claims in the US are, besides mammographic misinterpretation, related to failure of open communication with patients about these errors[101,102]. Discussing errors with patients may reduce the number of malpractice claims in the US, whereas the possibility of a 'no-win-

no-fee" policy for US lawyers and the high compensation paid to patients following a jury verdict could influence the number of claims. Honest and open communication between the coordinating radiologist and women who contacted the screening organization for additional information may probably have prevented them to initiate a litigation procedure in the BOZ screening region. However we have to realize that the eagerness of patients to start a lawsuit will be influenced by national legislation and the expected success rate and height of insurance pay-outs. Until now details of claims are not routinely registered by screening organizations in the Netherlands. Only one published claim regarding a woman with an interval cancer is available[103], and this claim was rejected following the conclusion that the abnormality at screening was a so-called minimal sign lesion that did not warrant referral. One claim of the three claims in our screening region was rejected (also on the basis of a minimal sign abnormality) and the verdicts of the two other claims (both interval cancers with a lesion missed at the previous screen) are still under appeal.

It should be made clearer to the public that each diagnostic test will induce false negative and false positive results and that misdiagnosis will be more frequently encountered when testing a healthy population (in case the of screening) rather than when evaluating a symptomatic person (e.g., a woman with a palpable lump). Therefore, screening will always result in a relatively high percentage of missed cancer[104]. The radiologist's interpretation is a complex interplay of factors that influence visual perception and it is known that cancers can be misinterpreted or overlooked. The prevalence of abnormalities in visual search tasks influences observer performance, the so called prevalence effect. Several researchers describe the prevalence effect as a possible explanation of the relatively low detection rate of cancer at screening[105]. Increasing referral rate with the goal to increase cancer detection, will simultaneously result in an increase of the number of women who experience a false positive referral, although the relation between referral rate and cancer detection is not straightforward[106].

When radiologists are subjected to litigation for alleged faults in diagnosing cancer, the judge will have to assess whether the radiologist effected his duty with due care. This cannot be judged on the basis of the individual cases. Especially in malpractice lawsuits concerning mass screening an alternative procedure is needed for the traditional role of the expert witness[104]. The re-examination of screens with prior knowledge of the outcome, which is the situation in case of an expert witness, is not comparable with the original screening situation. The introduction of radiologists who are blinded to the clinical outcome is, for instance, suggested as a more objective method of evaluating legal cases[107]. Despite increasing complaints of experts in the field of screening mammography in Europe and the US, no specific guidelines for review of screen





detected cancers and interval cancers have been yet proposed by the authorities, or by the association of radiologists in the Netherlands so far. Education and information for women involved in breast cancer screening seems crucial to prevent future problems with regard to malpractice claims in the Netherlands. The implementation of digital screening mammography will probably not decrease the proportion of missed cancers. Previous research has shown that the percentages of missed cancers (33% for interval cancers and 20% for screen-detected cancers) are in accordance with those of cancers missed at screen film mammography[108]. As has been mentioned before in the context of early diagnosis of contralateral breast cancer, computer aided detection (CAD) in screening mammography could perhaps play a small role in improving cancer detection in the future. Detection may be improved by implementation of breast tomosynthesis in the screening programme as mentioned earlier.

The radiologists' performance can be improved by the regular review of (missed) interval cancers, because learning about the characteristics of these cancers can help to detect them in future mammograms[109]. Prompt review of interval cancers is recommended by European screening guidelines and is part of quality assurance of screening mammography in the Netherlands[110]. Missed cancers should not only be regarded as diagnostic errors, they should also be seen as a learning opportunity[111]. Therefore close monitoring and timely registration of interval cancers is of utmost importance.

We conclude that in our population women rarely filed a malpractice claim, although a substantial proportion of (screen detected an interval) cancers had been missed at previous screen and a delay in cancer diagnosis was experienced in 5% of referred women. The study suggests that open communication between women seeking additional information and the screening organization may help to refrain women from starting a litigation procedure.

## FUTURE DIRECTIONS

### Extended data collection within the screening programme

The efforts of the screening radiologists in the BOZ-region can be seen as a local programme for quality control of the regional screening units, but at the same time has an important scientific purpose. The extended database gives the opportunity to evaluate both the screening performance and its outcome. Being able to directly communicate the screening outcome with screening radiologists, makes them more aware and critical towards the impact or consequences of their work. As was mentioned previously, in the Netherlands the NETB and LRCB evaluate the quality and the results of the screening

programme at the regional and national level, which is done in close collaboration with the screening units. The primary goal of this evaluation is to optimize the impact of the screening programme on breast mortality.

TABLE 1. Factors influencing screening performance

| | Determinants of screening sensitivity |
|---|---|
| Patient related | Breast density<br>Previous breast surgery |
| Image related | Image quality (radiographer dependent)<br>Number of views<br>Screening round<br>Screen film or digital screening |
| Screening situation related | Screening method (single vs. double reading)<br>Radiologist performance<br>Screening interval<br>Breast cancer prevalence |

Screening results are dependent of several factors (Table 1). Previously, differences in availability of screening outcome data as well as differences in actual screening parameters have been reported among the different regional screening units[10]. Restricted availability of the screening performance data, especially with respect to interval cancers, has been a problem for several years now in many countries, including the Netherlands[112]. In the Netherlands there has been an unacceptable lack of information on interval cancers for several regions since 1994.

Between 2006 and 2010 the RIVM Centre for Population Screening established a nationwide digital network, with linkage of all 65 (mobile) research centres, administrative units and review units. This nationwide system has a central database of digital breast images, creating a paperless and uniform workflow. The recent linkage at national level between the screening and cancer registry databases has provided data of interval cancers among women who had been screened in 2004 for 7 out of 9 former screening regions. The data on interval cancers from more recent years are yet awaited[17]. Incomplete data hamper the proper evaluation of the programme. There will always be some degree of underreporting of interval cancers, which is estimated to be approximately 4%[113]. However with the extent of data lacking, the sensitivity and specificity of the national program





cannot be fully evaluated for the last decade. The recent restricted data (for the year 2004) provide a programme sensitivity of 70.8% for both initial and regular subsequent screens. The programme specificity was between 97.9% and 99.3% for respectively initial and subsequent screens. The reason for the long lasting absence of the interval data can be largely explained by the reorganization of the regional cancer registries into one national registry, which caused a serious delay in linkage of the databases of the regional screening units with the cancer registry for women screened after 2000.

Differences in regional screening performances with regard to referral and detection rate, PPV and tumour stage have been described[10] which can be partly explained because by previously mentioned variables (Table 1). Radiologist and radiographer dependent factors may be of influence as well, and these could be improved if warranted, with education and training.

Currently, the amount of information collected by the NETB and LRCB, both in terms of the number and level of detail of the parameters evaluated, is much more limited than in the BOZ-region (Table 2a en b). Extension of the data (Table 2b) might be considered

TABLE 2A. Data routinely collected at the moment (LRCB/NETB)

| Data routinely collected |
|---|
| Invitations |
| Screens (initial or subsequent screen) |
| Non participants |
| Non responders |
| Referrals |
| False positive referrals |
| Work-up (non-invasive or invasive) |
| Tumour histology |
| Tumour stage |
| Client reactions |

TABLE 2B. Suggestions for extended data collection

| Additional data | |
|---|---|
| Non-participants and non-target | Reasons for non-participation |
| Interval cancers | true interval cancers or missed/minimal sign lesions |
| Sensitivity<br>Specificity | |
| Breast density | |
| BI-RADS classification | referral and clinical |
| Discrepancies in referral advice | reading strategy |
| Work-up | - Kind of imaging: mammography, tomosynthesis, US, MRI<br>- Kind of invasive procedure: FNAC, CNB, vacuum assisted biopsy, surgical excision |
| Delay | in work-up, in cancer diagnosis |
| Tumour biology | tumour grade and receptor status |
| Treatment regimen | surgery, radiotherapy, (neo)adjuvant systemic therapy |
| Reattendance after referral | |
| Questionnaire | quality of life assessment, psychological impact referral and / or work-up |

worthwhile for the future evaluation of screening performance. Implementation of a new standard of data management has become much easier since the digital network has been established. Especially, extended data collection concerning work-up after referral, possible delays and treatment would be valuable. Also data with regard to screening BI-RADS and clinical BI-RADS classification would be very informative. The BI-RADS category assigned at screening, may have consequences for the clinical approach and erroneous assignment may lead to a delay in breast cancer diagnosis. With BI-RADS classification data the extent of previously described discrepancies in BI-RADS assignment could be established. Furthermore data could be completed concerning work-up strategies after referral (with a possible delay). More effort should be put into the identification of interval cancers. The screening organisation might try completing data of all women screened, instead of only those women who are referred. Maybe, parallel to the questionnaire filled in at the time of screening mammography, the implementation of a questionnaire (i.e. a quality of life assessment) could be considered to evaluate the impact of (false positive) referral at clinical work-up (i.e. by nurse practitioner) and/or at subsequent screening (radiographer). With extended data collection, improvements in screening on basis of quality control can be achieved.





Previous studies in the BOZ region have shown valuable results i.e. with regard to the identification of :

- delays in cancer diagnosis after referral[88,114]
- trends in diagnostic costs and utilization of diagnostic procedures after referral[52]
- the influence of different reading policies[115,116]
- the effect of two-view versus single-view mammography at subsequent screening[117]
- the influence of previous breast surgery on sensitivity of screening mammography[118]
- the impact of digital reading policies on screening outcome[119]
- trends in detection of advanced cancers at screening mammography[34.]

Although it creates extra work, extending the evaluation of the screening programme may allow more screening related questions to be answered. Possibilities will even increase by routinely linking cancer registry and screening databases. This could lead to a more extensive information supply to women eligible for the screening programme (screenees) and those responsible for managing the referrals and those inviting them. Both screening organizations as well as cancer registries have demonstrated the importance of cancer surveillance. At this moment European initiatives are effectuated in order to ameliorate cancer control and strengthening of population-based cancer research in Europe, such as Eurocourse (EUROpe against Cancer: Optimisation of the Use of Registries for Scientific Excellence in research), with the main purpose of Eurocourse being improvement of the use of cancer registries in European countries, with encouraging the cooperation between cancer registries and cancer screening organisations with three main tasks within the so-called WP5 programme (Table 3).

TABLE 3.

| Main tasks Eurocourse<br>(Europe against cancer: optimisation of the Use of Registries for Scientific Excellence in research) |
|---|
| How to improve cancer registry practice in order to monitor and evaluate cancer screening better in target populations |
| To develop standards and recommendations on the data items and key indicators for individual-level cancer screening registries |
| To suggest research priorities and collaborative projects within the European setting for developing cancer screening |

*Source Eurocourse WP5 expert workshop February 2013*

In November 2012 the Department of Public Health, MGZ, of the University Medical Centre Rotterdam, in cooperation with NETB, on behalf of the RIVM, has initiated a report on future quality descriptors that will be recorded by the screening organisations in close cooperation with the Netherlands Cancer Registry. In this report already additional parameters, in relation to the current data, have been proposed for both quality assurance as well as research purposes[120].

The complexity of creating an adequate data model should not be underestimated. There should be efforts to get uniform basic features of the data to be collected (both screening and follow-up data). Interfaces in those databases (information details that will be shared in the different databases in the future) should be carefully defined, because uniform documentation with clear interfaces will enable accurate linking with other databases.

## Open communication an education

As mentioned before, information supply to screenees has turned out to be very important. It is likely that, as a consequence of the continuing flow of new studies and the continuing debate on the benefits and harms of breast cancer screening in the leading medical journals as well as in mainstream media, confusion among women about attending screening programmes has occurred. Therefore official authorities and public health programmes might consider to re-inform women about the breast cancer screening programme in the Netherlands at short notice. Women should be made aware of the effects of screening on mortality, as well as the impact of (false positive) referral and a possible diagnosis and meaning of non-invasive cancer. The latest systematic review published in the Lancet as well as the extensive work of the Euroscreen working group have been serious attempts to present a more balanced view on breast cancer screening[2,4,57,121], which also takes into account the secular changes in incidence and mortality. Health-care professionals should also realize that although screening might become less effective because of further treatment optimisation, if screening related morbidity is accepted by participating women (informed decision making) and (re)attendance is stable, organized screening is preferred compared to opportunistic screening. The latter might increase exponentially when the national screening programme would come to an end. Moreover opportunistic screening is far more difficult to evaluate and does not guarantee equity of access or balanced information, and especially opportunistic screening is far less cost effective[122]. Clear communication of these harms and benefits to women is of great importance and could decrease the impact of morbidity, hereby increasing the effectiveness of service screening.





## Primary prevention

Because breast cancer incidence is more and more independent of increase as a result of screening, perhaps not only secondary prevention by screening could be encouraged, but primary prevention should be considered as well[123]. The largest reduction in cancer deaths in the US for instance has appeared due to the decrease in smoking[124]. Besides focussing on improvement of breast cancer screening (early detection) we may have to pay more attention to possibilities of decreasing breast cancer incidence[11]. Information, education and public campaign with the aim to reduce risk factors for breast cancer with lifestyle modification, could be considered, since breast cancer awareness has already shown to be important in the field of breast cancer health care. The goal of risk communication is to help women to understand their health risks more accurately and to become acquainted with their own influence in decreasing breast cancer risks.

## Tailor made screening

Finally, the effectiveness of the breast cancer screening programme may be increased by 'tailor made' screening, whereby the screening protocol could be adapted for specific groups of women, depending on their individual risk of breast cancer. Screening protocols with variation in screening interval, or screening age (start before the age of 50, or continue after the age of 75 years could be considered[125,126]. The results of the DENSE trial (Breast Cancer Screening With MRI in Women Aged 50-75 Years With Extremely Dense Breast Tissue) and the upcoming ASSURE project (Adapting Breast Cancer Screening Strategy Using Personalised Risk Estimation)[86] could result in a more personalized screening protocol for women with dense breast tissue.

# CONCLUSION

In conclusion, after decades of experience and divergence of the effectiveness of breast cancer screening (manifested screening related decrease in mortality) and manifested screening related morbidity (false positive referrals and overdiagnosis and treatment), breast screening is still considered to be an established preventive health care service in the Netherlands. However there is room for improvement. We explored possibilities for improving screening mammography in the south of the Netherlands where circumstances for such research were more optimal. Increased awareness of bilateral breast cancer at screening mammography, might lead to decrease in the delay of diagnosis of the contralateral cancer. Re-attendance in the screening programme for women who experienced a false positive referral, could be improved. This might be achieved by better communication and education about the importance of re-attendance for the timely detection of breast cancer. Our work suggests that a diagnostic delay following a repeated

referral and unnecessary second referral, might be reduced by adopting a more intensive diagnostic approach to assessment after the first referral. Open and honest communication between the screening organisation and women seeking additional information, may help to refrain women from starting a litigation procedure. As long as breast cancer treatment will not be able to clearly outweigh the benefit of early detection, we should focus on improving this valuable service. This also means providing all the figures and facts to allow women to make a well informed decision for screening and providing extra training to the (screening) radiologists. Intensifying and improving the evaluation of screening through extended data collection in uniform and clear databases and regular linkage with cancer registries, will assure quality control and may allow more screening related questions to be answered at both a regional and national level.





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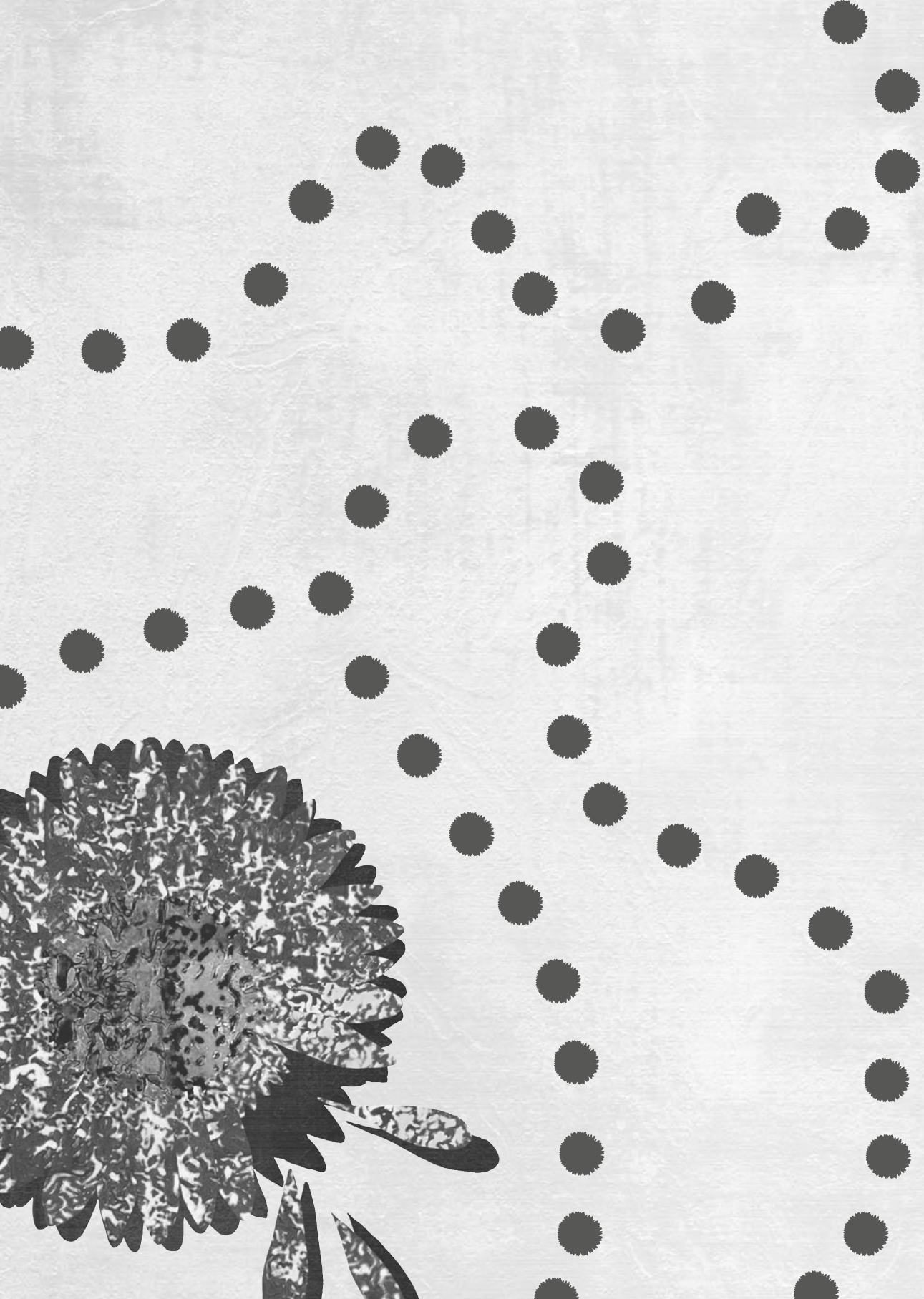
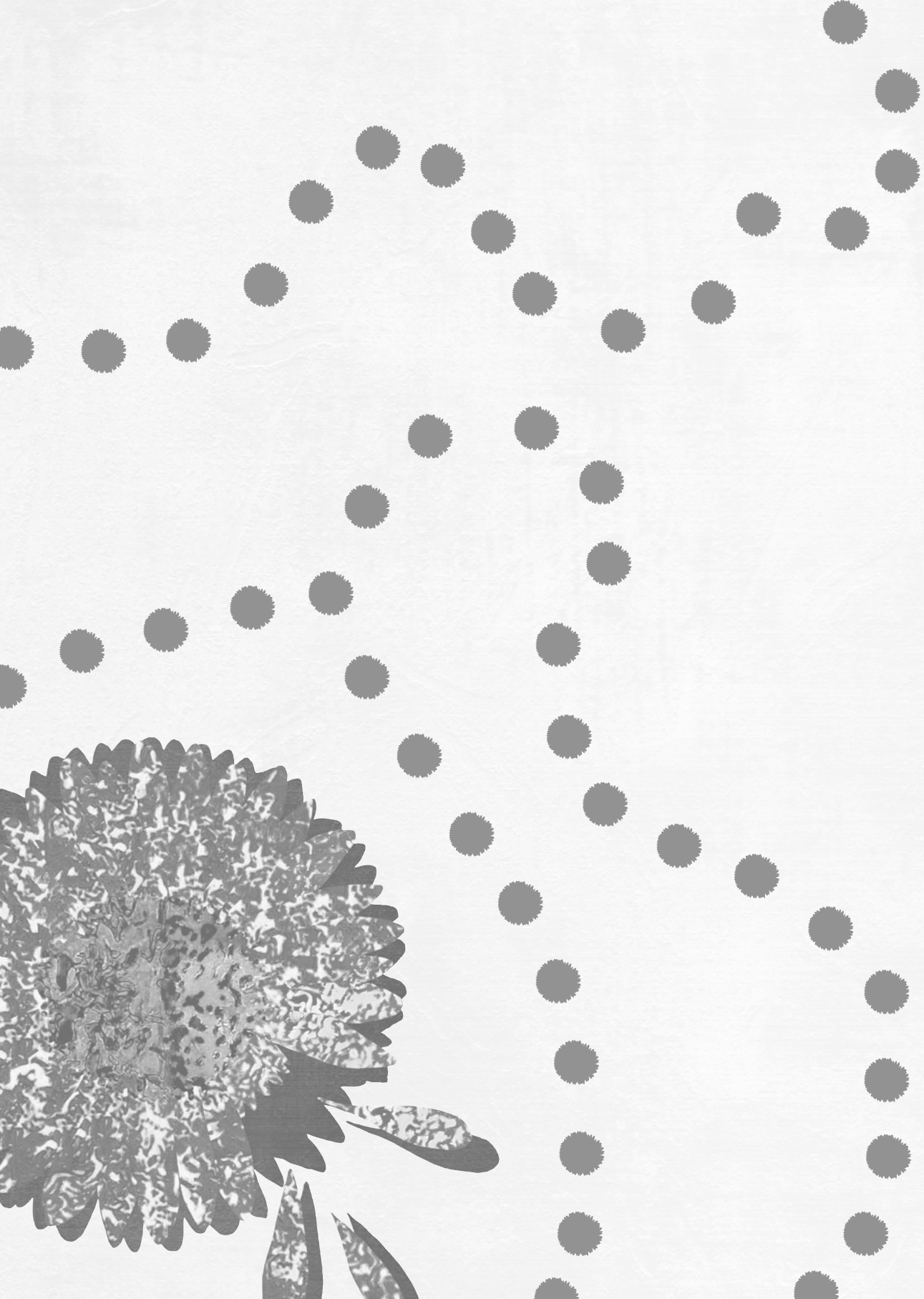


# Chapter 8

## Summary and acknowledgements



# 8.1

## Summary

## RATIONALE

Breast cancer is an important public health problem, remaining the most commonly diagnosed cancer in women in the Netherlands, as well as in most other (developed) countries. Globally it is the leading cause of death in women. The incidence of breast cancer in the Netherlands is still increasing, which can be explained by the incorporation of the screening programme and adverse changes of (hormone related) risk factors, especially lower parity, decrease in lactation, and postmenopausal obesity.

The breast cancer stage at detection is strongly correlated with the chances of survival. The rationale for secondary prevention (screening) of breast cancer is that when disease is detected early, before metastasis occur to lymph nodes or distant organs, the prognosis might be better and mortality may decrease. A reduction in morbidity might also be expected because of less extensive surgery without necessity of adjuvant therapy in case of early detection. Until now mammography is the best and most cost effective tool for screening postmenopausal women with an average risk of breast cancer. The sensitivity of mammography for the detection of breast cancer is influenced by several factors, most importantly being breast density, radiologist performance and image quality.

In the Netherlands an organised programme-based, biennial screening programme started around 1990, from 1998 onwards the age limit was extended to 75 years, and in 2009 the programme changed from screen-film mammography to digital screening. Worldwide there are profound differences in screening protocols and screening parameters such as referral rate and cancer detection rate. Since the start of breast cancer screening, continuous improvements have been made in the awareness of breast cancer, detection and treatment of breast cancer and in the Netherlands a profound decrease (31%) in breast cancer mortality has been established. However, early detection because of screening and better treatment may interact, and the true extend of mortality decrease through screening alone is difficult to establish nowadays.

About 10 years ago the first critical appraisals were published on the effectiveness of breast cancer screening. The debate has focussed on the reduction in mortality attributable to screening and the number of women overdiagnosed and subsequently overtreated. Dutch studies concluded so far that breast cancer screening indeed reduces the risk of breast cancer death, although there is still room for improvement as interval cancer rates and the detection of advanced cancers have more or less remained stable since the introduction of screening.

Screening a healthy (asymptomatic) population involves weighing benefits against harms. Overdiagnosis is considered the major harm, as certain screen detected (both in situ and

invasive) cancers would have never become clinically evident or lethal if left undiscovered. An excessive increase in in-situ cancers (DCIS) has been observed, and these cancers are treated with surgery, mostly combined with adjuvant radiotherapy. Currently we still lack detailed tumour behaviour knowledge to identify those (in-situ) cancers, which will never progress or metastasize. Therefore the true extend of overdiagnosis cannot be established yet. Psychological discomfort related to especially false positive referrals has turned out to be another significant side-effect, which appears to be larger and lasting longer than initially thought. In addition a false positive referral generates diagnostic work-up costs, such as additional breast imaging examinations and biopsy procedures, with a concomitant increase in the financial burden of screening. Whether or not receiving a false-positive mammogram undermines screening attendance at subsequent scheduled screening mammography is controversial.

In the light of all developments in screening mammography the main objective of this thesis is to assess which aspects in the screening process need further improvement to increase the net effect of the screening programme. Using systematically collected screening data on diagnostic procedures and outcome parameters of all women screened in a southern part of the Netherlands in the last 15 years, insights could be gained on the results of screening in specific subgroups of women. Focussing on women with bilateral breast cancer at screening mammography and those women experiencing a false positive referral, improvements could be achieved in cancer detection, screening related morbidity and screening re-attendance.

## BILATERAL BREAST CANCER AT SCREENING MAMMOGRAPHY

We concluded that screening mammography has a surprisingly low sensitivity for the detection of bilateral breast cancer, with a sensitivity of 19% for the contralateral cancer, compared to an overall screening sensitivity of 73% for unilateral cancer in our population. It appeared that at clinical evaluation a substantial part (33%) of contralateral abnormalities are not recognised either, which can lead to an unnecessary delay in diagnosis of contralateral breast cancer. Patients experiencing a delay might have to undergo two separate treatment courses rather than a single one, with a substantial psychological and physical burden for these women as well as high additional medical costs. Early detection would therefore provide a major benefit. We could not identify women at high risk for bilateral breast cancer on the basis of patient characteristics, lesion characteristics, or tumour biology. However significantly more often the contralateral cancer comprises an invasive lobular carcinoma, which could make us more aware of the possible subtle mammographic signs of lobular cancers in the contralateral breast. Possibilities for





improving detection of contralateral cancers include additional work up with MRI in specific cases. Especially the introduction of tomosynthesis in screening might increase the detection of bilateral breast cancer. We found a bilateral breast cancer incidence of 2-3% at screening (both screen detected and interval cancers) and incidence is increasing. The increase could partly be explained because of improvements in diagnosis, however particularly better treatment of breast cancer together with a growing life expectancy are expected to increase the number of women at risk for bilateral breast cancer. We feel that knowing the contralateral cancer is easily missed at screening mammography, both screening and clinical radiologists, should pay explicit attention to the contralateral breast to detect bilateral malignancies without a delay.

## FALSE POSITIVE SCREENING MAMMOGRAPHY; A DIFFERENT POINT OF VIEW

For effective screening, both high re-attendance rates as well as repeated sequential screening with adequate intervals are essential to reduce breast cancer mortality. Our research showed that the overall attendance for subsequent mammography in and outside the screening programme after previous false positive referral is satisfactory, with an overall mammography adherence of 94.6% for women who experience a false positive referral, which was comparable to the re-attendance rate of women who had not been referred. However almost one third of women who experienced a false positive screen underwent surveillance mammography at the time they were scheduled for subsequent screening mammography. So there is room for improvement with regard to re-attendance in the screening programme. Those women where cancer is ruled out at work-up after referral by imaging or additional biopsy (BI-RADS I and BI-RADS II abnormalities) are expected to re-attend the screening programme at 2 years. In women where the mammographic abnormality is classified as BI-RADS III, follow-up can be advised until 30 months, therefore these women are expected to re-attend at 4 years. We observed however a significant decrease in the overall adherence to 85% after 4-year follow-up, with a relatively high (20%) percentage of women who continued with clinical surveillance mammography, instead of re-attending the screening programme again. Prolonged clinical surveillance of women with a previous false positive screen results in additional costs compared to mammography performed within the national screening programme. Previous research in our screening population showed that a prolonged screening interval within the screening programme is associated with the detection of breast cancer in a more advanced stage. Our findings stress the importance of clear communication and advice with regard to re-attendance in the screening programme for women experiencing a false positive referral.

Taking into account the negative psychological effects of a false positive screening result, it is important to minimise the number of women experiencing a repeated false positive referral. We found that nearly 3% of women had been referred for a second time, after a previous false positive screen, and 42% of these women were referred twice for the same lesion. The cancer risk for lesions referred twice at screening mammography was comparable for all lesions referred at screening (36%). Women diagnosed with breast cancer at second referral for the same lesion experienced a significant delay in cancer diagnosis. Although our study provided no evidence for a worse tumour stage in patients with cancers missed after first referral, the delay in diagnosis was substantial and may impact long-term outcomes. Patient and tumour characteristics were of no value to differentiate between women diagnosed with breast cancer with, or without delay. We found that densities at first referral and no biopsy at first referral, were associated with increased cancer risk at second referral. Our work suggests that a diagnostic delay and an unnecessary second referral (with additional stress and costs) might be reduced by adopting a more intensive diagnostic approach to assessment after the first referral. This approach should include a careful correlation of imaging, pathological and clinical findings, as well as additional efforts to acquire a more uniform BI-RADS classification.

## EXPERIENCES WITH MALPRACTICE CLAIMS AT SCREENING MAMMOGRAPHY

The sensitivity of screening mammography in our screening region is currently 73%. We found that at review over 20% of screen detected cancers and 24% of interval cancers were considered to be missed at the previous screen. Nevertheless, only three out of more than 85,000 screened women, directly initiated an insurance claim for financial compensation of their interval cancer, without contacting the screening organization. A total of 19 women had contacted the screening organization for additional information about their screen detected or interval cancer, but filed no claim, although 14 of these women were diagnosed with advanced cancer (tumour size > 2cm and/or positive lymph nodes). Lawsuits concerning delays in breast cancer diagnosis are based on the fact that a delay may reduce breast-conserving treatment options and prognosis. In our population a more than 3-month delay in cancer diagnosis occurred in 5% of women. Nearly 60% of diagnostic delays were due to an incorrect BI-RADS classification and 20% were due to false negative percutaneous biopsy results. An advanced tumour stage at time of surgery was found in 27% of women, compared to 19% of women who did not experience a diagnostic delay. We conclude that in our population women rarely filed a malpractice claim, although a substantial proportion of (screen detected an interval) cancers had been missed at previous screen with a substantial delay for some women. The study





suggests that open communication between women seeking additional information and the screening organization may help to refrain women from starting a litigation procedure. The number of women that contacted the screening organisation increased over the years, and also the number of malpractice claims in the future may increase. We feel that is important that the Radiological Society of the Netherlands (NVvR) will develop a protocol for the communication with women who contact the screening organisations with questions related to missed cancers.

## FUTURE DIRECTIONS

We experienced that the construction of an extensive screening database as had been prepared in the BOZ-region for the last 15 years (including information on screening outcome parameters, pathology outcome and surgical management), in a close cooperation between screening radiologists, BOZ-, and IKZ colleagues, is very valuable for evaluation and feedback of screening performance and outcome.

### Extended data collection within the screening programme

We think that, especially in the present digital time era, future refinement of breast cancer screening should be achieved evolving an extended data collection within the national screening programme by creating uniform databases, with the possibility or linking these data between screening organisations, cancer registries, and the pathology archive. By means of a more standardised data management, quality assurance can be achieved as well as various possibilities for research purposes.

### Open communication and education

Clear communication of the harms and benefits to women participating in the screening programme is of great importance and could decrease the impact of morbidity, hereby increasing the effectiveness of service screening.

### Primary prevention

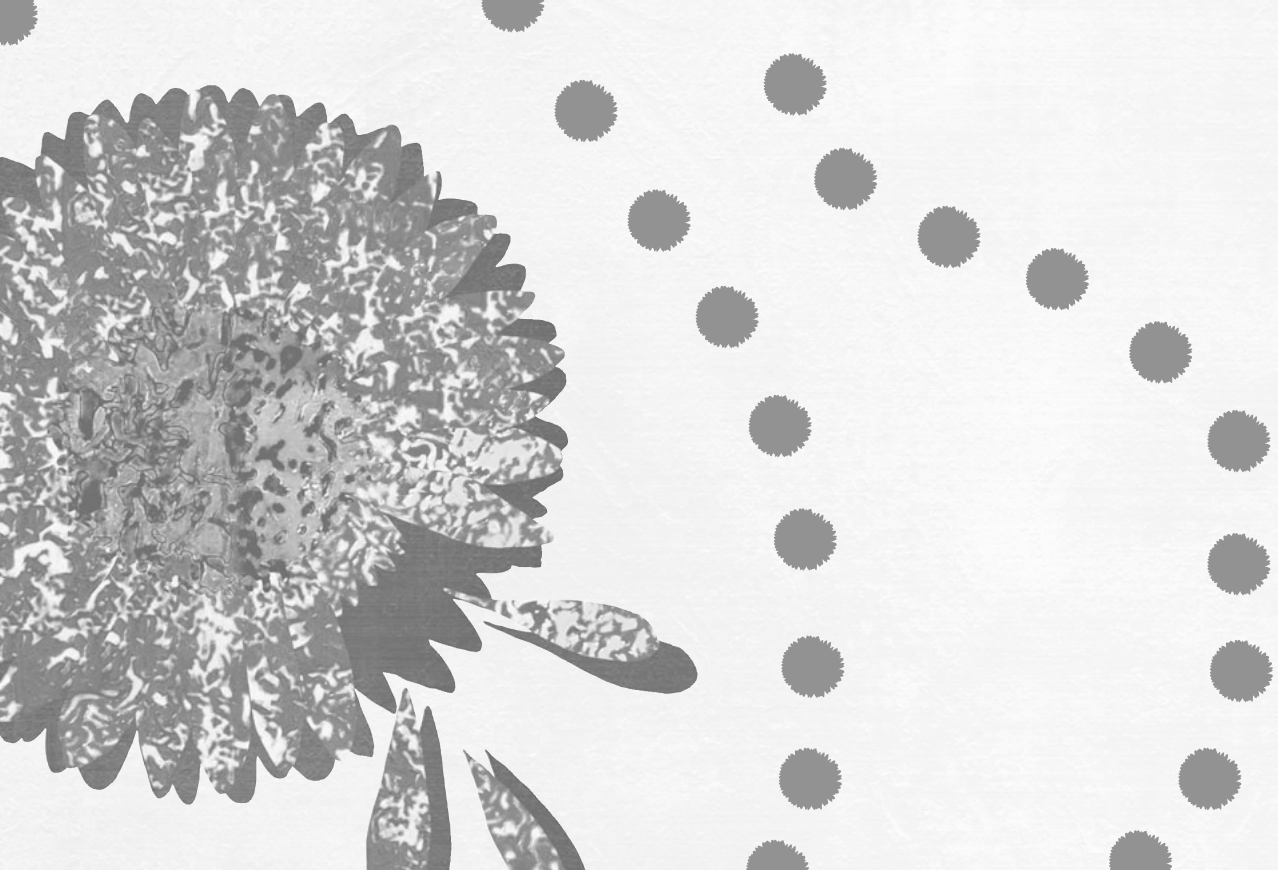
Because of the continuing increase in breast cancer incidence, perhaps we have to pay more attention to possibilities of reducing risk factors for breast cancer, in order to decreasing cancer incidence.

### Tailor made screening

Adapting the screening protocol for specific subgroups of women, depending on their individual breast cancer risk, might increase effectiveness and decrease screening related morbidity.

## CONCLUSION

After decades of experience on evidence of the effectiveness of breast cancer screening, as well as manifested screening related morbidity, breast screening is still considered to be an established health care service in the Netherlands. However there is room for improvement. The endless discussion about the extent of the benefit and harms of screening mammography will not resolve the screening dilemma. It is about time to stop rephrasing the familiar arguments both in favour and against screening mammography, and instead join forces to tackle the relevant issues in breast cancer screening. We explored possibilities for improved detection of (bilateral) breast cancer at screening mammography, for increase in participation especially after previous false positive referral, and decrease in numbers of repeated (false positive) referrals, and we evaluated the issue of malpractice claims in the Dutch screening programme. As long as breast cancer treatment will not be able to clearly outweigh the benefit of early detection, we should focus on improving this valuable service. This also means providing all the figures and facts to allow women to make a well informed decision for screening and providing extra training to the (screening) radiologists. Intensifying and improving the evaluation of screening through extended data collection in uniform and clear databases and regular linkage with cancer registries, will assure quality control and may allow more screening related questions to be answered at both a regional and national level.



# 8.2

## Samenvatting

## ACHTERGROND

Borstkanker is de meest voorkomende vorm van kanker bij vrouwen in Nederland en in de meeste andere (ontwikkelde) landen. In Nederland heeft een vrouw een kans van 1:7 om tijdens haar leven met de diagnose borstkanker geconfronteerd te worden. Voor vrouwen is deze ziekte wereldwijd tevens de meest voorkomende oorzaak van kankersterfte. De incidentie van borstkanker neemt in Nederland nog steeds toe. Deze stijging kan gedeeltelijk worden verklaard door de invoering van het landelijke bevolkingsonderzoek naar borstkanker, maar ook ongunstige veranderingen in blootstelling aan (hormoon) gerelateerde risicofactoren voor het ontwikkelen van borstkanker spelen een rol, zoals de afname van pariteit (aantal keren dat een vrouw zwanger is geweest), de afname in duur van het geven van borstvoeding en het stijgend aantal vrouwen met postmenopauzale zwaarlijvigheid.

De kans om aan borstkanker te sterven is direct gerelateerd aan het stadium waarin de ziekte wordt ontdekt. Secundaire preventie van borstkanker middels het vervaardigen van een tweejaarlijks mammogram heeft als doel de ziekte in een zo vroeg mogelijk stadium te ontdekken, waarmee de kans op (lymfeklier) metastasen afneemt, de prognose verbetert en de kans op overlijden afneemt. In bepaalde gevallen kan door een vroege diagnose van de kanker ook volstaan worden met een minder uitgebreide operatie of kan adjuvante behandeling met chemotherapie achterwege blijven, waardoor de kans op behandeling gerelateerde klachten of ziekten afneemt.

Op dit moment is het vervaardigen van een mammogram de best beschikbare en tevens meest kosteneffectieve manier om postmenopauzale vrouwen met een gemiddeld risicoprofiel voor het ontwikkelen van borstkanker, te screenen. Een mammogram is een röntgenfoto van de borsten, welke een gedetailleerde afbeelding geeft van de samenstelling van de borst, namelijk klier- en vetweefsel. De gevoeligheid (sensitiviteit) van het mammogram voor de detectie van borstkanker wordt beïnvloed door meerdere factoren, waarbij de dichtheid van het borstklierweefsel, de beeldkwaliteit en de kundigheid van de screeningsradioloog de belangrijkste zijn. De beoordeling van een (screenings) mammogram is een complex proces, waarin perceptie en interpretatie van bevindingen van groot belang zijn.

Gerandomiseerde studies binnen en buiten Europa hebben aangetoond dat screening met mammografie borstkankersterfte kan doen afnemen. In Nederland is het landelijke bevolkingsonderzoek op borstkanker rond 1990 van start gegaan. Sinds de start van het bevolkingsonderzoek op borstkanker hebben er continue, parallelle, ontwikkelingen plaatsgevonden in de diagnose en de behandeling, maar ook in de bewustwording van vrouwen ten aanzien van deze ziekte. Vergeleken met de situatie voorafgaand aan de invoering van het bevolkingsonderzoek borstkanker, is een duidelijke daling (circa 30%)

in borstkanker sterfte vastgesteld. Echter door eerder genoemde gelijktijdig optredende verbeteringen in de borstkankerzorg, kan het precieze aandeel van de screening in de sterftedaling niet goed worden bepaald.

Na ruime praktijkervaring met het bevolkingsonderzoek op borstkanker is ongeveer 10 jaar geleden in de wetenschappelijke literatuur de discussie opgelaaid over de mate waarin screening de borstkankersterfte reduceert, alsmede de omvang van de nadelen van screeningsmammografie, en dan in het bijzonder overdiagnose en gerelateerde overbehandeling en de (psychologische) impact van fout- positieve verwijzingen. Overdiagnose houdt in dat bepaalde door screening ontdekte kankers nooit symptomatisch, laat staan dodelijk zouden zijn geworden, indien ze niet waren ontdekt. Overdiagnose leidt tot overbehandeling, waarbij van belang is dat de behandeling van borstkanker een significante invloed kan hebben op de kwaliteit van leven van een vrouw. Overdiagnose betreft in het bijzonder de zogenaamde in-situ kankers (DCIS, ductaal carcinoma in situ). Deze in situ carcinomen kunnen een voorloper van invasieve kanker (met kans op uitzaaiingen) zijn, maar niet altijd zullen ze een dergelijke progressie vertonen, of zullen ze tot symptomen leiden. Een deel van de door screening gevonden in situ carcinomen betreft derhalve zogenaamde pseudo-ziekte. Met de huidige medische kennis is echter niet met zekerheid vast te stellen of een ductaal in situ carcinoom wel of niet tot ziekte zal leiden, waarvoor behandeling noodzakelijk is. Tot dusver worden dan ook alle vrouwen met DCIS behandeld alsof er sprake is van een potentieel levensbedreigende ziekte. Het tweede nadeel van screeningsmammografie is de kans op een fout-positieve verwijzing. Dit houdt in dat een vrouw wordt verwezen vanwege een verdachte afwijking op het screeningsmammogram, maar dat bij aanvullende onderzoek geen kanker wordt gevonden. Uit (inter)nationaal onderzoek is gebleken dat vrouwen die een vals positieve verwijzing hebben ervaren daar veel en langdurige stress en angst van kunnen ondervinden. Mogelijk beïnvloedt dit ook de bereidheid van deze vrouwen om deel te nemen aan de volgende ronden van de screening. De internationale discussie over de balans tussen voordelen en nadelen van screenen op borstkanker is nochtans niet beslecht.

Nederlandse studies hebben tot dusver geconcludeerd dat screening op borstkanker wel degelijk de aan borstkanker gerelateerde sterfte vermindert en dat de voordelen opwegen tegen de nadelen. Ondanks de gunstige resultaten is er in Nederland nog steeds ruimte voor verbetering van de borstkanker screening. Opvallend is namelijk dat het percentage intervalkankers (tumoren die tussen twee screeningsronden in worden ontdekt buiten de screening om) en het percentage kankers dat wordt gediagnosticeerd in een verder gevorderd stadium (invasieve tumoren groter dan 2 cm en/of de aanwezigheid van uitzaaiingen in de lymfeklieren bij diagnose) niet of nauwelijks is gedaald sinds de invoering van de screening.





Bijzonder in bovengenoemde discussie is dat screenen op de aanwezigheid van ziekte in een asymptomatische populatie per definitie balanceren is tussen de voor- en nadelen. De insteek kan zijn om (relatief) veel vrouwen te verwijzen, waarvan een groot deel uiteindelijk geen borstkanker blijkt te hebben (d.w.z. veel fout positieve verwijzingen), en op deze manier weinig tumoren te missen. Er kan echter ook voor worden gekozen om juist (relatief) weinig vrouwen te verwijzen. Hierdoor zal het aantal fout positieve verwijzingen gereduceerd worden, maar zullen meer (subtiele) tumoren gemist worden (d.w.z. veel fout negatieve verwijzingen) en zal de kans op een verder gevorderd ziekte stadium ten tijde van de uiteindelijke diagnose toenemen. Deze balans is cruciaal in de discussie. Het feit dat er wereldwijd grote verschillen bestaan tussen de opzet van screening programma's en de mate van doorverwijzen, maakt een onderlinge vergelijking van de uitkomsten vrijwel onmogelijk. Verder is veel onderzoek naar het effect van screening onderhevig aan meerdere vormen van methodologische vertekening (bias).

## ONDERZOEKSDOEL

Het bevolkingsonderzoek naar borstkanker is in Nederland een gewaardeerd onderdeel van de gezondheidszorg, getuige ook de hoge deelname percentages van meer dan 80%. Wel blijkt het als gevolg van de diverse parallelle ontwikkelingen binnen de borstkanker zorg erg moeilijk om te meten welke mate van effect het bevolkingsonderzoek op de borstkankersterfte heeft gehad. In dit proefschrift zijn meerdere aspecten van de screening geëvalueerd aan de hand van een systematisch opgezette gegevensverzameling in de regio Eindhoven. Dit gebeurde in goede samenwerking met het Bevolkingsonderzoek Zuid en het Integraal Kankercentrum Zuid (IKZ). In de evaluatie zijn het verwijstraject, het vervolgtraject na verwijzing, de uitkomstparameters en deelname na eerdere verwijzing in kaart gebracht. Hierbij lag het accent op gescreende vrouwen met dubbelzijdig borstkanker binnen de screening en vrouwen die een fout positieve verwijzing hebben ervaren. Het doel hierbij was om aspecten van het screenings proces te identificeren die verbeterd kunnen worden, waardoor de kwaliteit en effectiviteit toenemen.

## BEVINDINGEN

### Hoofdstuk 2 en 3

#### Dubbelzijdig borstkanker in het bevolkingsonderzoek: vergeet de andere borst niet!

De data uit de studie populatie laten zien dat de gevoeligheid van screeningsmammografie voor het detecteren van dubbelzijdige borstkanker opmerkelijk laag is, met een sensitiviteit van 19% voor het detecteren van de kanker in de contralaterale borst, vergeleken met

een sensitiviteit van 73% voor het detecteren van enkelzijdige borstkanker. Niet alleen tijdens het screenen, maar ook na verwijzing blijkt een substantieel deel (33%) van de contralaterale afwijkingen niet herkend te worden, wat kan leiden tot een onnodige vertraging in de diagnose van dubbelzijdige borstkanker. Hierdoor moeten patiënten soms twee aparte behandelingstrajecten ondergaan, met een overmatige fysieke en psychologische belasting en extra medische kosten tot gevolg.

In onze screeningpopulatie konden geen specifieke kenmerken onderscheiden worden om vrouwen met een verhoogd risico op dubbelzijdige borstkanker op basis van patiëntkarakteristieken, tumorkarakteristieken of tumor biologische kenmerken te identificeren. De contralaterale tumor betrof wel significant vaker (36% vs. 14-17%) een invasieve tumor van het lobulaire type in vergelijking met de zogenaamde index tumor of vergeleken met vrouwen met enkelzijdige borstkanker. Invasieve tumoren van het lobulaire type kunnen gepaard gaan met specifieke, doch vaak subtiele afwijkingen op het screeningsmammogram, zoals bijvoorbeeld een architectuurverstoring of asymmetrie welke vaak beter op de cranio-caudale opname (in plaats van de medio-lateraal-oblique opnamen) te beoordelen zijn. Deze kennis kan worden gebruikt om (de contralaterale) lobulaire tumoren beter en dus vroeger te detecteren. In dit proefschrift werd een prevalentie van 2-3% van dubbelzijdig borstkanker gevonden in de screeningpopulatie. De verwachting is dat dit percentage in de toekomst verder zal stijgen. Om onnodige vertraging in de diagnose van dubbelzijdige borstkanker in de toekomst te voorkomen is het van groot belang voor (screenings)radiologen om specifieke aandacht te hebben voor de andere borst, in het geval een vrouw reeds wordt verwezen voor één zijde.

## Hoofdstuk 4 en 5

### Het fout positieve screeningsmammogram: het belang van het vervolg traject

Voor effectieve screening is zowel een hoge opkomst noodzakelijk als een adequaat screenings interval tussen de opeenvolgende screeningsrondes. Dit geldt voor alle deelnemende vrouwen, dus ook voor vrouwen met een fout positieve verwijzing. In de gescreende populatie bleek dat het overgrote deel van de vrouwen (95%) met een fout positieve verwijzing na twee jaar (op het moment van de volgende screeningsronde) weliswaar een controlemammogram had laten vervaardigen, maar dat 30% het controlemammogram in het ziekenhuis had laten vervaardigen, in plaats van terug te keren naar bevolkingsonderzoek. Na 4 jaar werd een significante daling waargenomen van het percentage vrouwen dat na een fout positieve verwijzing opnieuw een mammogram had laten vervaardigen; na 2 jaar was dat 95% en na 4 jaar 85%, waarbij relatief groot deel van de vrouwen (30% en 20%) in het ziekenhuis onder controle bleef. De terugkeer naar het bevolkingsonderzoek na een fout positieve verwijzing is daarmee minder goed dan





verwacht (slechts 65 % zowel 2 als 4 jaar na verwijzing) en het aandeel vrouwen wat in het ziekenhuis onder controle blijft opvallend hoog.

De afwijking waarvoor een vrouw is verwezen wordt bij aanvullende onderzoek geclassificeerd naar waarschijnlijkheid van maligniteit door middel van de wereldwijd gebruikte BI-RADS classificatie (Breast Imaging-Reporting and Data System). De diagnose BI-RADS 1 of 2 (normaal of goedaardig) na aanvullend onderzoek betekent dat een vrouw terug kan keren in het bevolkingsonderzoek. Uit de eindclassificatie BI-RADS 3 (waarschijnlijk benigne, maligniteitskans <2%) volgde een advies voor een punctie of biopt van de laesie danwel een radiologisch controle-onderzoek 6, 18 en 30 maanden na verwijzing. Vier jaar na een fout positieve verwijzing is de verwachting dat alle vrouwen, ook diegene met een langer controle traject in het ziekenhuis voor een BI-RADS 3 laesie, terugkeren naar het landelijke screenings programma. Controlemammografie in het ziekenhuis in plaats van binnen het bevolkingsonderzoek leidt tot hogere kosten. Daarnaast is een verlengd screeningsinterval binnen het bevolkingsonderzoek geassocieerd is met een verhoogde kans op detectie van kanker in een later stadium. Een deel van de vrouwen (5% na 2 jaar en 15 % na 4 jaar) keert helemaal niet meer terug in het ziekenhuis of naar het bevolkingsonderzoek en valt daarm ee buiten alle controles. De bevindingen van dit onderzoek benadrukken het belang van een goede informatievoorziening voor vrouwen die te maken krijgen met een fout positieve verwijzing. Het communiceren van het belang van terugkeer naar het bevolkingsonderzoek door alle betrokken zorg instanties (screenings eenheid, huisartsen, radiologen, chirurgen en mamma-care verpleegkundigen) kan de opkomst en daarmee de effectiviteit van het bevolkingsonderzoek vergroten.

Er is uitgebreide literatuur over de negatieve psychologische effecten die een fout positieve verwijzing kan veroorzaken. Daarom is het van groot belang om een tweede fout positieve verwijzing te voorkomen. In de screeningpopulatie bleek 3% van de vrouwen voor een tweede keer te worden verwezen na een eerdere fout positieve verwijzing, waarbij 42% van deze vrouwen werd verwezen voor dezelfde afwijking op het screeningsmammogram als bij de eerste verwijzing. De kans op de diagnose borstkanker was onafhankelijk van het feit of een vrouw voor de eerste of tweede keer werd verwezen en bedroeg in beide gevallen 36%. Indien pas na tweede verwijzing voor dezelfde afwijking borstkanker wordt aangetoond, is er sprake van een substantiële vertraging in de diagnose. De kans op borstkanker bij een tweede verwijzing was significant groter indien vrouwen waren verwezen voor een densiteit (in plaats van microcalcificaties, een architectuurverstoring of asymmetrie) en indien vrouwen geen biopt hadden ondergaan bij de eerste verwijzing. Een fout negatieve pathologie-uitslag komt relatief weinig voor, maar moet weldegelijk worden overwogen bij discrepanties tussen beeldvorming en PA-diagnose. Een onjuiste

BI-RADS classificatie bleek verder regelmatig voor te komen bij vrouwen met een verlate borstkankerdiagnose. Dit onderzoek suggereert derhalve dat een substantiële vertraging in borstkankerdiagnose en een onnodige tweede verwijzing voorkomen kunnen worden door een meer intensief diagnostisch traject na verwijzing.

## Hoofdstuk 6

### Medische schadeclaims en gemiste tumoren in de screening: het belang van communicatie

De sensitiviteit voor screeningsmammografie in screeningsregio in Zuid-Nederland is 73%. Herbeoordeling van eerdere screeningsmammogrammen toonde dat circa 20% van de middels screening ontdekte borstkanker en tot 24% van de intervalkankers reeds zichtbaar waren op het voorgaande mammogram, maar niet als dusdanig waren geïnterpreteerd of waargenomen. Uiteindelijk dienden 3 van de 85.000 vrouwen in de studieperiode direct een schadeclaim in voor financiële compensatie in verband met de diagnose van een intervalkanker. Eén claim is afgewezen, de andere twee moeten nog worden afgerond. Daarnaast namen in de onderzoeksperiode 1997 tot 2011, 19 vrouwen contact op met de screeningsorganisatie voor meer informatie nadat bij hen borstkanker was vastgesteld. Geen van deze vrouwen dienden uiteindelijk een claim in, hoewel 14 van hen waren gediagnostiseerd met een tumor in een gevorderd stadium. Het aantal vrouwen dat contact opnam met de screeningseenheid nam in de loop van de jaren toe. Schadeclaims in verband met een verlate borstkanker diagnose zijn gebaseerd op de achterliggende gedachte dat een vertraging in de diagnose een negatieve invloed heeft op de prognose en de mogelijkheden. In de screeningpopulatie was er bij 5% van de vrouwen sprake van een vertraging in de diagnose van borstkanker van meer dan 3 maanden. In bijna 60% van de gevallen werd deze vertraging veroorzaakt door het toekennen van een verkeerde BI-RADS classificatie bij vervolgonderzoek na verwijzing en in 20% van de gevallen als gevolg van een fout negatieve uitslag van een punctie of biopt. Bij 27% van de vrouwen met een verlate diagnose was sprake van een tumor in een gevorderd stadium en bij vrouwen zonder vertraging in de diagnose van borstkanker was dat 19%. Uit deze gegevens kan worden geconcludeerd dat er vanuit de screening zelden een schadeclaim wordt ingediend of om nadere informatie wordt gevraagd, hoewel een substantieel deel van de tumoren reeds bij het voorgaande screeningsonderzoek opgespoord had kunnen worden. Een belangrijke verklaring voor het lage aantal claims zou gelegen kunnen zijn in de open communicatie tussen screeningsorganisatie en/of screeningradioloog en de betreffende vrouwen. Dit wil echter niet zeggen dat de huidige werkwijze een garantie is voor het voorkomen van claims in de toekomst. De kans bestaat dat, in navolging van de situatie in de Verenigde Staten, ook in Nederland het aantal claims zal toenemen. Daarom is het van belang dat er vanuit de Nederlandse Vereniging voor Radiologie een protocol

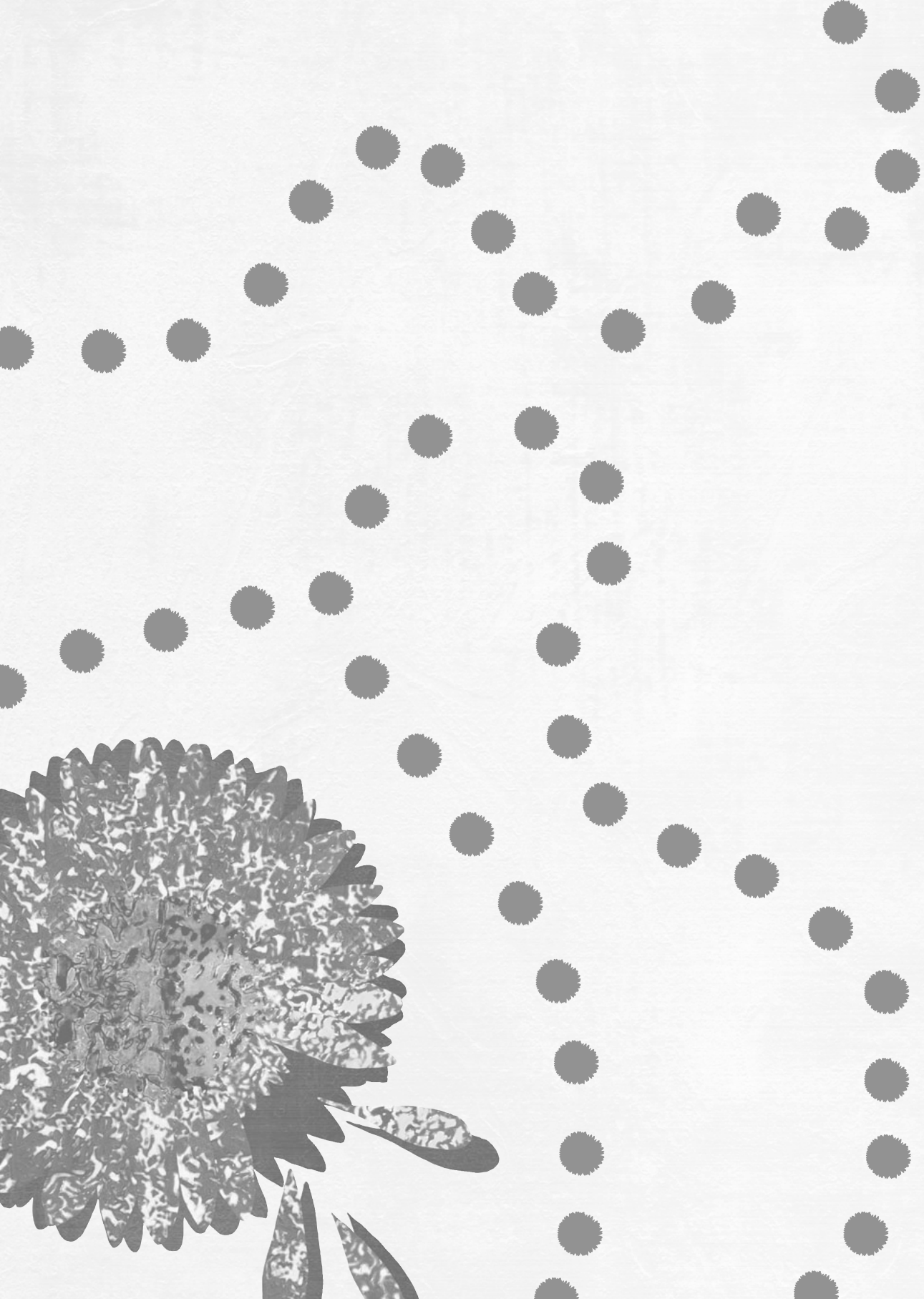




wordt opgesteld ten aanzien van de communicatie over vragen met betrekking tot gemiste tumoren in het kader van het bevolkingsonderzoek, alsmede over de te volgen procedure in het geval van een medische schadeclaim.

## CONCLUSIE

Na meer dan twee decennia ervaring met borstkanker screening, met overtuigend bewijs van zowel de voordelen als de nadelen van screening, is het bevolkingsonderzoek voor het merendeel van de vrouwen in Nederland nog steeds een gewaardeerd onderdeel van de gezondheidzorg voor vrouwen in Nederland. Dit neemt niet weg dat er ruimte is voor verbetering. De niet aflatende discussie over het nut van het bevolkingsonderzoek naar borstkanker illustreert het dilemma wat onlosmakelijk verbonden is met screening op ziekte in een overwegend gezonde populatie. In plaats van een aanhoudende herhaling van argumenten voor of tegen screening is het nu tijd om een stap voorwaarts te zetten en gezamenlijk naar oplossingen te zoeken voor de geconstateerde tekortkomingen. In dit proefschrift zijn enkele vraagstukken geëvalueerd en mogelijkheden aangedragen ter optimalisering van de screening, namelijk het verbeteren van de detectie van (dubbelzijdige) tumoren binnen de screening, het verbeteren van de opkomst na een fout positieve verwijzing, het reduceren van een herhaalde (fout positieve) verwijzingen en als laatste het vergroten van het inzicht in vraagstukken ten aanzien van medische schadeclaims binnen de screening. Zolang de prognose van borstkanker nog niet onafhankelijk is geworden van het stadium (vroeg of gevorderd) van borstkanker bij diagnose, zal vroeg opsporing door middel van screening een waardevol en kosteneffectief onderdeel van de gezondheidszorg zijn, waarbij we ons moeten blijven concentreren op mogelijkheden tot verbetering. Dit betekent dat we vrouwen die in aanmerking komen voor screening op borstkanker moeten voorzien van objectieve, begrijpelijke en goed toegankelijke informatie, zodat ze tot een afgewogen besluit kunnen komen om wel of niet deel te nemen aan het bevolkingsonderzoek. Verder zouden op reguliere basis trainingen georganiseerd kunnen worden voor (screenings) radiologen teneinde meer uniformiteit in BI-RADS classificering te bereiken en prestaties te optimaliseren door regelmatige terugkoppeling van screeningsresultaten. Een breder opgezet en meer uniform gegevensbeheer, waarin de uitwisseling en koppeling van gegevensbestanden tussen de betrokken instanties de standaard is, kan zorgen voor een optimale kwaliteitscontrole van het bevolkingsonderzoek op borstkanker.



# 8.3

## Acknowledgements | Dankwoord

## DANKWOORD

*Heerlijk* is het eerste woord wat me te binnen schiet nu het einde in zicht is, *eindelijk* is het tweede woord. Voor een goede drie eenheid moet een derde woord volgen ...dat komt als deze promotie voltooid is! Tijd is er wat mij betreft te weinig in een dag (en een nacht); gedurende deze 'proeve van bekwaamheid' heb ik leren plannen, maar ook leren accepteren dat mijn 'deadlines' niet de meest betrouwbare zijn! Gelukkig kwam dit proefschrift tot stand dankzij de hulp van vele gewaardeerde collega's, vrienden en familie, die ik bij deze graag hartelijk wil danken voor al hun bijdragen. In de volgende alinea's wil ik enkelen van hen in het bijzonder toespreken.

Prof. dr. J.W. Coebergh, mijn promotor, beste Jan Willem, je universele kennis en visie op kanker(bestrijding) hebben bij mij een stevige indruk achtergelaten. Weinig mensen beheersen de kunst om via de juiste omwegen tot een wezenlijke kern van de zaak te kunnen komen, jij kan het! Dank voor je waardevolle inbreng over de zaken binnen maar ook zeker buiten de onderwerpen van dit proefschrift.

Dr. L.E.M. Duijm, mijn copromotor, beste Lucien, de initiator en katalysator achter dit verhaal. Ik ben begonnen met één artikel, maar dankzij jou werd het een heel boek. Jouw inzet voor het gegevensbestand van de screeningspopulatie in regio zuid is niet te evenaren, en je inspiratie en wetenschappelijke ideeën zijn onuitputtelijk. Dank voor je tijd, je kritische blik en waardevolle suggesties. Jouw snelle inzichten en efficiëntie in het schrijven zijn inspirerend! Mijn soms chaotische inslag heeft jou vast (meer dan) eens de wenkbrauwen doen rijzen, maar er wordt ook wel gezegd: bij geestelijke arbeid is orde een zeldzaamheid.... (François Fénelon).

Dr. A.C. Voogd, mijn tweede copromotor, beste Adri, ik had het niet beter kunnen treffen. Samenwerken met jou is uitermate plezierig en motiverend. Jouw inzicht en altijd opbouwende kritiek maken enthousiast en je waardevolle inbreng gaf richting in het geheel, erg welkom als ik die juist even kwijt was!

De leden van de kleine commissie, Prof. dr. Klijn, Prof. dr. Den Heeten, en Dr. Verkooijen, wil ik hartelijk danken voor de tijd en energie die zij gestoken hebben in de beoordeling van het manuscript. Alle leden van de promotiecommissie wil ik danken voor de interesse en bereidheid hierover van gedachten te wisselen.

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stimuleren was de juiste, wat het plezier ten goede komt! Vivian, dank voor je goede gezelschap, je nuchterheid en droge humor. Het van dichtbij mogen meegenieten bij jouw promotie en je kennis als ervaringsdeskundige in het laatste traject van promoveren heb ik erg gewaardeerd! Ik ben blij dat we ondanks de afstand, nu jij en je gezin in Johannesburg verblijven, het contact in stand houden! Joost, dank voor je onmisbare kennis van zaken op het gebied van SPSS, Excel en Reference Manager, weet ook dat ik je relaxte, onbevangen en integere instelling erg waardeer! De afronding van jouw boekwerk laat niet lang meer op zich wachten: succes met de laatste stappen.

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veel goeds! Weet dat ik gebaald heb van dingen die ik vergat in de drukte van de dag en ik zie uit naar een lege agenda om vol te plannen!

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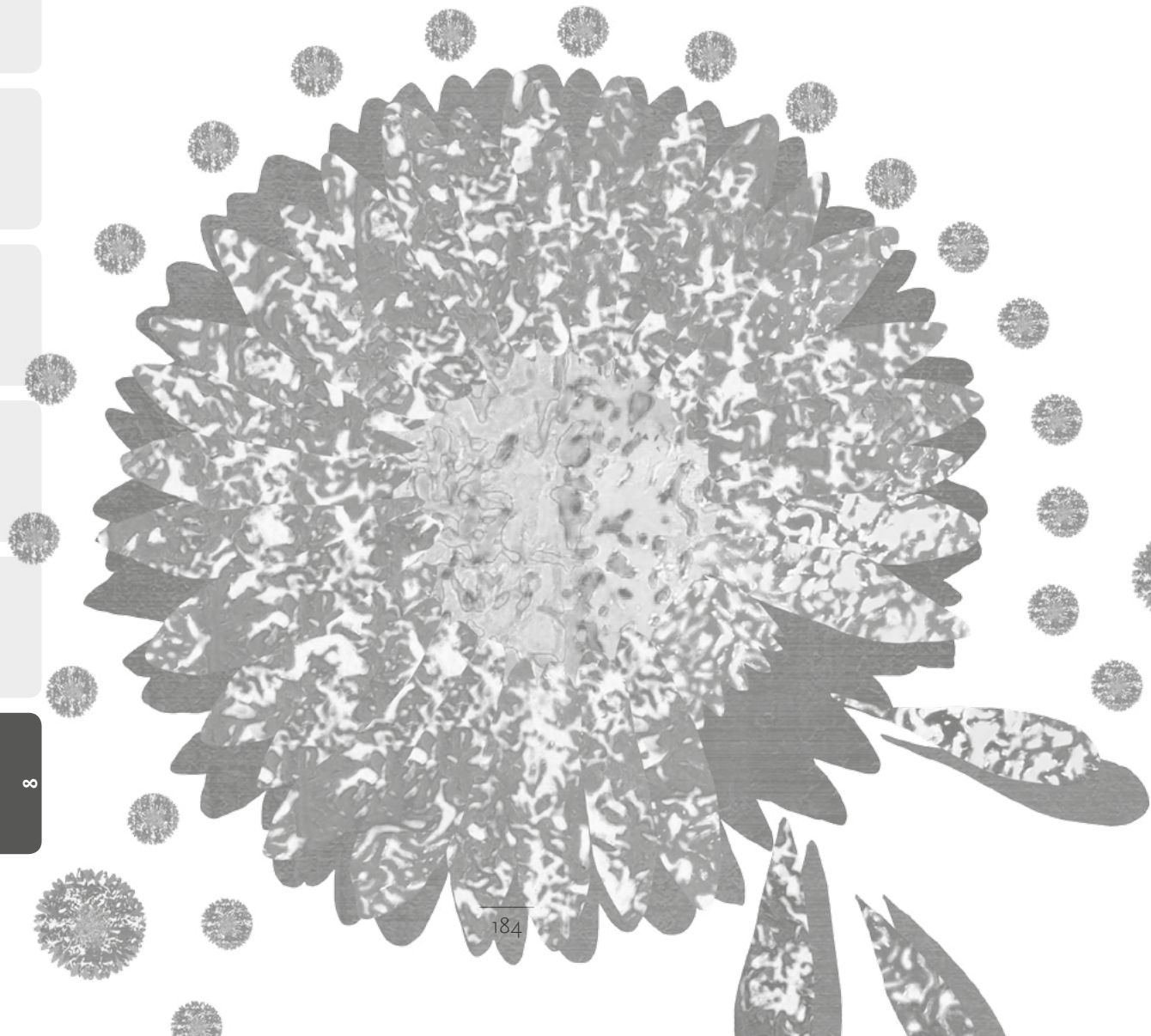
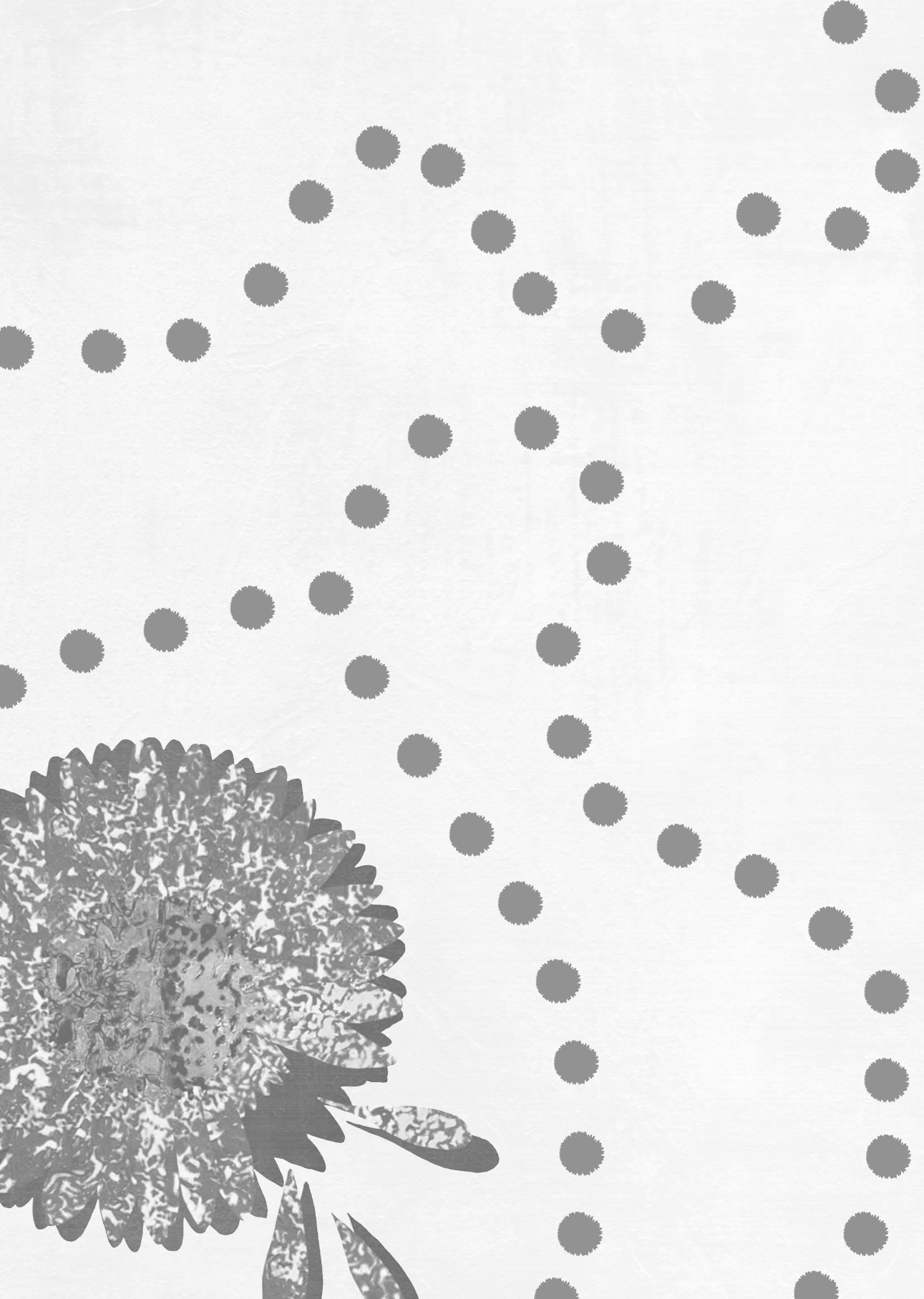
Als allerlaatste, mijn allerbeste Maikel, jouw 'relativiteits theorieën' doen mij altijd weer stralen. Jouw scherpzinnigheid blijft mij verbazen (en bij tijd en wijlen heerlijk irriteren). Ik

heb ooit gelezen: ‘Don’t marry someone you can live with, marry someone you can’t live without,’ Dat is o zo goed gelukt; ik zou niet zonder je kunnen en bovenal niet willen! Samen met jou en de kinders wordt ‘huisje boompje beestje’ een heerlijk ‘huisje boompje feestje.’





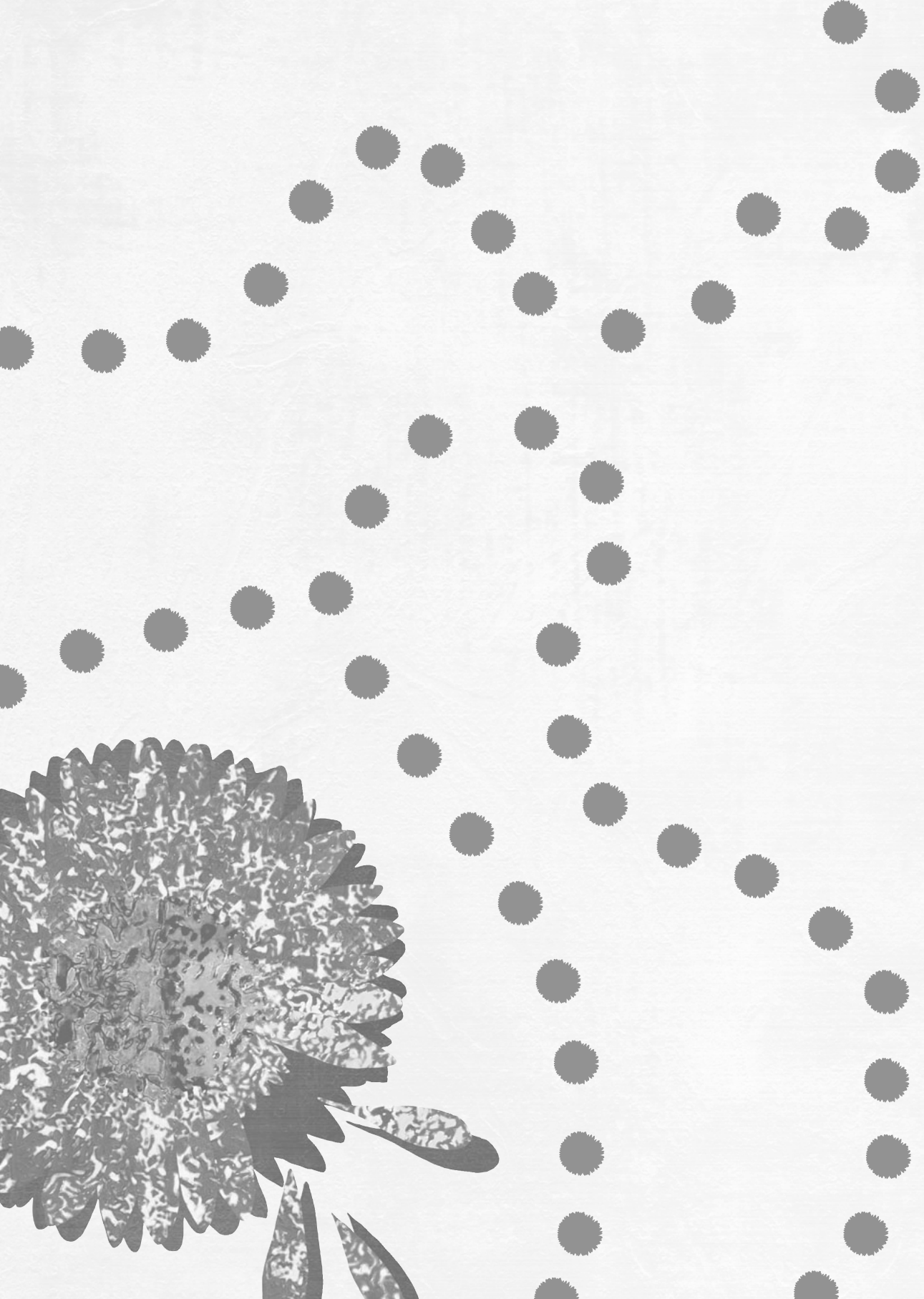
# 8.4

## Curriculum vitae

## CURRICULUM VITAE

Wikke Setz-Pels werd in Eindhoven geboren op 27 oktober 1975. In 1994 behaalde zij haar Gymnasiumdiploma aan het Lorentz Lyceum te Eindhoven en in datzelfde jaar startte zij, na uitgeloot te zijn voor Geneeskunde, met de studie Biomedische Gezondheidswetenschappen aan de Radboud Universiteit in Nijmegen. In het kader van deze studie liep zij stage op de afdeling Obstetrie en Gynaecologie (onder leiding van Prof. D.K. James en Dr. L. Kean) van het Queens Medical Centre in Nottingham (G.B.). Later volgde een wetenschappelijke stage in het UMC St. Radboud in samenwerking met de afdeling Klinische Genetica, Obstetrie en Gynaecologie, en Epidemiologie (onder leiding van Prof. dr. N. Hoogerbrugge, Prof. dr. L.F.A.G. Massuger en Prof. dr. L.A.L.M. Kiemeney). In 1996 begon zij met de studie Geneeskunde aan de Radboud Universiteit. In 2001 behaalde zij haar doctoraal Gezondheidswetenschappen, afstudeerrichting Epidemiologie, evenals haar artsexamen (met predicaat cum laude) en werd zij aangenomen als arts-onderzoeker en arts-assistent op de afdeling Obstetrie en Gynaecologie in het UMC St Radboud te Nijmegen. Naast het coördineren van de klinische trial ('Randomized Survival Study of Monoclonal Antibody Radioimmuno-therapy in patients with ovarian carcinoma using the HMFG1 (THERAGYN) antibody labeled with Yttrium') verrichtte zij preklinisch onderzoek naar de behandeling van het ovarium carcinoom middels intraperitoneale radioimmunotherapie (onder leiding van Prof. dr. L.F.A.G. Massuger en Prof. dr. O.C. Boerman). In 2003 gooide zij het roer om en begon met de opleiding tot radioloog in het UMC St Radboud (opleider Prof. dr. J.G. Blickman) en het Jeroen Bosch Ziekenhuis (opleider Dr. J.C.M. Rutten). Na het voltooien van de opleiding begon zij in 2010 als radioloog (Chef de Clinique) in het Catharina Ziekenhuis te Eindhoven. In hetzelfde jaar startte zij met het onderzoek wat geleid heeft tot dit proefschrift. Sinds 2012 maakt zij deel uit van de maatschap radiologie in het Catharina ziekenhuis met als aandachtsgebied buiten de mammaradiologie, de abdominale en cardiovasculaire radiologie.

Wikke is getrouwd met Maikel en samen zijn zij de trotse ouders van Mila (2006), Chiel (2007) en Juup (2008).



# 8.5
## List of publications

## PUBLICATIONS

- **Setz-Pels W**, Duijm LE, Coebergh JW, Rutten M, Nederend J, Voogd AC. Re-attendance after false positive screening mammography; a population based study in the Netherlands. Br J Cancer 2013 Oct 15;109(8):2044-50. doi: 10.1038/bjc.2013.

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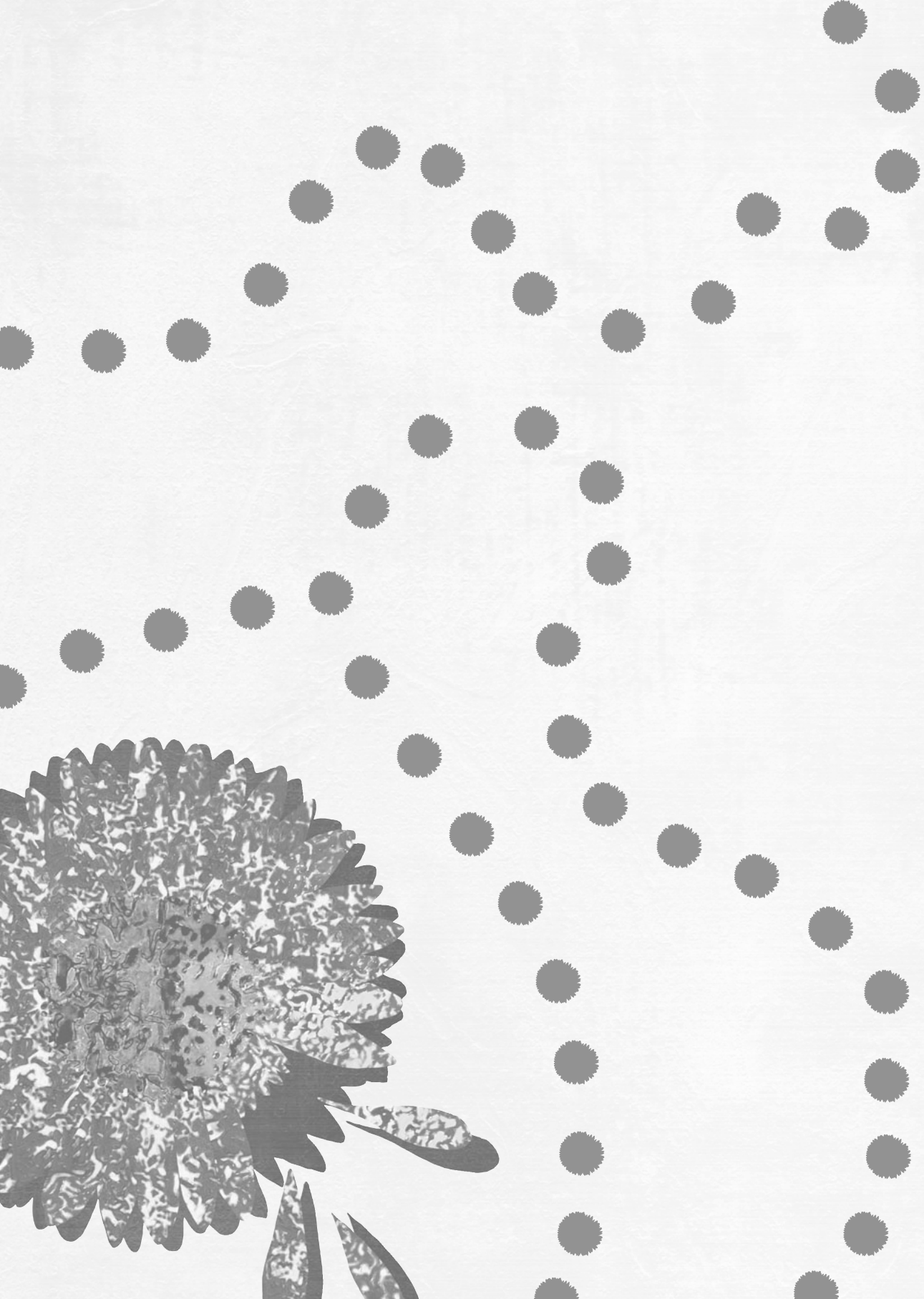
- Harrie CM van den Bosch, Jos JM Westenberg, **Wikke Setz-Pels**, John Wondergem, Ron Wolterbeek, Lucien EM Duijm, Joep A.W. Teijink, Albert de Roos. Site-specific Coupling between Aortic Pulse Wave Velocity, Carotid Vessel Wall Thickness and Peripheral Stenosis Severity at 3T MRI in Peripheral Arterial Occlusive Disease. Submitted Radiology



# 8.6
## Abbreviations

## ABBREVIATIONS

| | |
|---|---|
| BI-RADS: | Breast Imaging Reporting and Data System |
| BOZ: | Bevolkingsonderzoek Zuid/ Cancer Screening South |
| CAD: | Computer-aided detection |
| QALY: | Quality Adjusted Life Years |
| CC: | Craniocaudal view |
| CCMO: | Dutch Central Committee on Research involving Human Subjects |
| CI: | Confidence interval |
| CNB: | Core Needle Biopsy |
| DCIS: | Ductal carcinoma in situ |
| ECR: | Eindhoven Cancer Registry |
| ESR: | European Standardised Rate |
| EUSOMA: | European Society of Breast Cancer Specialists |
| FFDM: | Full field digital mammography |
| FNAC: | Fine Needle Aspiration Cytology |
| GBA: | Gemeentelijke Basisadministratie Persoonsgegevens/ Municipal register of Death |
| IKZ: | Integraal Kankercentrum Zuid/ Comprehensive Cancer centre South |
| IC: | Interval cancer |
| IDC: | Invasive ductal carcinoma |
| ILC: | Invasive lobular carcinoma |
| MISCAN: | MIcrosimulation Screening Analyses |
| MLO: | Mediolateral-oblique view |
| MRI: | Magnetic Resonance Imaging |
| NABON: | Nationaal Borstkanker Overleg Nederland |
| NCR: | National Cancer Registry |
| NETB: | National Evaluation Team for Breast cancer screening |
| PALGA: | Pathologisch anatomisch landelijk geautomatiseerd archief/ national automated pathology archive |
| PPV: | Positive predicted value |
| RIVM: | National Institute of Public Health and the Environment |
| SDC: | Screen detected cancer |
| SFM: | Screen film mammography |
| TNM: | Tumour-Node-Metastasis classification |
| US: | Ultrasound |
| VA: | Vacuum assisted biopsy |
| WHO: | World Health Organisation |

## Notes



# STELLINGEN BEHORENDE BIJ HET PROEFSCHRIFT

1. De lage sensitiviteit van screeningsmammografie voor kanker detectie in de contralaterale borst benadrukt het belang van een zorgvuldige beoordeling van de contralaterale borst door radiologen indien reeds eenzijdig een mammografisch suspecte afwijking is gedetecteerd.
   *(dit proefschrift)*
2. Bij verwezen vrouwen dienen (screenings) radiologen extra alert te zijn op de subtiele radiologische kenmerken van een eventueel lobulair carcinoom in de contralaterale borst.
   *(dit proefschrift)*
3. Na een fout positieve verwijzing blijft een te groot percentage van deze vrouwen in het ziekenhuis onder controle, in plaats van terug te keren naar het bevolkingsonderzoek.
   *(dit proefschrift)*
4. De kans op borstkanker bij een tweede verwijzing voor dezelfde afwijking is groter indien vrouwen worden verwezen voor een suspecte densiteit op het screeningsmammogram en indien bij aanvullend onderzoek na de eerste verwijzing alleen beeldvorming is verricht.
   *(dit proefschrift)*
5. Bij bijna 60% van de vrouwen bij wie borstkanker wordt vastgesteld meer dan drie maanden na verwijzing, is een onjuiste BI-RADS classificering de oorzaak van deze vertraging in borstkanker diagnose.
   *(dit proefschrift)*
6. Het nalaten van gerichte dataverzameling binnen de preventieve gezondheidszorg houdt impliciet in dat we als beroepsgroep van onze patiëntenpopulatie niets weten, niets leren en niets wijzer worden.
   *(dit proefschrift)*
7. Het elimineren van de term carcinoma in de diagnose “ductaal carcinoma in situ” (DCIS) kan de gemoedsrust van zowel dokter als patiënt bevorderen en schept meer mogelijkheden voor een expectatief beleid.
   *(naar V. Galimberti 2013, Breast)*
8. Het vermogen om te horen, garandeert niet dat we ook luisteren. Luisteren is een vaardigheid die onderwezen in plaats van verondersteld moet worden, ter bevordering van communicatie in de breedste zin van het woord.
   *(naar D. Stauffer 1998, Harvard Management Update)*
9. De dingen simpel houden is vrij moeilijk. De dingen moeilijk maken daarentegen vrij simpel.
   *(naar E.W. Dijkstra, 2000, “in pursuit of symplicity”)*
10. Politiek is de wetenschap hoe wie wat krijgt, wanneer en waarom. Alles is politiek, maar politiek is niet alles.
    *(naar H. Kuitert 1985)*
11. De wereld zou een stuk beter af zijn als muggen vet in plaats van bloed zouden zuigen.

***Wikke Setz-Pels,*** *20 februari 2014*