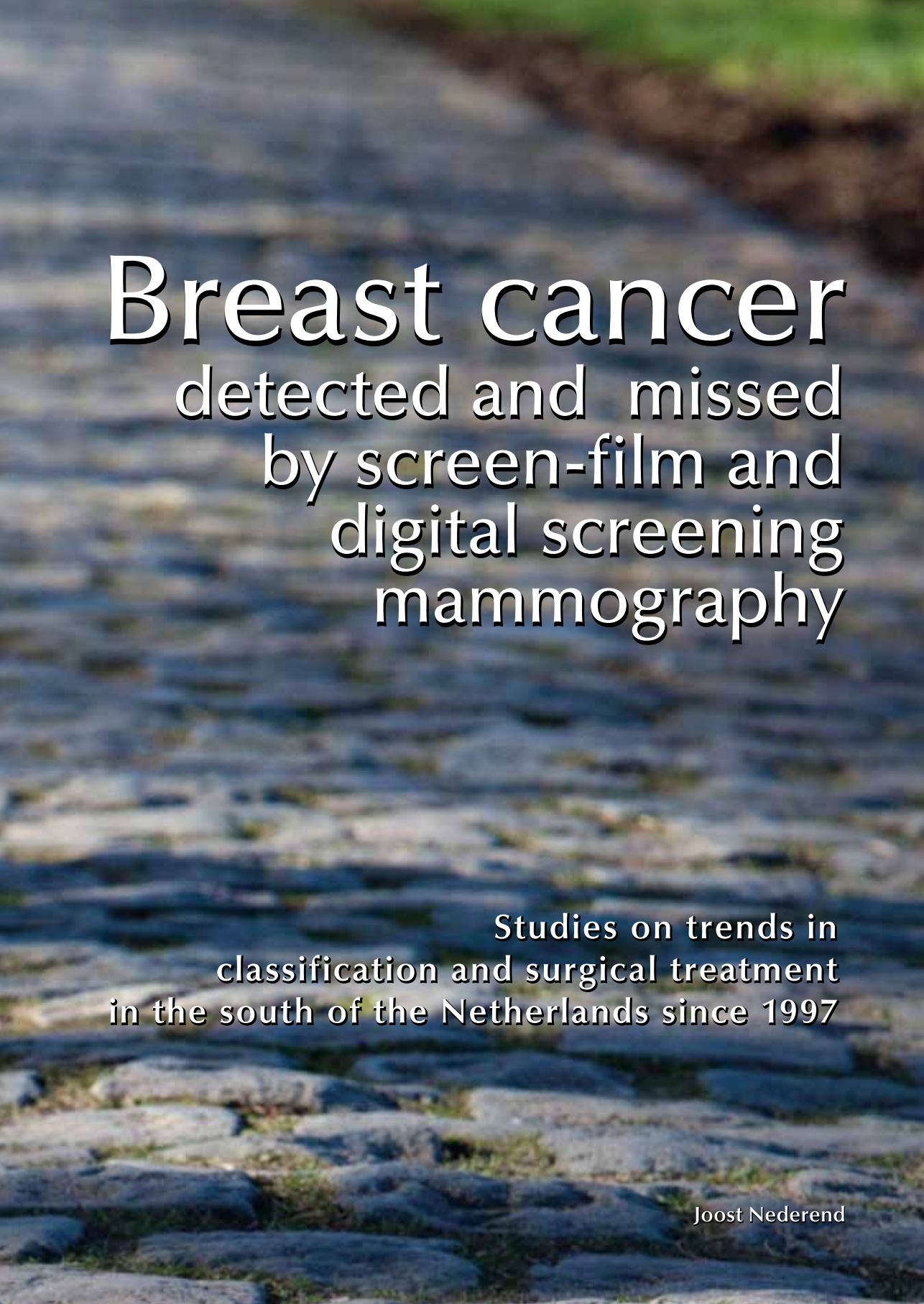

Breast cancer
detected and missed by screen-film and digital screening mammography

Studies on trends in classification and surgical treatment in the south of the Netherlands since 1997

Joost Nederend

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Design: Publiciteitsfotografie Henk Swinkels, Eindhoven
Printing: drukkerij GVO Drukkers & Vormgevers BV | Ponsen & Looijen
ISBN: 978 90 807955 0 1
Coverphoto: Publiciteitsfotografie Henk Swinkels, Eindhoven
Executive Publisher: Publiciteitsfotografie Henk Swinkels, Eindhoven

The publication of this thesis was financially supported by:
Catharina ziekenhuis Eindhoven; Bracco imaging Europe B.V.; Guerbet Nederland B.V.; Intergraal kankercentrum Nederland, locatie Eindhoven; Bevolkingsonderzoek Zuid; Tromp Medical B.V.

Breast Cancer Detected and Missed by Screen-film and Digital Screening Mammography

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Borstkanker gedetecteerd en gemist door analoge en digitale screeningsmammografie

Studies naar trends in classificatie en chirurgische behandeling in het zuiden van Nederland sinds 1997

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

vrijdag 19 september 2014 om 11:30 uur

Joost Nederend,
geboren te 's Gravenhage

ERASMUS UNIVERSITEIT ROTTERDAM

Promotor:	Prof.dr. J.W.W. Coebergh
Overige leden:	Prof.dr. M.A.A.J. van den Bosch Dr. M.J. Broeders Prof.dr. C. Verhoef
Copromotoren:	Dr. L.E.M. Duijm Dr. A.C. Voogd

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Breast cancer detected and missed by screen-film and digital screening mammography

Chapter 1

General Introduction

General introduction

In the South of the Netherlands there is a long-standing cancer registry which has recorded the marked changes in incidence, detection, stage, staging, treatment of and mortality from breast cancer already since 1955[1,2]. Since the introduction in 1995 of mammography screening in the region around Eindhoven, a southern part of the Netherlands, over 700,000 screens have been performed, and thanks to extensive data collection of screening results by one of the screening radiologists in this region a unique database has been created.

This thesis will explore screening outcome throughout the years, focusing on the impact of the introduction of digital mammography at breast cancer screening since 2009 in the Netherlands.

This general introduction describes:

- the epidemiology of breast cancer;
- the background of population-based screening for breast cancer;
- the on-going debate on the effectiveness of breast cancer screening;
- screening specificity;
- the need of monitoring incidence of advanced breast cancer;
- the transition from screen-film to digital screening mammography;
- the outline of this thesis;
- and methods and population.

Epidemiology of breast cancer

Breast cancer is the most common malignancy in women in the Western world. In the Netherlands, a country with 16.7 million inhabitants, currently about 14,000 women are diagnosed with breast cancer yearly, mostly localized to the breast or lymph nodes. The lifetime risk for developing breast cancer nowadays is 1 in 7 for women living in the Netherlands[3]. Breast cancer is the second most common cause of cancer death for Dutch women; lung cancer is the most common cause since 2006[4].

In the Netherlands, the incidence of breast cancer is still rising, from 9,500 newly diagnosed breast cancer cases in 1995 to 14,600 in 2013, and is among the highest in Europe[4]. Also when looking at the standardized incidence rates, a remarkable increase in the incidence of breast cancer can be observed during the last decades; between 1989 And 2011, the European Standardized Rate increased from 85 per 100,000 women per year to almost 155 per 100,000 per year[4]. The cause of this increase is multifactorial and includes the introduction of the national screening programme, an increased awareness among women of early symptoms of breast cancer, as well unfavourable developments in the exposure to risk factors, especially increasing age at first birth and lower parity[5].

Population based screening for breast cancer

Early detection of breast cancer has become an important aspect of current breast cancer management. Evidence for the effectiveness of breast cancer screening dates back to the early 1960's, when Shapiro at al. showed a 25% reduction of breast cancer deaths in a screened population[6,7]. The Netherlands is regarded as a pioneer in the field of breast cancer screening and the first pilot projects date back to the seventies with the DOM project in Utrecht ('Diagnostisch Onderzoek Mammacarcinoom'), a research project on causes of breast cancer[8], the experiment on breast examination by volunteers in Leiden[9], and the radiology-born breast cancer mammography screening pilot in Nijmegen[10], in which breast cancer mortality was compared to the unscreened female population of the neighbouring city of Arnhem. In 1985, after the positive results of the Utrecht and Nijmegen studies and the equally positive results of the Swedish two county trial[11], the decision was taken to introduce breast cancer screening in the Netherlands. Because of lengthy discussions about standards for the quality of mammography, pathology and surgical treatment, and the time needed for the training and recruitment of specialist radiographers, the screening programme did not start until 1989. From that year on, the screening programme was introduced region by region.

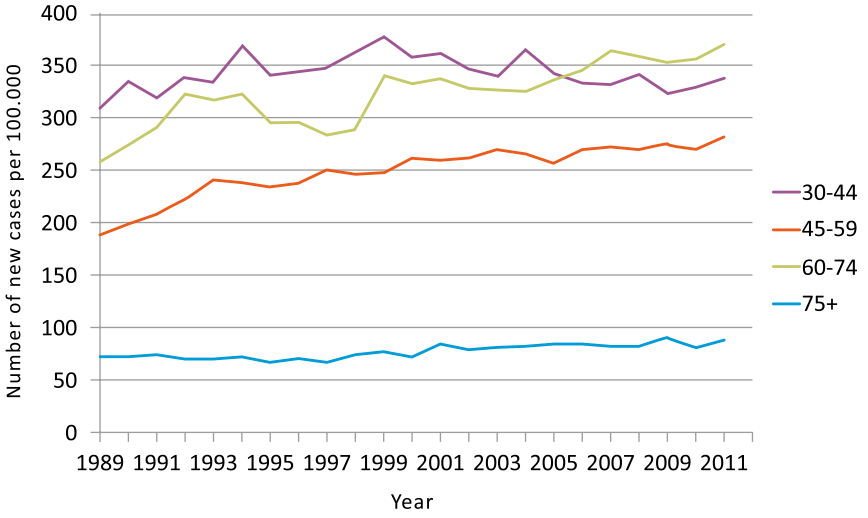
The Dutch breast cancer-screening programme offers biennial mammography screening to women aged 50-70 years of age. In 1998 – again after much debate and consultation of experts – the upper age-limit was extended to 75 years. In the Southern Netherlands, mass screening was gradually introduced between 1991 and 1995, first in Breda and Venlo, and in 1995 in the region of Eindhoven.
In 1996, the Comprehensive Cancer Centre South (IKZ) developed a so called 'visie-lering' (see and learn) project, in which a small committee consisting of a surgeon, pathologist and radiologist together with an epidemiologist visited all hospitals performing diagnostics and treatment of early breast cancer. The aim of this project was to improve the quality of the care for those women referred to the hospital because of a positive screening test.

On-going debate on usefulness / effectiveness of screening

In spite of the generally positive outcomes of several trials and population-based studies, the effectiveness of breast cancer screening has been under discussion since its introduction. Especially the simultaneous decrease of the mortality rate in unscreened women (both women younger than 50 years of age and women in countries without a mass screening programme) is the main argument for questioning the degree of effectiveness of breast cancer screening (Figure 2). Several factors have simultaneously contributed to the lowering of the breast cancer mortality rate through the years:

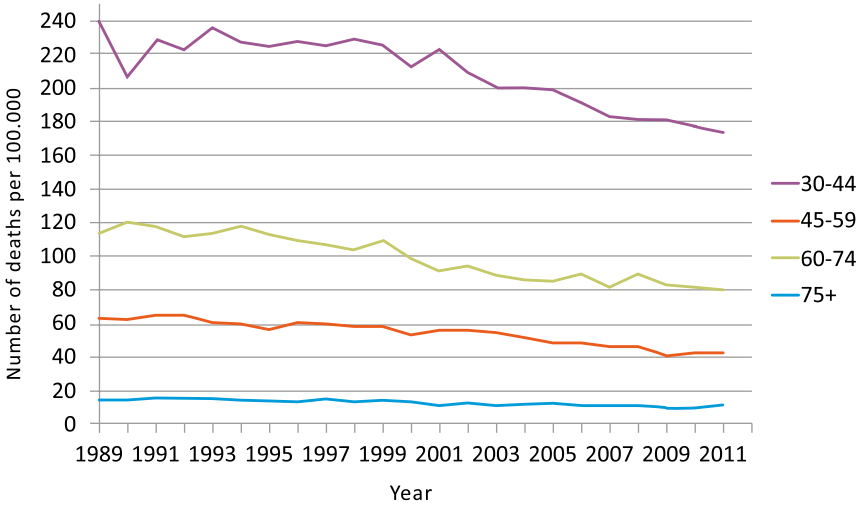
- improved treatment breast cancer, also of recurrent and/or progressive disease;
- the introduction of breast cancer screening;
- and increased cancer awareness among women[12-14].

Figure 1. **Age-specific incidence of invasive breast cancer in the Netherlands** *Source: www.ikcnet.nl*



However, the continuous rise of the background incidence of breast cancer may have had the opposite effect on breast cancer mortality[1,15]. As a result, it is almost impossible to quantify the contribution of each factor to the decreased breast cancer mortality, also because of the long duration of the disease once it has been diagnosed[16].
Other arguments in the discussion on the effectiveness of screening include the harms of mammography screening, especially the consequences of false-positive findings.

Figure 2. **Age-specific mortality of invasive breast cancer** *Source: www.ikcnet.nl*



In 2000, a Danish review of the Nordic Cochrane Centre[17], by Peter Gøtzsche and colleagues, criticized the methodological quality of the breast cancer screening trials. Several other studies have refuted the conclusions of the Nordic Cochrane Centre[18,19], with the Dutch conclusion being that "There seems no reason to change or halt the current nation-wide population-based screening programmes. Nor is there any justifiable reason for negative reports towards women or professionals"[19]. The conclusions from the mentioned Cochrane review[17], and other reports and publications, have not resulted in ending breast cancer screening. Nonetheless, there remains criticism of the effectiveness of breast cancer screening, mostly on the substantial risk for women of experiencing a false positive screening result or an interval cancer, which is breast cancer detected after screening mammography yielded a negative result. Another subject of debate is the risk of over-diagnosis. Over-diagnosis is the diagnosis of "disease" that will never (or after a very long time, i.e. more than 15 years) cause symptoms or lead to death during a patient's lifetime. Without screening most of these cancers would not have been detected. Estimates of the risk of over-diagnosis vary widely, from 2% in a Dutch study[20] to 52% in a study by Jorgensen et al.[21]. As mentioned recently by the Dutch researchers, the disparity of the estimates between the two studies is probably the result of methodological differences, lack of sufficient follow-up and differences in screening characteristics and performance[22]. Furthermore, the true problem might not be over-diagnosis, but overtreatment[23]. This issue is especially relevant in the current era of digital screening where more ductal carcinoma in-situ and small, low-grade invasive malignancies are detected. Complications of surgery (both local and axillary) and adjuvant therapy can cause significant morbidity and therefore over-treatment should be avoided. Further research, preferably in the form of randomised controlled trials, is needed to determine whether certain diagnosed invasive cancers and/ or in-situ carcinomas can be monitored rather than treated by surgery.

Screening specificity

A false positive referral is a potential harm of breast cancer screening, even more so if the women involved are not appropriately informed about this risk when invited for screening. Especially since the introduction of digital mammography screening, false positive referrals have become a subject of debate, as digital screening has a lower positive predictive value than screen-film mammography. Several studies have shown that a false-positive referral causes stress, anxiety, and could negatively influence re-attendance to the screening programme[24-27]. The observed severity of psychological distress in referred women with a benign outcome was higher than the psychological distress observed in women who were not referred[25]. Furthermore, screen-related costs increase due to unnecessary use of diagnostic tests, hereby compromising the cost-effectiveness of the screening programme[28,29].

The need of monitoring incidence of advanced breast cancer

Most breast cancer deaths occur in women with advanced breast cancer, diagnosed when the disease has already spread to lymph nodes or distant organs. Breast cancer screening aims to detect breast cancer at an early stage, when the disease has a better prognosis. Screening therefore is expected to lower the incidence of advanced breast cancer, followed by a reduction in breast cancer mortality. A critical view on breast cancer screening related to its impact on the incidence of advanced breast cancer, is expressed by a French research collaboration, led by Philippe Autier. Several studies of this collaboration showed the incidence of advanced breast cancer remained stable after the introduction of breast cancer screening, which suggests that it did not play a significant role in the observed reduction in mortality caused by breast cancer[30-32]. However, Autier et al. do not take into account that incidence of breast cancer, whether advanced or not, may just have risen because of later age at first birth as such but also as an indicator of (breast tissue favourable) lifestyle of young women[5]. Albeit certainly important, monitoring of the incidence of advanced breast cancer does not provide unequivocal information of the impact of screening on breast cancer mortality in the general population as advocated by Autier et al.[32].

Digital mammography: the Holy Grail for breast cancer screening?

Digital mammography screening was introduced in 2009 in the Eindhoven screening region. The technique was already available in the early 1980's[33], and the potential for digital mammography to improve the detection performance of radiologists for microcalcifications is already known since the early nineties[34]. Until today screen-film mammography was considered as the gold standard for breast cancer screening[17,35]. There is emerging evidence showing that digital mammography is superior to screen-film mammography with respect to sensitivity, especially in women under the age of 50 years and women with radiographically dense breasts[36,37]. Furthermore, digital mammography significantly improves workflow, especially important in a screening programme. These advantages have lead to the replacement of screen-film mammography by digital mammography in most western screening programmes.
Little is known about the influence of the introduction of digital mammography screening on screening sensitivity and breast cancer mortality. There is little data on interval cancers in the era of digital screening, cancers that arise between two screening rounds after a negative screen[38,39]. The overall higher cancer detection rate at digital screening comes with higher referral rates. Reports on the impact on positive predictive value vary, but on average the higher referral rate to digital mammography increases the number of women falsely referred[40-44]. Consequently, a larger proportion of screened women will experience unnecessary anxiety[24,25,45]. Finally, no data is available on the impact of digital screening on breast cancer mortality.

The scope of this thesis

The main objective of this thesis is the in-depth evaluation of varying aspects of the breast cancer programme in the south of the Netherlands as a way to identify key issues for improvement. This will be done by evaluating classification of breast cancer both detected and missed by mammography screening, as well as by determining the management of referred women with and without breast cancer since 1997.

The specific aims of this thesis are to:

- determine trends in incidence and detection of advanced cancer at screening mammography in the south of the Netherlands (Chapter 2).
- examine trends in the use of biopsies in referred women (Chapter 3.1) and surgical management of screen-detected breast cancer (Chapter 3.2).
- further explore effects of the introduction of digital mammography screening on the following screening outcome parameters:
  - surgical management of invasive and in situ breast cancer;
  - interval cancer rate;
  - characteristics of screen-detected and interval cancers (Chapter 4).

Finally, in chapter 5, the main results of the studies in this thesis are discussed, as well as their significance for the current and future breast cancer-screening programme in (the south of) the Netherlands.

Population, patients and methods

Since the implementation of breast cancer screening in the Eindhoven region in the Southern Netherlands from 1995, screening outcome has been closely monitored and registered. Since the start of the screening programme in 1995, over 700,000 screens have been made in one mobile and one stationary mammography centre (from 2009: 2 mobile centres and 3 mobile centres from 2013). In 1995 nine screening radiologists double read about 15,000 screens. Currently, a team of 13 certified screening radiologists double read 60,000 screens annually.

All data of referred women and those who presented with an interval cancer were recorded in an Excel-database, kept by the screening radiologist Lucien Duijm who is also a radiologist in one of the larger hospitals. This database was used for professional quality assurance of the screening programme in our region as well as for various scientific purposes. Furthermore, ample information is available on coinciding increasing adjuvant and palliative systemic treatment of women with breast cancer in the region[46,47].

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Chapter 2

Trends in incidence and detection of advanced breast cancer at screening mammography in the south of the Netherlands

Published as: Nederend J, *Duijm LE, Voogd AC, Groenewoud JH, Jansen FH, Louwman MW.* ***Trends in incidence and detection of advanced breast cancer at biennial screening mammography in The Netherlands: a population based study.*** *Breast Cancer Res 2012 9; 14: R10.*

Abstract

Background: The aims of this study were to determine trends in the incidence of advanced breast cancer at screening mammography and the potential of screening to reduce it.

Methods: We included a consecutive series of 351,009 screening mammograms of 85,274 women aged 50-75 years, who underwent biennial screening at a Dutch breast screening region in the period 1997-2008. Two screening radiologists reviewed the screening mammograms of all advanced screen-detected and advanced interval cancers and determined whether the advanced cancer (tumour > 20 mm and/or lymph node positive tumour) had been visible at a previous screen. Interval cancers were breast cancers diagnosed in women after a negative screening examination (defined as no recommendation for referral) and before any subsequent screen. Patient and tumour characteristics were compared between women with advanced cancer and women with non- advanced cancer, including ductal carcinoma in situ.

Results: A total of 1,771 screen-detected cancers and 669 interval cancers were diagnosed in 2,440 women. Rates of advanced cancer remained stable over the 12-year period; the incidence of advanced screen-detected cancers fluctuated between 1.5 - 1.9 per 1,000 screened women (mean 1.6 per 1,000) and of advanced interval cancers between 0.8 - 1.6 per 1,000 screened women (mean 1.2 per 1,000). Of the 570 advanced screen-detected cancers, 106 (18.6%) were detected at initial screening; 265 (46.5%) cancers detected at subsequent screening had been radiologically occult at the previous screening mammogram, 88 (15.4%) had shown a minimal sign, and 111 (19.5%) had been missed. Corresponding figures for advanced interval cancers were 50.9% (216/424), 24.3% (103/ 424) and 25.1% (105/424), respectively. At multivariate analysis, women with a > 30 months interval between the latest two screens had an increased risk of screen-detected advanced breast cancer (OR 1.63, 95%CI: 1.07-2.48) and hormone replacement therapy increased the risk of advanced disease among interval cancers (OR 3.04, 95%CI: 1.22-7.53).

Conclusion: We observed no decline in the risk of advanced breast cancer during 12 years of biennial screening mammography. The majority of these cancers could not have been prevented through earlier detection at screening.

Introduction

Most breast cancer deaths are due to advanced disease, diagnosed when it has already spread to lymph nodes or distant organs. Therefore, many countries have introduced breast cancer screening programs in order to detect breast cancer at an early stage. In the Netherlands, a nation-wide biennial screening program for women aged 50-69 years was implemented between 1989 and 1997. In 1998, the upper age limit for breast screening was extended to 75 years. The attendance rate at our screening region is 84%[1].

Several studies have shown that screening mammography is effective in reducing breast cancer mortality[2-4]. However, the authors of a recent comprehensive review stated that the positive results of randomized trials of mammography screening on breast cancer mortality should be interpreted with caution as these trials were carried out in an era before the use of anti-hormonal therapies and before major advances in other aspects of breast cancer treatment[5]. Autier et al. compared breast cancer mortality in 30 European countries and concluded that the reduction in breast cancer mortality was more profound in non-screened women (-37%) than in screened women (-21%)[6]. It remains a question of debate which part of the reduction can be attributed to screening and which part can be explained by other factors, such as the more extensive use of adjuvant systemic treatment[7,8]. Compared with rates in 1986-1988, Otto et al. reported a 19.9% reduction in breast cancer mortality rate in 2001 as a result of routine mammography screening in the Netherlands[4]. Kalager et al. calculated that only one third of the reduction in breast cancer mortality in Norway could be attributed to screening[8]. Jørgensen et al. did not find any effect of breast cancer screening on breast cancer mortality in Denmark and they contributed the lower mortality to changes in risk factors and improved treatment[9].

If a mortality reduction were due to screening rather than the result of adjuvant systemic therapy, one would expect that it is preceded by a decrease in risk of a diagnosis of advanced breast cancer. Screening may not be that effective if no stage shift is observed. Although Fracheboud et al. initially found a significant decrease in the incidence rate of advanced disease in women who participated in the Dutch screening program, they later reported an increase in advanced cancers detected at screening[10,11]. For more recent years of nation-wide screening, the National Evaluation Team for Breast Cancer Screening in The Netherlands found a more or less stable tumour size distribution of screen-detected cancers, as well as a stable rate of lymph node positive breast cancers[12]. Autier et al.[13] observed no significant changes in advanced breast cancer rates in several European countries, despite good participation at screening mammography programs.

So far, no data are available for predictors for a diagnosis of advanced disease. The primary goal of our population based study was to determine the trends in incidence and detection of advanced breast cancer in the Southern Region of the nationwide breast screening program in the Netherlands, during twelve years of biennial screening mammography. We also assessed the proportion of advanced cancers that potentially could have been prevented through earlier detection at screening and we identified patient and tumour characteristics that were related to an increased risk of advanced breast cancer.

Methods

Study population

We included 351,009 consecutive screens (46,155 initial screens and 304,854 subsequent screens) of 85,274 women, who underwent biennial screening mammography at two specialized analogue screening units in the Southern Region (BOBZ, Bevolkings Onderzoek Borstkanker Zuid) of the Dutch nationwide breast cancer screening program between January 1, 1997 and January 1, 2009. All but three women had given written informed consent to use their screening and follow-up data for evaluation purposes. The Central Committee on Research Involving Human Subjects (CCMO) in The Hague, The Netherlands, waived ethical approval for this study.

Screening procedure and referral

Details of our nation-wide breast cancer screening program, offering biennial screening mammography for women aged 50-75 years, are described elsewhere[14,15]. In brief, all mammograms were obtained by specialized screening mammography technologists and independently double read by certified screening radiologists. In the Southern Region, technologists have been actively participating in the assessment of screening mammograms, in addition to the double reading by the radiologists[16]. Fifteen certified screening radiologists were involved, all of who evaluated at least 5,000 screening mammograms yearly. Prior screening mammograms were always available for comparison at the time of subsequent screening. Women were asked to fill in a questionnaire prior to screening mammography with questions about date, type and reason of previous breast surgery, family history of breast cancer and hormonal replacement therapy. For all women with a positive screening mammogram or interval cancer, we recorded the information of this questionnaire in a database that is used for quality assurance of our screening program. We consulted the clinical records of the hospital to which a woman had been referred for the completion of seldom cases of insufficient data.
If screening mammography showed a suspicious or malignant lesion, the woman was referred to a surgical oncologist or breast clinic for further analysis of the mammographic abnormality.

Workup facilities at hospitals

A total of 16 hospitals in the southern region were involved in the diagnostic workup, of which four centrally located hospitals accounted for the workup of 93% (4,137/4,450) of referred women[17]. These four hospitals performed between 2,000-3,500 diagnostic mammographic examinations yearly. Further evaluation depended on the workup protocols and facilities available, and consisted of additional mammographic views, breast ultrasound, magnetic resonance mammography, percutaneous fine needle aspiration or core biopsy (usually image guided), or open surgical biopsy. Outpatient breast clinics were introduced between 1999 and 2007, and systematic discussion of positive screens by a multidisciplinary team of physicians between

2002 and 2007. New diagnostic techniques were also introduced over time, including Magnetic Resonance Mammography (2000-2004), 14-Gauge stereotactic core needle biopsy (2000-2007), axillary ultrasound with lymph node sampling (1998-2000), and 9- or 10-Gauge stereotactic vacuum-assisted core biopsy (2004-2007). One hospital mainly performed ultrasound guided fine needle aspiration cytology of solid breast lesions, whereas the other three hospitals gradually replaced cytology by 14-18 Gauge core biopsies.

Follow-up procedure

During a follow-up period of two years, we collected data on diagnostic and surgical procedures, histopathology and TNM (tumour-node-metastasis) classification[18] of all screen-detected cancers and interval cancers. Interval cancers were defined as breast cancers diagnosed in women after a screening examination yielded negative results (defined as no recommendation for referral) and before any subsequent screen was performed. Procedures for the detection of interval cancers have been described previously[19].

Breast cancers were divided into ductal carcinoma in-situ and invasive cancers; lobular carcinoma in-situ was considered to be a benign lesion. Ductal carcinoma in situ was included in the group of non-advanced breast cancers. Advanced cancers were defined as cancers with TNM stage IIA or higher, i.e. tumour size exceeding 20 mm (T2) and/or presence of lymphatic metastasis in the sentinel node or axillary lymph nodes. Sentinel nodes were classified negative if they harboured isolated tumour cells or sub-micrometastases (<0.2 mm) and were considered positive (N+) if they contained micrometastases (0.2-2 mm) or macrometastases (>2 mm). A further subdivision of advanced cancers in T1N+, T2+N- and T2+N+ was also made to be able to determine a possible effect of the introduction of sentinel node biopsy and concomitant stage migration on our findings analysed our data using different definitions (T1N+, T2+N- or T2+N+) of advanced cancer.

Incidence rates of advanced cancers in the South-eastern Netherlands between 1985 and 2009 were calculated for women aged 50-75 years (whether screened or not) using the population-based Eindhoven Cancer Registry[20].
Invitation letters for screening mammography are routinely sent 23-26 months after the previous screening round. If a woman is not able to attend screening, she is given the opportunity to make a new appointment within 6 months. Screening intervals exceeding 30 months usually involve women who have missed one or more screening rounds. Therefore, we considered a screening interval of more than 30 months to be a prolonged screening interval. For each woman with a screen-detected cancer and a screening interval of more than 30 months prior to the latest screening examination, we determined if she had undergone clinical mammography at any of the hospitals located at our screening region within 30 months prior to final screening. If the latter was the case (n=6), then the woman was considered to have a screen interval of less than 30 months.

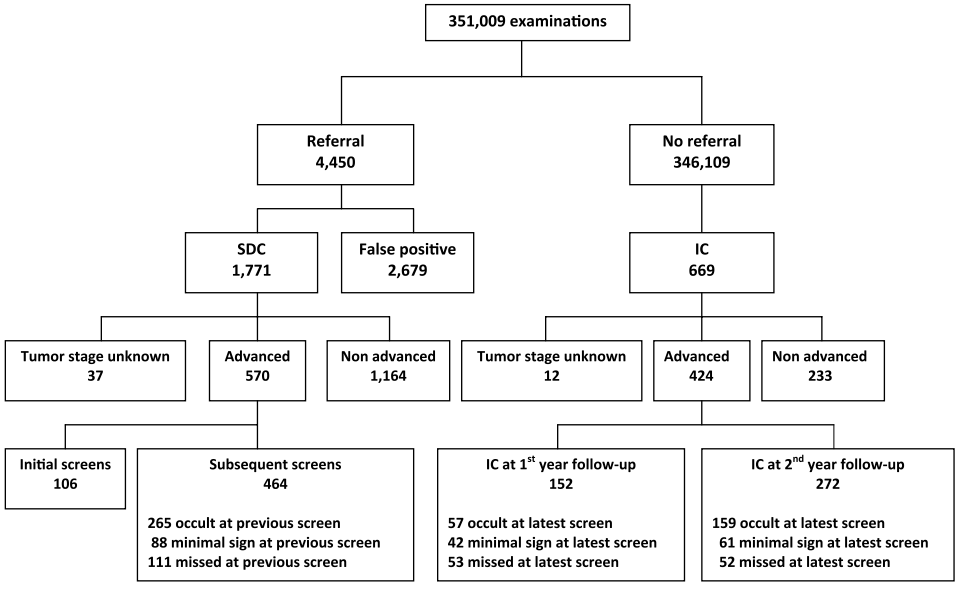
Review of screening mammograms of advanced breast cancers

Two experienced screening radiologists (LD, FJ) reviewed the two most recent screening mammograms of all women with advanced screen-detected breast cancers at a subsequent screen. Older screening examinations were available for comparison if desired by the radiologists. They determined whether or not the cancer had been missed, had shown a minimal sign[21] or had been occult at the previous screen. For each advanced interval cancer, the radiologists correlated the clinical mammogram, on which the interval cancer had been diagnosed, with the latest screening examination and also determined whether the cancer had been visible at the latest screen. The radiologists classified the mammographic abnormality of each advanced breast cancer into one of the following, mutually exclusive, categories:

1. Suspicious high density (e.g., spiculated density or density with indistinct borders);
2. Suspicious microcalcifications (e.g., pleomorphic, branching, or amorphous/indistinct microcalcifications);
3. High density in combination with microcalcifications;
4. Architectural distortion or;
5. Breast parenchyma asymmetry.

Finally, the breast density of the latest screen (and of the last but one screen in case of subsequent screening) was assessed, according to the BI-RADS criteria[22]. The radiologists were initially blinded to each other's review and consensus reading followed discrepant readings.

Figure 1. **Mammography screening outcome at 2-year follow-up**



SDC = screen- detected cancer; IC = interval cancer

Statistical analysis

Statistical analyses were performed per 2-year screening periods. All data were entered into a computerized spreadsheet (Excel; Microsoft, Redmond, WA, USA). Statistics were performed using the SAS program version 9.1.3 (Statistical Analysis Software; SAS/STAT software®, Cary, NC, USA). A double sided t-test was used to test differences between continuous variables, and the χ^2-test to test differences between categorical variables. Logistic regression was performed to investigate which factors significantly affected the risk of a diagnosis of advanced breast cancer among patients with screen-detected and interval breast cancer. The significance level was set at 5%.

Figure 2. **Time trend in incidence of advanced breast cancer among women aged 40-49 years and 50-75 years in southeastern Netherlands, 1980-2009**

Results

Overall screening results

The biennial number of screening examinations gradually increased from 48,721 (1997/1998) to 67,530 (2007/2008) and the biennial referral rate varied between 0.9% and 1.6% (mean 1.3%). Breast cancer was diagnosed in 1,771 of 4,450 referred women (including 287 ductal carcinomas in situ), resulting in an overall cancer detection rate of 5.1 per 1,000 screens and an overall positive predictive value of 39.8% (Table 1, Figure 1). In addition, 669 interval

cancers (including 27 ductal carcinomas in situ) were diagnosed. Mean sensitivity of breast cancer screening was 72.6% (1,771/2,440). Screening sensitivity was higher for non-dense breasts (ACR breast density category I+II), that is, 75.3% (1,189/1,580), than for dense breasts (ACR breast density category III+IV), that is, 67.7% (582/860) ($p < 0.001$). The proportion of advanced cancers among all cancers was 40.7% (994/2,440). This proportion did not change significantly through the years and ranged from 37.8% (1997/1998) to 45.5% (2001/2002) ($p = 0.6$, Table 1). Visibility of screen-detected cancers and interval cancers on previous screening rounds remained constant during the twelve year screening period and the proportion of occult cancers, minimal signs and missed cancers for both groups neither changed ($p = 0.4$ and $p = 0.5$, respectively). Figure 2 shows that the ESR standardized rate for advanced cancer was stable between 1985-2009 and showed no decline after the introduction of screening mammography in southeastern Netherlands.

Advanced breast cancers detected at screening

Of screen-detected cancers, 570 were advanced cancers and 1,164 non advanced cancers. The tumour stages of the remaining 37 screen-detected cancers could not be properly classified, including TxN- cancers (negative lymph nodes but unknown tumour size) and T1Nx cancers (invasive cancers <20 mm with unknown lymph node status); these were excluded from further analysis. The proportion of advanced screen-detected cancers per 2-year screening period fluctuated between 28.7% (2003/2004) and 35.4% (2007/2008) ($p=0.6$, Table 1). Univariate analysis showed no statistically significant differences between women with advanced or non-advanced breast cancer regarding family history of breast cancer, use of hormone replacement therapy, percentage initial screens, interval between screens, prior visibility or breast density (Table 2). Compared to non-advanced cancers, advanced screen-detected cancers were more frequently characterized by abnormal densities and less frequently by suspicious microcalcifications at screening ($p<0.001$) and comprised more invasive lobular cancers and fewer invasive ductal cancers ($p<0.001$, Table 2).

After adjustment for all other variables (Table 3), we found that an interval of 30 months or more between the latest two screens was associated with increased risk of advanced screen-detected breast cancer (OR 1.63, 95% CI: 1.07-2.48). High breast density was borderline significantly associated with increased risk of advanced breast cancer (OR 1.25, 95% CI: 0.99-1.57), as was a family history of breast cancer (OR 1.20, 95% CI: 0.93-1.56).

Of the 570 advanced screen-detected cancers, 106 (18.6%) had been detected at the initial screen and 464 (81.6%) at a subsequent screen. Of the latter, 265 (57.1%) were considered mammographically occult at the last but one screen at retrospect; whereas 88 (19.0%) showed a minimal sign and 111 (23.9%) were missed at the last but one screen. Thus, at least 65.1% (106+265/570) of advanced cancers could not have been diagnosed at an earlier stage. We observed no significant changes in the proportions of T1N+, T2+N- and T2+N+ screen-detected cancers during our twelve-year screening period (Figure 3).

Advanced interval breast cancers

Advanced breast cancers comprised 63.4% (424/669) of all interval cancers (Figure 1). Of advanced interval cancers, 35.8% (152/424) were diagnosed in the first year after the latest negative screen, and 64.2% (272/424) in the second year. Of interval cancers diagnosed in the first or the second year after the latest negative screen, respectively 65.0% (152/234, 95%CI: 58.8–72.1) and 62.5% (272/435, 95%CI: 60.0–67.1) were advanced cancers. At review, 50.9% (216/424) of advanced interval cancers were considered mammographically occult at the latest screen, whereas 103 (24.3%) showed a minimal sign and 105 (24.8%) had been missed. At univariate analysis, we found no significant difference between advanced and non-advanced interval cancers in family history of breast cancer, percentage initial screens, interval between screens, prior visibility, tumour histology, or breast density (Table 2). Compared to the non-advanced cancers, advanced interval cancers were more frequently characterized by breast parenchymal asymmetries and less frequently by suspicious microcalcifications or abnormal densities ($p = 0.04$) and more women with advanced interval cancer used hormone replacement therapy ($p = 0.005$), (Table 2). The use of hormone replacement therapy was an independent risk factor for advanced breast cancer at multivariate analysis (OR 3.04, 95% CI: 1.22-7.53, Table 3). Similar to advanced screen-detected cancers, we found no significant changes in the proportions of T1N+, T2+N- and T2+N+ interval cancers during twelve years of screening (Figure 3).

Figure 3. **Distribution of breast cancer stage at 6 consecutive 2-year screening periods**

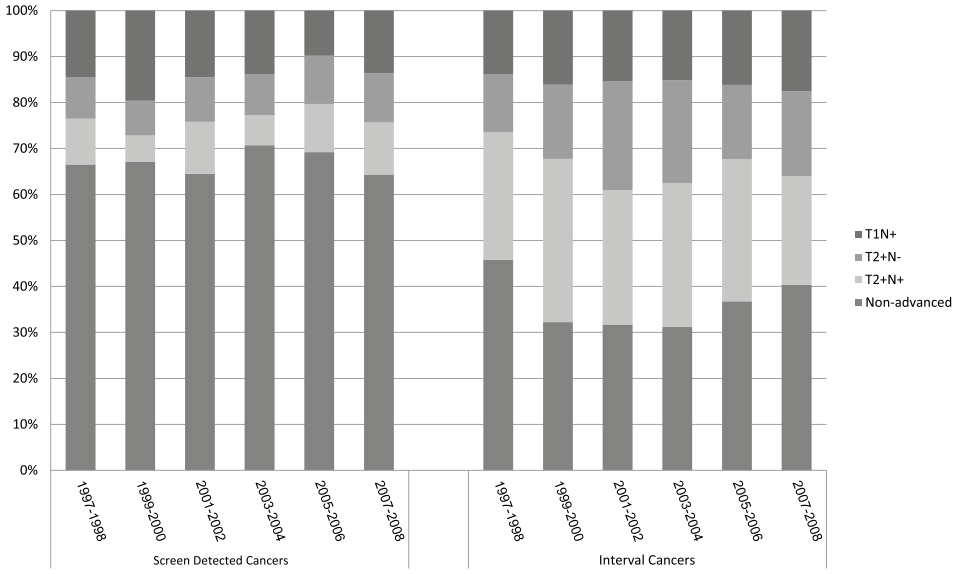


Table 1. **Screening results at 6 consecutive 2-year screening periods**

Screening period	**1997/1998**	**1999/2000**
Mammograms, No	48,721	53,718
Referral, No	536	499
Referral rate, % (95% CI)	1.1 (1.0-1.2)	0.9 (0.9-1.0)
Screen detected breast cancers, No	224	274
Advanced cancers, No (rate*; 95% CI)	74	87
	(1.5; 1.2-1.9)	(1.6; 1.3-2.0)
Non-advanced cancers, No (rate*; 95% CI)	147	178
	(3.0; 2.5-3.5)	(3.3; 2.8-3.8)
Unknown tumor stage, No (rate*; 95% CI)	3	9
	(0.1; 0.0-0.1)	(0.2; 0.1-0.3)
Cancer detection rate* (95% CI)	4.6 (4.0-5.2)	5.1 (4.5-5.7)
PPV of referral, % (95% CI)	41.8 (37.6-46.0)	54.9 (50.8-59.5)
Interval cancers, No	75	94
Advanced cancers, No (rate*; 95% CI)	39	63
	(0.8; 0.5-1.1)	(1.2; 0.9-1.5)
Non-advanced cancers, No (rate*; 95% CI)	33	30
	(0.7; 0.4-0.9)	(0.6; 0.4-0.8)
Unknown tumor stage, No (rate*; 95% CI)	3	1
	(0.1; 0.0-0.1)	(0.0; 0.0-0.1)
Sensitivity, % (95% CI)	74.9 (70.3-80.1)	74.5 (70.0-78.9)
Proportion of advanced cancers among screen detected cancers + interval cancers, % (95% CI)	37.8 (32.4-43.4)	40.7 (36.3-46.3)

*per 1,000 women screened; CI = confidence interval; PPV = positive predictive value

Table 1. **Screening results at 6 consecutive 2-year screening periods** *(continued)*

2001/2002	2003/2004	2005/2006	2007/2008	Total
53,489	61,251	66,300	67,530	351,009
553	985	874	1003	4450
1.0 (1.0-1.1)	1.6 (1.5-1.7)	1.3 (1.2-1.4)	1.5 (1.4-1.6)	1.3 (1.2-1.3)
254	345	321	353	1,771
88	99	97	125	570
(1.6; 1.3-2.0)	(1.6; 1.3-1.9)	(1.5; 1.2-1.8)	(1.9; 1.5-2.2)	(1.6; 1.5-1.8)
160	239	218	222	1,164
(3.0; 2.5-3.5)	(3.9; 3.4-4.4)	(3.3; 2.9-3.7)	(3.3; 2.9-3.7)	(3.3; 3.1-3.5)
6	7	6	6	37
(0.1; 0.0-0.2)	(0.1; 0.0-0.2)	(0.1; 0.0-0.2)	(0.1; 0.0-0.2)	(0.1; 0.1-0.1)
4.7 (4.2-5.3)	5.6 (5.0-6.2)	4.8 (4.3-5.4)	5.2 (4.7-5.8)	5.1 (4.8-5.3)
45.9 (41.9-50.2)	35.0 (32.0-38.0)	36.7 (33.5-39.9)	35.2 (32.1-38.0)	39.8 (38.3-41.2)
128	116	139	117	669
86	79	87	70	424
(1.6; 1.3-1.9)	(1.3; 1.0-1.6)	(1.3; 1.0-1.6)	(1.0; 0.8-1.3)	(1.2; 1.1-1.3)
39	35	50	46	233
(0.7; 0.5-1.0)	(0.6; 0.4-0.8)	(0.8; 0.5-1.0)	(0.7; 0.5-0.9)	(0.7; 0.6-0.7)
3	2	2	1	12
(0.1; 0.0-0.1)	(0.0; 0.0-0.1)	(0.0; 0.0-0.1)	(0.0; 0.0-0.0)	(0.0; 0.0-0.1)
66.5 (61.8-71.2)	74.8 (70.9-78.8)	69.8 (65.6-74.0)	75.1 (72.0-79.8)	72.6 (71.0-74.5)
45.5 (40.0-50.0)	38.6 (34.2-43.1)	39.9 (35.7-44.7)	41.5 (37.0-46.0)	40.7 (38.8-42.7)

Table 2. **Characteristics of women with breast cancer**

	Screen detected cancer			Interval cancer		
	Advanced N = 570	Non-advanced N = 1,164	P-value	Advanced N = 424	Non-advanced N = 233	P-value
Mean age, years (95%CI)	62.0 (61.3 – 62.6)	62.4 (62.0 – 62.8)	0.24	59.5 (58.9 – 60.2)	59.3 (58.4 – 60.2)	0.76
Family history of breast cancer[±], No (%)	123 (21.6)	218 (18.7)	0.16	76 (17.9)	43 (18.5)	0.87
Previous breast surgery[#]	58 (10.0)	130 (11.2)	0.53	72 (15.6)	34 (15.0)	0.43
Use of hormone replacement therapy, No (%)	59 (10.4)	95 (8.2)	0.13	70 (13.1)	20 (6.3)	0.005
Initial screens, No (%)	106 (18.6)	183 (15.7)	0.13	64 (13.5)	32 (11.8)	0.64
Interval between 2 latest screens, No (%)			0.08	-	-	
< 30 months	527 (92.5)	1,101 (94.1)				
≥ 30 months	43 (7.5)	63 (5.4)				
Breast density at latest screening mammogram, No (%)			0.45			0.49
≤50%	375 (65.8)	787 (67.4)		243 (60.7)	140 (60.1)	
>50%	195 (34.2)	377 (32.4)		181 (39.3)	93 (39.9)	
Mammographic abnormality, No (%)			< 0.001			0.04
Density	426 (74.8)	740 (63.6)		133 (64.6)	78 (70.9)	
Microcalcifications	35 (6.1)	280 (24.1)		26 (12.6)	18 (16.4)	
Density with microcalcifications	82 (14.4)	112 (9.6)		16 (7.8)	6 (5.5)	
Architectural distortion	22 (3.9)	24 (2.1)		11 (5.3)	7 (6.4)	
Breast parenchyma asymmetry	4 (0.9)	8 (0.7)		20 (9.7)	1 (0.9)	
Breast cancer visible at previous screening mammogram	199 (42.9)*	418 (42.7)[¥]	0.95	208 (47.6)	112 (47.4)	0.81
Tumor histology of invasive cancers, No (%)			< 0.001			0.09
Ductal	414 (72.6)	682 (77.7)		304 (71.8)	155 (77.7)	
Lobular	93 (16.3)	85 (9.7)		87 (21.3)	30 (10.9)	
Mixed ductal-lobular	37 (6.5)	41 (4.7)		18 (4.0)	10 (5.9)	
Invasive other	24 (4.2)	68 (7.7)		11 (2.0)	11 (5.5)	
Unknown	2 (0.4)	2 (0.2)		4 (0.9)	0 (0.0)	

[±]At least one first-degree relative (mother, sister, daughter) with a diagnosis of breast cancer before the age of 50 years or at least two second-degree relatives with breast cancer

[#]Surgery for benign conditions (e.g., excisional biopsy, breast reduction, breast augmentation, mastitis) and malignant conditions (lumpectomy, mastectomy)

*464 subsequent screens; [¥]979 subsequent screens

Table 3. **Odds of having advanced breast cancer among women with breast cancer, each variable adjusted for all others**

		Advanced vs. non-advanced screen detected cancers			Advanced vs. non-advanced interval cancers		
		OR	95%CI	P-value	OR	95%CI	P-value
Age	50-59	1			1		
	60-69	0.73	0.57-0.95	0.02	1.41	0.80-2.48	0.2
	70+	0.83	0.61-1.12	0.2	0.71	0.33-1.52	0.4
Family history of breast cancer	No	1			1		
	Yes	1.20	0.93-1.56	0.16	1.24	0.66-2.33	0.5
Previous breast surgery	No	1			1		
	Yes	0.90	0.64-1.26	0.5	0.90	0.41-2.04	0.8
Use of hormone replacement therapy	No	1			1		
	Yes	1.16	0.80-1.68	0.4	3.04	1.22-7.53	0.02
Initial screen	No	1			1		
	Yes	1.19	0.88-1.61	0.2	0.91	0.41-2.04	0.8
Interval between 2 latest screens							
< 30 months		1			-		
> 30 months		1.63	1.07-2.48	0.02			
Breast density at latest screening mammogram							
<50%		1			1		
>50%		1.25	0.99-1.57	0.06	1.03	0.62-1.72	0.9
Mammographic abnormality							
Density		1			1		
Microcalcifications		0.20	0.14-0.29	0.0001	1.41	0.64-3.13	0.4
Density with microcalcifications		1.24	0.91-1.69	0.2	0.39	0.11-1.42	0.2
Architectural distortion		1.49	0.82-2.72	0.2	0.98	0.35-2.73	1.0
Breast parenchyma asymmetry		0.79	0.23-2.66	0.7	1.43	0.52-3.94	0.5
Tumor histology of invasive cancers[1]							
Ductal		1			1		
Lobular		2.00	1.44-2.78	0.0001	1.48	0.70-3.14	0.3
Mixed ductal-lobular		1.55	0.97-2.48	0.07	0.65	0.20-2.06	0.5
Invasive other		0.63	0.39-1.02	0.07	0.84	0.21-3.32	0.8
Unknown		1.70	0.23-12.3	0.6	-[2]		

1. Calculated for invasive cancers only

2. Not calculated because all 4 patients with unknown histology had advanced breast cancer

Discussion

During twelve years of biennial screening, we did not observe a decline in advanced breast cancers. After review of previous mammograms, it had to be concluded that the majority of advanced breast cancers could not have been detected at an earlier tumour stage. Multivariate analysis showed that a screening interval of 30 months or more significantly increased the risk of detecting breast cancer in an advanced stage.

In a meta-analysis on randomized controlled mammography screening trials, Autier et al. calculated an equal decrease in breast cancer mortality for each unit decrease in incidence of advanced breast cancer[23]. We expected to find a reduction of advanced cancers in our screened population over time, as a result of increasing experience of the screening radiologists, continuous quality assurance, introduction of additional film reading by technologists and the increased use of 2-view mammography at subsequent screening mammography[16,24]. The incidence rate of advanced screen-detected cancers and advanced interval cancers remained constant in our study and this finding is in line with a recent meta-analysis of regional and nation-wide screening programs, where annual per cent changes in advanced breast cancer were stable or even increasing back to pre-screening rates[13]. As expected, the incidence of advanced breast cancer was lower in subsequent screens due to lead-time.

The majority of advanced cancers in our biennial screening program of women aged 50-75 years could not have been detected earlier. More than half of advanced breast cancers detected at a subsequent screen were not visible at previous screening mammography. This high percentage may partly be due to our definition of advanced cancer, which included small (<20 mm) but lymph node positive invasive cancers. Almost one-fifth of all advanced screen-detected cancers had been discovered during the first screening round.

A previous study showed that the introduction of sentinel node biopsy in the Southeast region of The Netherlands had led to stage migration, as was reflected by an increased proportion of patients with positive axillary lymph nodes after adjustment for tumour size and age[25]. In order to prevent bias in our findings by this stage migration, we therefore analysed our data using different definitions of advanced breast cancer. We found no decrease in advanced cancers over time, neither when advanced cancers were defined as invasive tumours exceeding 20 mm in size, nor when a definition of lymph node positive tumours was used for advanced cancers. Although introduction of the sentinel node technique has changed the diagnostic procedure for lymph node involvement, it is likely that determination of tumour size has remained constant over time and across institutions.

Almost 20% of our advanced screen-detected cancers showed a minimal sign at the previous screen. Earlier referral of these women may potentially decrease the proportion of advanced cancers. However, minimal signs were found to be present in 10% of screening mammograms, whereas less than 1% of these lesions turned out to be malignant[21]. The Dutch screening program would no longer be cost-effective if all these women are being referred[26]. Moreover, the maximum reduction in advanced cancers will probably be less than 20% as some minimal signs may be early signs of already advanced tumours, and thus will compromise the gain.

One quarter of advanced screen-detected cancers had been missed at the previous screening

examination and this proportion did not change significantly over time. In 2009, just after the end of our study, digital units replaced the two analogue screening units in the Southern Region. Moreover, independent double reading has been replaced by blinded double reading and all screening radiologists receive information about their individual screening performance at regular intervals. Full-field digital mammography has been shown to have similar or higher sensitivity and higher specificity than conventional mammographic screening and may ultimately lead to a decrease of advanced cancers detected at screening[27,28]. The introduction of digital screening in the Netherlands has resulted in increased referral rates and increased overall cancer detection rates[29,30]. The ultimate impact of all these changes on the future incidence of advanced cancers at screening mammography is not yet known.

At multivariate analysis, a prolonged screening interval was independently associated with advanced screen-detected breast cancer and women aged 60-69 were also at risk of being diagnosed with advanced cancer. Further research on the reasons for skipping one or several screening rounds is needed in the effort to maximize screening adherence and thus minimize extended intervals between two screens. Cancers characterized by suspicious microcalcifications at screening were associated with a lower risk of advanced screen-detected cancer, which can be explained by the fact that ductal carcinoma in-situ frequently shows microcalcifications as the only mammographic abnormality. This finding confirms the high sensitivity of mammography for the detection of calcium deposits that are typical of ductal, often in situ, non-dangerous breast cancers. Screening sensitivity is lower in dense breasts and, in our study; high breast density was borderline significantly associated with advanced cancer detected at screening. Postmenopausal women taking hormone replacement therapy are at increased risk of breast cancer[31,32] and, in our study, in women with interval cancers, hormone therapy was associated with an increased risk of having the cancer diagnosed at an advanced tumour stage. Tumour histology differed significantly between advanced cancers and early cancers detected at screening. Invasive lobular cancer was diagnosed more frequently in the advanced cancer group. Compared to invasive ductal cancers, invasive lobular cancers are more difficult to detect at mammography as these tumours more commonly present as subtle architectural distortions or focal asymmetric densities resembling that of normal breast parenchyma, or show no mammographic abnormalities at all[33].

The percentage of advanced cancers among women with interval breast cancer was almost twice the percentage of advanced cancers among women with screen-detected cancer and also remained stable throughout our twelve-year screening period. Our observation that tumour stages of interval cancers were worse than those of screen-detected cancers is expected and in line with previous reports[34,35]. Similar to advanced cancers detected at screening, half of the advanced interval cancers were mammographically occult at the latest screen and another quarter had been missed. Other studies also retrospectively classified 20-35% of all interval cancers as missed cancers[36,37]. Our observation of a similar proportion of advanced interval cancers among the total group of interval cancers diagnosed in the first and second year is in line with the findings reported by Porter et al[37]. The finding that a majority of both early stage and advanced interval cancers were diagnosed in the second year after the latest negative screen suggests that shortening of our screening interval may potentially lower the number of

advanced interval cancers. For screen-detected cancers however, two US studies found no increase in late-stage disease for women aged 50 years or older with a 2-year versus 1-year screening interval[38,39]. Moreover, annual screening will be more expensive and the concomitant larger numbers of false positive referrals probably increases patient anxiety and thus may have a negative impact on future screening adherence. For these reasons, investigators still argue about the optimal screening interval[40].
In the Netherlands, the incidence of breast cancer is still increasing, with a current lifetime risk of 13%41. Although screening is effective in reducing breast cancer mortality, a possible future decrease in breast cancer mortality in screened women may rather be the result of advances in breast cancer treatment than the result of improved detection at screening mammography. Moreover, the rate of advanced cancer after implementation of screening mammography was comparable to pre-screening rates. Another detrimental effect of screening is the generation of false positive referrals, leading to increased levels of anxiety and additional diagnostic work-up costs[42,43]. Finally a potential harmful effect of screening is the phenomenon of so-called over-diagnosis of breast cancers, i.e. diagnosis of breast cancers that if left undiscovered, would never become clinically evident and, thus, would never become lethal[44,45].
While non-advanced cancer rates have increased since the introduction of screening[20], we did not observe an expected decrease in advanced breast cancer rates. This finding may partly be explained by differences in tumour biology between non-advanced cancers and advanced cancers and our results suggest that screening may not be effective in detecting highly proliferative, aggressive breast cancers at an early stage. The stable rate of advanced cancers in our study also implies that a significant portion of breast cancers detected at screening represents over-diagnosis. A gradual increase in advanced breast cancer rate was observed in women below 50 years of age and this upward trend may reflect an underlying increase in background incidence of advanced disease.

Our study has several strengths and limitations. To our knowledge, this is the first study with virtually complete follow-up in which we determined the percentage of unavoidable advanced cancers at screening and assessed risk factors for advanced cancer at an individual level. Unfortunately, a stratified analysis of stage III and IV tumours was not possible due to low numbers of these cancers in our study. Furthermore, extrapolation of our results to other screening programs may be limited as the study designs of these programs show considerable variations. For example, the Dutch nation-wide screening program is characterized by a much lower referral rate than that of other screening programs. Moreover, 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 are screened every 3 years in the UK and US programs often offer annual screening[2,46].
In summary, we found no decline in advanced screen-detected cancers and advanced interval cancers during twelve years of screening mammography and a majority of these advanced cancers could not be prevented at biennial screening. In order to obtain a modest reduction of advanced cancers detected a screening, efforts are needed to minimize extended screening intervals.

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Chapter 3

Trends in the management of women referred at screening mammography in the south of the Netherlands

Chapter 3.1

Trends in breast biopsies for abnormalities detected at screening mammography

Published as: *van Breest Smallenburg V,* ***Nederend J,*** *Voogd AC, Coebergh JW, van Beek M, Jansen FH, Louwman WJ, Duijm LE.* ***Trends in breast biopsies for abnormalities detected at screening mammography: a population-based study in the Netherlands.*** *Br J Cancer. 2013 Jul 9;109(1):242-8. doi: 10.1038/bjc.2013.253. Epub 2013 May 21.*

Abstract

Background: Diagnostic surgical breast biopsies have several disadvantages; therefore, they should be used with hesitation. We determined time trends in types of breast biopsies for the workup of abnormalities detected at screening mammography. We also examined diagnostic delays.

Methods: In a Dutch breast cancer screening region 6230 women were referred for an abnormal screening mammogram between 1 January 1997 and 1 January 2011. During two-year follow-up clinical data, breast imaging-, biopsy-, surgery- and pathology- reports were collected of these women. Furthermore, breast cancers diagnosed 43 months after referral (delays) were examined, this included review of mammograms and pathology specimens to determine the cause of the delays.

Results: In 41.1% (1997–1998) and in 44.8% (2009–2010) of referred women imaging was sufficient for making the diagnosis ($p<0.0001$). Fine-needle aspiration cytology decreased from 12.7% (1997–1998) to 4.7% (2009–2010) ($p<0.0001$), percutaneous core-needle biopsies (CBs) increased from 8.0 to 49.1% ($p<0.0001$) and surgical biopsies decreased from 37.8 to 1.4% ($p<0.0001$). Delays in breast cancer diagnosis decreased from 6.7 to 1.8% ($p = 0.003$).

Conclusion: The use of diagnostic surgical breast biopsies has decreased substantially. They have mostly been replaced by percutaneous CBs and this replacement did not result in an increase of diagnostic delays.

Introduction

Breast cancer is worldwide the most frequently diagnosed cancer, and the leading cause of cancer death among females[1]. Also in the Netherlands, breast cancer is an important threat for public health. Breast cancer incidence in the Netherlands is among the highest in the world with the age-standardised rate being 128 out of 100000 person years (European Standardised Rate) and the incidence is still increasing[2]. Breast cancer survival has, fortunately, improved over the last decades[3-5], and this improved survival is probably due to the introduction of mammography screening and improvements in breast cancer treatment[5,6]. In the Netherlands, women aged 50–75 years are invited every 2 years to undergo mammography screening and in case of a mammographic abnormality, women are referred to a hospital for further diagnostic workup. This workup may consist of additional imaging and biopsy. There are various breast biopsy procedures, including percutaneous fine-needle aspiration cytology (FNAC), percutaneous core-needle biopsy (CB) (ultrasound-guided or stereotactic vacuum-assisted) and invasive surgical biopsy. Surgical biopsies for diagnostic purposes should be omitted, as they increase unnecessary psychological distress in false-positive referrals[7,8] and benign breast surgery complicates interpretation of subsequent mammograms due to postoperative changes[9-13]. Surgical biopsy should also not be used for histological confirmation of a radiologically suspicious or malignant lesion. Confirmation of breast cancer by percutaneous biopsy allows a better preoperative planning[14,15] and it is associated with a lower likelihood of multiple breast surgeries[16,17]. In the current population- based study, we determined time trends in types of breast biopsies for abnormalities detected at screening mammography. We also determined the proportion of referred women who experienced a delay in breast cancer diagnosis and examined the causes of these delay.

Methods

Study population

We included all women who were referred after screening mammography at one of two specialised screening units (one fixed unit and one mobile unit) in a breast cancer screening region in the south of the Netherlands between 1 January 1997 and 1 January 2011. Women participating in the Dutch screening programme are asked to give written informed consent regarding the use of their screening and follow-up data for evaluation purposes. All women, except for three, approved. The three women who did not approve were not included in our study population. According to the Dutch Central Committee on Research involving Human subjects, institutional review board approval was not required for our type of study.

Screening procedure and diagnostic workup. Details of the nation-wide breast cancer screening programme have been described previously[18,19]. The Dutch nation-wide breast cancer screening programme offers biennial screening mammography to women aged 50–75 years. Digitisation of the breast cancer screening programme has recently been completed and

in our breast screening region, transformation from analogue to digital screening took place in May 2009. Specialised screening mammography radiographers obtained all mammograms in this study, and a group consisting of 12 certified screening radiologists independently double read the examinations. Each of the screening radiologists evaluates at least 5000 screening mammograms yearly. From 2003, in addition to radiologist double reading, the radiographers also actively participated in the assessment of the screening mammograms[20]. Prior screening mammograms were always available for comparison in case of subsequent screening. In case of suspicious or malignant findings at screening mammography, the woman was referred by her general practitioner to a surgical oncologist at a regional hospital. A total of 16 hospitals were involved in the diagnostic workup of the referred women. The women underwent a physical examination by an oncologist, which was followed by mammographic workup of all suspect areas. The radiologist classified the radiological findings according to the American College of Radiology BI-RADS[21] and decided whether additional procedures such as breast ultrasonography, MRI and/or biopsy were indicated. The choice of additional procedures depended on the diagnostic workup protocols and the facilities available at the specific hospital involved in the workup. The radiologists' decision furthermore depended on national guidelines. In 2000, the first Dutch national guideline for breast cancer screening was published. This guideline required a target for preoperative diagnoses in women with suspected breast cancer of at least 70%. The guideline also suggested that one should use a percutaneous method, either FNAC or CB, for making the preoperative diagnosis[22]. In 2008, a new guideline increased the target for preoperative diagnoses to 90%[23]. Radiologists always performed biopsy of non-palpable lesions in our study population, whereas sampling of palpable lesions was done either by surgeons or radiologists. During the 14-year period of our study, various breast biopsy procedures were used for the diagnostic workup, including FNAC, CB (ultrasound-guided or stereotactic vacuum-assisted) and open surgical biopsy. Between 1999 and 2007, out-patient breast clinics became available at the hospitals involved in this study and between 2002 and 2007 multidisciplinary teams were implemented for the routine evaluation of the clinical, radiological and biopsy results of all referred women.

Follow-up procedure

For each referred woman, we collected data on radiology, pathology and surgical procedures at the hospitals where the mammographic screening abnormalities were evaluated. The follow-up period for all screened women included the time through the next screening round (the screening interval was >2 years).

Delay in breast cancer diagnosis. A definite diagnosis of breast cancer 43 months after referral was considered as a diagnostic delay[24]. To determine whether a diagnostic delay could be attributed to an erroneous radiologic assessment, two breast radiologists (LD, FJ) independently reviewed the clinical breast images of all women with a diagnostic delay. Each reviewer classified the lesions according to BI-RADS and discrepant assessments were resolved by consensus reading. To determine whether a delay in cancer diagnosis could be attributed to a false- ne-

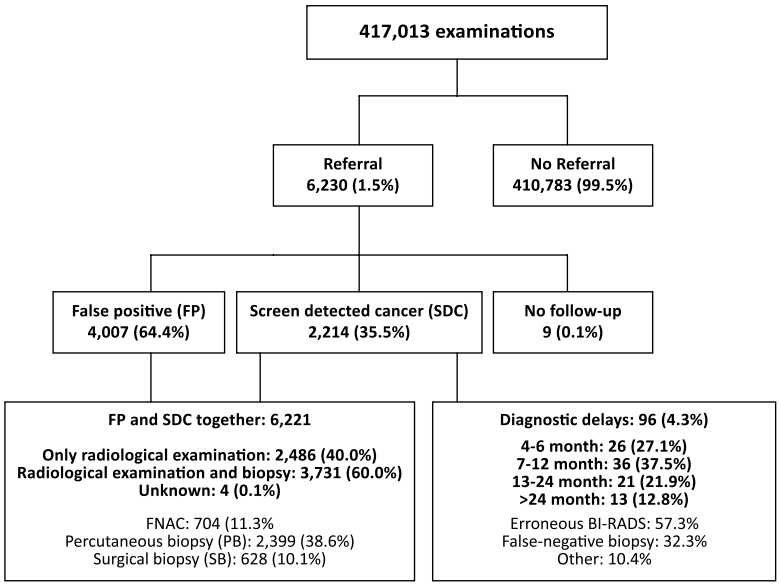
gative histopathological result, a pathologist reviewed the biopsy specimen of women with a delay in breast cancer diagnosis who had had a prior breast biopsy with benign outcome. False-negative results due to erroneous pathologic assessments and due to sampling errors were both regarded as false-negative biopsy results. At review, both the radiologists and the pathologist knew that they reassessed cases with a delay in cancer diagnosis.

Statistical analysis

Statistical analyses were performed per 2-year screening periods. The primary outcome measures were the time trends of imaging only, FNAC, percutaneous CBs, surgical biopsies at workup and the percentage of women who experienced a delay in breast cancer diagnosis. All data were entered into a computerised spreadsheet (Excel; Microsoft, Redmond, WA, USA). Statistics were performed using the SAS programme version 9.1.3 (Statistical Analysis Software; SAS/STAT Software, Cary, NC, USA). A χ^2-test was used to test the differences between categorical variables. Mean age according to hospital was tested using the ANOVA model. A regression analysis was performed to calculate odds ratios and their confidence intervals for determination of time trends in various breast biopsy types, adjusting for age and hospital. The significance level was set at 5%.

Results

Figure 1. **Mammography screening outcome January 1997- January 2011**



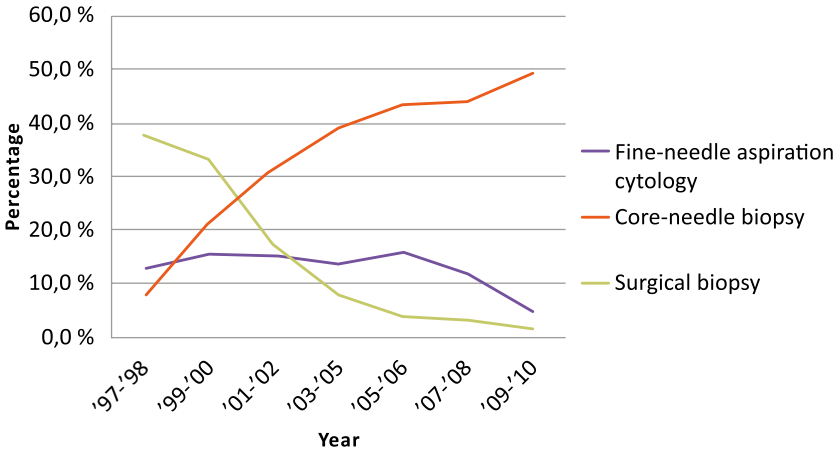
Overall screening results

From 1 January 1 1997 to 1 January 2011 a total of 417 013 screening examinations had been performed (Figure 1). Altogether, 6230 women were referred for further diagnostic workup of a mammographic abnormality (referral rate, 1.5%). Breast cancer was diagnosed in 2214 referred women, yielding a cancer detection rate of 5.3 per 1000 screening examinations and a true-positive referral rate of 35.5%. Nine women had either not been referred by their general practitioner or their follow-up was unknown, and 4007 (64.4%) women had a benign outcome (i.e., false-positive referrals).

Diagnostic workup after referral

In 2486 (40.0%) of the 6230 referred women, evaluation of the abnormality detected at screening mammography consisted of imaging only (additional mammographic views, breast ultrasonography and/or MRI). In the remaining 3731 (60.0%) women, imaging was not sufficient for the establishment of a final diagnosis. Many women underwent a combination of biopsy types because of inconclusive results from FNAC and/or percutaneous CB (Table 1). A final diagnosis was obtained by FNAC in 704 (11.3%) referred women, by CB in 2399 (38.6%) women and by surgical biopsy in 628 (10.1%) women (Table 1). The use of FNAC sharply decreased in the final years of the study period; in 1997–1998 12.7% (68 out of 535) of the

Figure 2. **Trends in biopsy procedures after referral, January 1997-January 2011**



diagnoses was made by FNAC, compared with 4.7% (84 out of 1777) in 2009–2010 ($p < 0.0001$) (Figure 2). The percentage of women with a diagnosis obtained by CB increased from 8.0% (202 out of 535) in 1997–1998 to 49.1% (24 out of 1777) in 2009–2010 ($p < 0.0001$). Simultaneously, the percentage with a diagnosis made by surgical biopsy decreased from 37.8% (70 out of 535) in 1997– 1998 to 1.4% (20 out of 1777) in 2009–2010 ($p < 0.0001$) (Table 1, Figure 2). Also after adjustment for age and hospital, FNAC significantly decreased, diagnoses made by percutaneous CBs significantly increased and surgical biopsies significantly decreased (Table 2). The mean age of referred women was 60 and this was comparable between the 16 hospitals ($p = 0.3$). Main reasons for performing a surgical biopsy in women referred in 2009–2010 were possible (pre)cancerous lesions or inconclusive results at FNAC or CB (19 out of 24, 79.2%).

Diagnostic delays

In 96 of the 2214 women with breast cancer (4.3%), the diagnosis was made >3 months after referral. This delay in breast cancer diagnosis was 4–6 months in 26 (27.1%) women, 7–12 months in 36 women (37.5%), 13–24 months in 21 women (21.9%) and >24 months (24–28 months) in 13 women (13.8%). Most women presented with a delay within 12 months because a follow-up had been recommended at the assessment after referral from screening. The causes of the delays, the tumour stage distribution and axillary lymph node status are presented in Table 3. A total of 27 women with a delay (28.1%) had an advanced tumour stage at the time of diagnosis (advanced cancers were defined as invasive cancers with a tumour size >20 mm (T2) and/ or the presence of metastasis in axillary lymph nodes). The total amount of women with a diagnostic delay decreased, from 6.7% (15 out of 224) in 1997–1998 to 1.8% (8 out of 344) in 2009–2010 ($p = 0.003$). The majority of the diagnostic delays resulted from an erroneous BI-RADS assessment (57.3%, 55 out of 96) or false- negative biopsy result (32.3%, 31 out of 96). Ten delays resulted from other reasons, including errors made by surgeons and patient-related delays. The majority of the delays (68.8%) that resulted from false-negative biopsies consisted of CB. Details of the biopsy procedures are also presented in Table 3. The pathologist reported that all false-negative biopsy results were due to sampling errors and not the result of erroneous pathologic assessments.

Discussion

Surgical biopsies for diagnostic purposes have several disadvantages. We have reported in earlier studies that benign breast surgery, including surgical biopsy, can result in a lower sensitivity for breast cancer detection at subsequent screening mammography[12,13]. Furthermore, invasive assessments increase the unnecessary psychological distress of false-positive referrals[7,8]. In malignant cases, it is also desirable to avoid diagnostic surgical biopsies as a preoperative confirmation of breast cancer gives the patient and surgeon the possibility to discuss treatment options. A preoperative diagnosis also allows a better surgery planning[14,15] and it is associated with a lower likelihood of multiple breast surgeries[16,17]. During the 14-year period of our study, the use of FNAC fluctuated and then decreased in the most recent years. Fine-needle aspiration cytology is important for the assessment of cystic lesions and is, therefore, still useful in the workup of breast abnormalities[23]. However, for solid lesions, FNAC has a higher insufficient sample rate and a lower diagnostic accuracy than other biopsy methods. Additional CB is frequently required following inconclusive FNAC results[25-27], thus extending the period of anxiety and uncertainty before the final diagnosis has been made. For these reasons, FNAC should not be considered the diagnostic procedure of first choice for solid breast lesions. We attribute the strong decrease of FNAC in 2009 and 2010 to the implementation of digital screening in 2009. Digital screening especially increased the referral rate of women with suspicious microcalcifications[28], which in turn resulted in an increase in the use of stereotactic-guided percutaneous vacuum-assisted CBs. The diagnostic workup of suspicious breast lesions by percutaneous CBs showed a substantial increase during the 14-year period of our study, whereas surgical biopsies became rare. Percutaneous CBs are equally accurate to surgical biopsies and have several advantages over surgical biopsy, including lower costs, a more rapid way of providing a diagnosis and lower complication rates[29-32]. As a result, percutaneous CB is currently a widely used technique for evaluating breast abnormalities and CB has worldwide been accepted as a reliable alternative to surgical biopsy[33-35]. Despite the high diagnostic accuracy of CBs, equivocal biopsy results or discordance between radiological and histological findings is present in B10% of core-needle biopsy procedures, necessitating repeated biopsy[36]. Obviously, it is desirable to obtain a diagnosis in one biopsy session. More than one tissue sample should be taken and it is also advisable to assess the characteristics of these samples at biopsy. If the core sample is stiff, predominantly white, and sinks as soon as it is put in formalin, it is likely a diagnostic biopsy[36]. Only in a limited number of cases surgical biopsies still have an additional value.
A surgical biopsy is, for example, justified in case of a non- representative CB and in cases showing high-risk lesions or premalignant findings at CB[23,37,38]. Furthermore, a surgical biopsy can be the biopsy-method of choice when patient characteristics (for example, extreme obesity or dementia) impede percutaneous biopsy. The replacement of surgical biopsies by percutaneous CBs was probably mainly the result of the introduction and revision of Dutch breast cancer guidelines. As mentioned before, the 2000 guideline required a target for a preoperative diagnosis in women with suspected breast cancer of at least 70% by using either FNAC or CB[22], and the 2008 guideline increased this target to 90%[23].

Besides the trends in biopsies, we also determined the frequency and causes of diagnostic delays in referred women, because the replacement of surgical biopsies by CBs may hypothetically have resulted in more false-negative biopsies and a higher proportion of women that experienced a delay in breast cancer diagnosis. The amount of delays in breast cancer diagnosis in our study population, however, decreased from 6.7 to 1.8% ($p = 0.003$). The introduction of breast-care units and multidisciplinary teams in the Dutch hospitals probably mainly explains this decline in delays. Also the introduction of breast cancer guidelines and the growing importance of quality indicators in Dutch breast cancer care have probably contributed to the decline in delays. The importance of multidisciplinary teams to improve the assessment of breast lesions has been described in several studies and the use of these teams is also recommended by breast cancer guidelines[23,39,40]. The majority of diagnostic delays in our study resulted from erroneous BI-RADS assessments (57.3%) and false-negative biopsy results (32.3%). Diagnostic delays due to erroneous mammographic assessments are not uncommon, lesions can be missed, misinterpreted or overlooked[41-43]. Also false-negative biopsy results are known as probable causes of diagnostic delays[36]. The majority of false-negative biopsy results in our study consisted of CBs (68.8%); all were due to sampling errors. Researchers describe that ≈4% of CB results, both ultrasound- and stereotactic guided, are false negative[23]. Therefore, attention for radiologic–histologic correlation is very important[36,44,45] and sometimes a repeated biopsy is needed. False-negative results and delays in diagnosis from both erroneous BI-RADS assessments and false-negative biopsies can be reduced with optimisation of multidisciplinary approach and clear post-biopsy protocols. An additional time trend finding of our study was the increase of false-positive referrals from 57.9 to 75.5%. The most important explanation for this finding is probably the transition from screen-film mammography to full-field digital mammography screening in 2009, which resulted in increased referral rates, with a concomitant increase in both cancer detection rate and false-positive referral[28].

There are certain strengths and limitations of our study. First, both the radiologists and the pathologist knew that they reassessed cases with a delay in cancer diagnosis. The pathologist did not find any erroneous pathologic assessments, however, radiologist review bias may have resulted in a higher amount of cases judged as 'missed cancers' due to erroneous BI-RADS assessments. Second, extrapolation of our results to other screening programmes may be limited by the fact that the design of the Dutch breast cancer screening programme and workup strategies differs from other countries. The Dutch referral rate of 1.5–2.5% is much lower than the 3–6% referral rates observed in other European countries and the referral rate of 10% or more in the United States[46,47]. Furthermore, the incidence of open surgical biopsy is much higher in the United States than in the United Kingdom and the Netherlands. Recent data suggest that in the United States, 30–40% of diagnostic breast biopsies still consist of surgical biopsies[48,49]. One of the strengths of our study is that with the information on biopsy time trends we are able to verify whether national guidelines are followed at our screening region. Furthermore, women who attend the screening programme can now be optimally informed on the steps that will be taken following referral.

We conclude that women in a southern screening region of the Netherlands are nowadays rarely confronted with a diagnostic surgical biopsy for the workup of a screening mammography abnormality. Diagnostic surgical biopsies have mostly been replaced by percutaneous CBs. The replacement of surgical biopsies by percutaneous CBs did not increase the amount of delays in breast cancer diagnosis.

Table 1. **Diagnostic procedures after referral for a screening mammography abnormality**

	97-98	99-00	01-02
Total screens	48,721	53,718	53,489
Referrals, No (%)	537 (1.1)	499 (0.9)	553 (1.0)
False positive referrals (FP), No (%)	311 (57.9)	223 (44.7)	299 (54.1)
True positive referrals (TP), No (%)	224 (41.7)	276 (55.3)	254 (45.9)
Referrals unknown outcome, No (%)	2 (0.4)	0 (0.0)	0 (0.0)
total FP+TP	535	499	553
imaging alone, No (%)	220 (41.1)	149 (29.9)	198 (35.8)
FNAC	68 (12.7)	76 (15.2)	85 (15.4)
FNAC+CB	7 (1.3)	22 (4.4)	29 (5.2)
CB	36 (6.7)	86 (17.2)	146 (26.4)
CB+ surgical biopsy	43 (8.0)	43 (8.6)	43 (7.8)
Surgical biopsy	159 (29.7)	123 (24.6)	51 (9.2)
Unknown	2 (0.4)	0 (0.0)	1 (0.2)
Total FNAC, No (%)	68 (12.7)	76 (15.2)	85 (15.4)
Total CB, No (%)	43 (8.0)	108 (21.6)	175 (31.6)
Total surgical biopsy, No (%)	202 (37.8)	166 (33.3)	94 (17.0)
surg biopsy/1,000 screens	4.15	3.09	1.76

Table 2. **Trends in biopsies adjusted for age and hospital**

		Odds	95% CI	p-value
FNAC	1997-1998	1		
	2009-2010	0.40	0.28-0.57	<0.0001
CB	1997-1998	1		
	2009-2010	9.95	7.15-13.85	<0.0001
SB	1997-1998	1		
	2009-2010	0.03	0.02-0.04	<0.0001

FNAC= fine-needle aspiration cytology / CB=core-needle biopsy / SB=sugical biopsy

Table 1. **Diagnostic procedures after referral for a screening mammography abnormality** *(continued)*

03-04	05-06	07-08	09-10	Totaal	p-value
61,251	66,300	67,530	66,004	417,013	
985 (1.6)	874 (1.3)	1,003 (1.5)	1,779 (2.7)	6,230 (1.5)	
632 (64.2)	550 (62.9)	648 (64.6)	1,344 (75.5)	4,007 (64.3)	
350 (35.5)	323 (37.0)	354 (35.3)	433 (24.3)	2,214 (35.5)	
3 (0.3)	1 (0.1)	1 (0.1)	2 (0.1)	9 (0.1)	
982	873	1,002	1,777	6,221	
383 (39.0)	323 (37.0)	417 (41.6)	796 (44.8)	2,486 (40.0)	<0.0001
135 (13.7)	138 (15.8)	118 (11.8)	84 (4.7)	704 (11.3)	
36 (3.7)	48 (5.5)	28 (2.8)	32 (1.8)	202 (3.2)	
349 (35.5)	330 (37.8)	410 (40.9)	840 (47.3)	2,197 (35.3)	
53 (5.4)	24 (2.7)	24 (2.4)	22 (1.2)	252 (4.1)	
26 (2.6)	10 (1.1)	5 (0.5)	2 (0.1)	376 (6.0)	
0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.1)	
135 (13.7)	138 (15.8)	118 (11.8)	84 (4.7)	704 (11.3)	<0.0001
385 (39.2)	378 (43.3)	438 (43.7)	872 (49.1)	2,399 (38.6)	<0.0001
79 (8.0)	34 (3.9)	29 (2.9)	24 (1.4)	628 (10.1)	<0.0001
1.29	0.51	0.43	0.36	1.51	<0.0001

Table 3. **Details of delays in breast cancer diagnosis after referral**

	97-98		99-00	
Total true positive referrals*. No (%)	224		276	
Delay in cancer diagnosis, No (%)	15	(6.7)	17	(6.2)
Length of diagnostic delay				
4-6 months	5	(33.3)	5	(29.4)
7-12 months	7	(46.7)	6	(35.3)
13-24 months	3	(20.0)	3	(17.6)
>24 months	0	(0.0)	3	(17.6)
Causes of diagnostic delay				
Incorrect BI-RADS	12	(80.0)	11	(64.7)
False negative biopsy	3	(20.0)	4	(23.5)
Other reason	0	(0.0)	2	(11.8)
Unknown	0	(0.0)	0	(0.0)
False negative biopsy according to type of biopsy procedure				
FNAC	2	(66.7)	1	(20.0)
CB	1	(33.3)	0	(0.0)
FNAC and CB	0	(0.0)	2	(40.0)
Surgical biopsy	0	(0.0)	2	(40.0)
Tumor size of cancers with diagnostic delay				
DCIS	4	(26.7)	5	(29.4)
T1a-b	4	(26.7)	5	(29.4)
T1c	6	(40.0)	4	(23.5)
T2+	1	(6.7)	3	(17.6)
Unknown	0	(0.0)	0	(0.0)
Axillary lymph node status				
N+	3	(20.0)	1	(5.9)
N-	12	(80.0)	14	(82.4)
Nx	0	(0.0)	2	(11.8)

*women diagnosed with breast cancer after referral

FNAC = fine needle aspiration cytology; CB = core biopsy; DCIS = ductal carcinoma in-situ

Table 3. **Details of delays in breast cancer diagnosis after referral** *(continued)*

01-02		03-04		05-06		07-08		09-10		Total	
254		350		323		354		433		2,214	
17	(6.7)	17	(4.9)	13	(4.0)	9	(2.5)	8	(1.8)	96	(4.3)
4	(23.5)	4	(23.5)	5	(38.5)	2	(22.2)	1	(12.5)	26	(27.1)
8	(47.1)	6	(35.3)	3	(23.1)	3	(33.3)	3	(37.5)	36	(37.5)
0	(0.0)	7	(41.2)	4	(30.8)	2	(22.2)	2	(25.0)	21	(21.9)
5	(29.4)	0	(0.0)	1	(7.7)	2	(22.2)	2	(25.0)	13	(13.5)
10	(58.8)	10	(58.8)	5	(38.5)	2	(22.2)	5	(62.5)	55	(57.3)
5	(29.4)	5	(29.4)	6	(46.2)	6	(66.7)	2	(25.0)	31	(32.3)
2	(11.8)	2	(11.8)	2	(15.4)	1	(11.1)	1	(12.5)	10	(10.4)
0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
0	(0.0)	1	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(12.5)
1	(20.0)	3	(60.0)	6	(10.,0)	3	(50.0)	1	(50.0)	15	(46.9)
0	(0.0)	1	(20.0)	0	(0.0)	3	(50.0)	1	(50.0)	7	(21.9)
4	(80.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	6	(18.8)
2	(11.8)	6	(35.3)	1	(7.7)	1	(11.1)	2	(25.0)	21	(21.9)
7	(41.2)	2	(11.8)	5	(38.5)	2	(22.2)	2	(25.0)	27	(28.1)
6	(35.3)	9	(52.9)	4	(30.8)	3	(33.3)	1	(12.5)	33	(34.4)
2	(11.8)	0	(0.0)	3	(23.1)	2	(22.2)	3	(37.5)	14	(14.6)
0	(0.0)	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	1	(1.0)
4	(23.5)	6	(35.3)	2	(15.4)	3	(33.3)	0	(0.0)	19	(19.8)
13	(76.5)	9	(52.9)	10	(76.9)	6	(66.7)	8	(100.0)	72	(75.0)
0	(0.0)	2	(11.8)	1	(7.7)	0	(0.0)	0	(0.0)	5	(5.2)

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Chapter 3.2

Trends in surgery for screen-detected and interval breast cancers

Published as: Nederend J, *Duijm LE, Louwman MW, Roumen RH, Jansen FH, Voogd AC.* ***Trends in surgery for screen-detected and interval breast cancers in a national screening programme.*** *Br J Surg. 2014 Jul;101(8):949-58. doi: 10.1002/bjs.9530. Epub 2014 May 15.*

Abstract

Background: This population-based study aimed to evaluate trends in surgical approach for screen-detected cancer versus interval breast cancer, and to determine the factors associated with positive resection margins.

Methods: Screening mammograms of women aged 50–75 years, who underwent biennial screening in a Dutch breast-screening region between 1997 and 2011, were included. Patient and tumour characteristics were compared between women who underwent mastectomy or breast-conserving surgery (BCS) for screen-detected or interval cancer, and women with a negative or positive resection margin after BCS.

Results: Some 417,013 consecutive screening mammograms were included. A total of 2,224 screen-detected and 825 interval cancers were diagnosed. The BCS rate remained stable (mean 6.1 per 1000 screened women; $p = 0.099$), whereas mastectomy rates increased significantly during the study from 0.9 (1997–1998) to 1.9 (2009–2010) per 1000 screened women ($p < 0.001$). The proportion of positive resection margins for invasive cancer was 19.6 and 7.6 per cent in 1997–1998 and 2009–2010 respectively ($p < 0.001$), with significant variation between hospitals. Dense breasts, preoperative magnetic resonance imaging, microcalcifications, architectural distortion, tumour size over 20 mm, axillary lymph node metastasis and treating hospital were independent risk factors for mastectomy. Interval cancer, image-guided tumour localization, microcalcifications, breast parenchyma asymmetry, tumour size greater than 20 mm, lobular tumour histology, low tumour grade, extensive invasive component and treating hospital were independent risk factors for positive resection margins.

Conclusion: Mastectomy rates doubled during a 14-year period of screening mammography and the proportion of positive resection margins decreased, with variation among hospitals. The latter observation stresses the importance of quality control programmes for hospitals treating women with breast cancer.

Introduction

Many countries have introduced breast cancer screening programmes with the aim of detecting malignancies at an earlier, non-palpable stage, and thus reducing breast cancer-related morbidity and mortality. In the Netherlands, a nationwide breast cancer screening programme was implemented gradually from 1989 until 1997, and from 1998 all women aged 50–75 years have been invited to attend biennial screening mammography. A preoperative diagnosis of breast cancer is currently obtained in more than 90 per cent of patients with breast cancer[1]. Ultrasound-guided or stereotactic core biopsy has become the reference standard for the preoperative confirmation of breast cancer, and surgical biopsy for diagnostic purposes is becoming increasingly rare. Cancers detected in the screening programme are usually non-palpable and smaller than breast cancers discovered clinically. Exact localization of these non-palpable cancers is very important for obtaining clear resection margins. Techniques for preoperative tumour localization include ultrasonography, stereotactic guidewire localization, radioactive seed localization or intratumoral injection of technetium-99m[2,3].

Surgery remains the primary treatment for breast cancer. Since the early 1980s breast-conserving surgery (BCS), rather than mastectomy, has gradually become the standard of treatment for early breast cancer. A re-excision is required if the surgical resection margins are positive, as this has been shown to be an important risk factor for local recurrence in patients undergoing BCS[4–6]. The re-excision rates in international hospital-based studies range from 20 to 50 per cent[7–9]. Other independent predictors of local recurrence following BCS are young age (less than 40 years), larger tumour size, dense breast tissue, and not receiving chemotherapy or hormone therapy[10,11].

Although the implementation of guidelines and the results of randomized clinical trials[12] have resulted in decreased mastectomy rates since the 1990s, several studies[8,13,14] have reported increasing mastectomy rates over the past few years. These have partly contributed the rising mastectomy rate to increased use of magnetic resonance imaging (MRI) and changing preferences among both surgeons and patients. In another study[15], however, which used population-based data from the Surveillance Epidemiology and End-Results database, this increase in mastectomy rates was questioned.

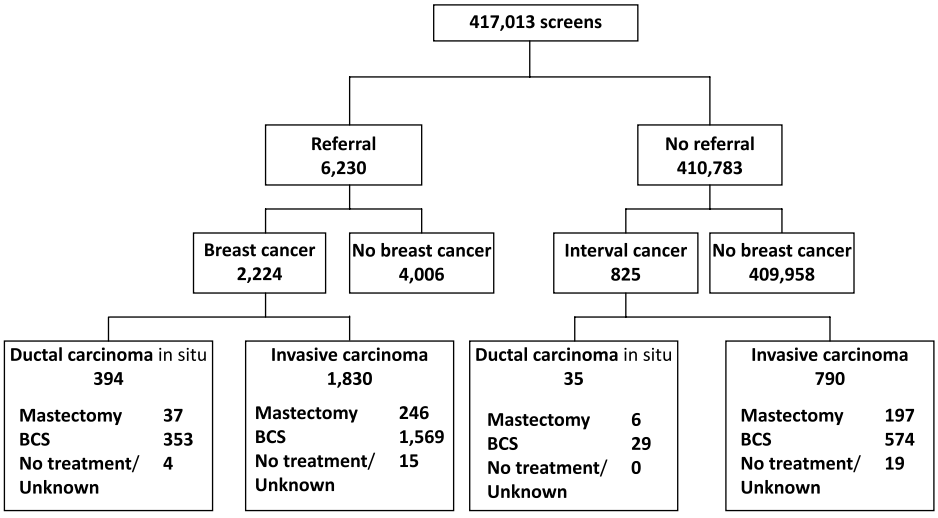
The present study addressed these issues and the factors associated with positive resection margins in patients with screen-detected or interval breast cancer, using data from the screening mammography programme in the Southeast Netherlands.

Methods

The study included all screening mammography examinations of women who underwent biennial screening mammography at one of three specialized screening units in a southern breast cancer screening region of the Netherlands (Bevolkings Onderzoek Borstkanker Zuid) between 1 January 1997 and 1 January 2011. Before a screening examination women were asked whether the screening and follow-up data could be used for evaluation purposes. Three

women did not provide written informed consent and were not included in the study. The Central Committee on Research Involving Human Subjects in The Hague, The Netherlands, waived ethical approval for this study.

Figure 1. **Screening mammography results and breast cancer treatments**



BCS = Breast conserving surgery

Screening procedure and referral

Details of the Dutch nationwide breast cancer screening programme, which offers biennial screening mammography for women aged 50–75 years, has been described elsewhere[16,17]. In brief, information on date, type and reason for previous breast surgery, family history of breast cancer and use of hormone replacement therapy were obtained from a questionnaire filled in by the screened women and from surgical correspondence. Specialized screening radiographers obtained all mammograms and these were double-read by a group of 15 certified screening radiologists. From 2003 onwards, the radiographers participated actively in the assessment of screening mammograms and also read the examinations, in addition to the two radiologists[18]. Each screening radiologist evaluated at least 5,000 screening mammograms yearly, and previous screening mammograms were always available for comparison at the time of subsequent screening. The breast density of both interval and screen-detected cancers was assessed by two screening radiologists in a blinded fashion and classified according to the American College of Radiology Breast Imaging – Reporting and Data System (BI-RADS) criteria[19]. Discordant readings were solved by consensus. If screening mammography showed a suspicious or malignant lesion, the woman was referred to a surgical oncologist or breast clinic

for further analysis of the mammographic abnormality. Depending on the evaluation protocols and facilities available, further evaluation consisted of additional mammography, breast ultrasound examination, magnetic resonance mammography, percutaneous fine-needle aspiration or core biopsy (usually image-guided), or an open surgical biopsy.

Follow-up procedure

During a 2-year follow-up, data were collected on diagnostic and surgical procedures, histopathology and tumour node metastasis (TNM) classification[20] of all screen-detected and interval cancers. Interval cancers are breast cancers diagnosed in women after a negative screening examination (defined as no recommendation for referral) and before any subsequent screen is performed. Procedures for the detection of interval cancers have been described previously[16]. A total of 16 hospitals were involved in the diagnostic evaluation, of which four centrally located hospitals, categorized as A, B, C and D, treated 88.6 per cent of the women diagnosed with breast cancer (2,702 of 3,049). The other 12 hospitals (pooled under category E) treated 11.4 per cent of these women. Characteristics of the hospitals in terms of diagnostic breast imaging facilities and multidisciplinary approach to newly diagnosed breast cancers have been described previously[21].

Tumour characteristics and surgical resection margins

Breast cancers were divided into ductal carcinoma in situ (DCIS) and invasive ductal as well as lobular cancers. Lobular carcinoma in situ was considered to be a benign lesion. The presence of more than eight ductilobular units with carcinoma in situ beyond the invasive tumour was considered as extensive ductal carcinoma in situ. The surgical margin status was recorded for all BCS procedures. A resection specimen was considered to have positive margins if more than 4 mm of invasive cancer or DCIS was present in the inked resection margin in more than two microscopic views at low power (magnification ×10). Specimens with negative resection margins or with focal positivity (4 mm or less) in the margins were considered to have negative resection margins[22,23].

Statistical analysis

Statistical analyses were performed for 2-year screening intervals. Unpaired t tests were used to compare groups with respect to continuous variables, and χ^2 tests for analysis of categorical variables. Logistic regression analyses were carried out to identify factors that significantly influence the risk of mastectomy and the risk of positive resection margins. Patients with missing information on tumour size, lymph node status or tumour histology were excluded from the logistic regression analyses, as were the 347 patients treated in hospital E. Patients with missing data with respect to any of the other co-variables of the model were included as a separate category. The significance level was set at 5 per cent for all analyses. Statistical analyses were performed using SAS® version 9.1.3 (SAS Institute, Cary, North Carolina, USA).

Results

Overall screening results

A series of 417,013 consecutive screening mammograms was included. The biennial number of screening examinations varied between 48,721 (1997–1998) and 67,530 (2007–2008), and the referral rate between 0.9 per cent (1999–2000) and 2.7 per cent (2009–2010); the mean referral rate was 1.5 per cent. Breast cancer was diagnosed in 2,224 of 6,230 referred women (including 394 cases of DCIS), resulting in an overall cancer detection rate of 5.3 per 1000 screens, and a positive predictive value for referral of 35.7 per cent. In addition, 825 interval cancers (including 35 cases of DCIS) were diagnosed. The mean sensitivity of breast cancer screening was 72.9 per cent (2,224 of 3,049) (Table 1). The use of preoperative MRI varied among hospitals: hospital A, 12.8 per cent (59 of 462); hospital B, 13.0 per cent (114 of 875); hospital C, 10.3 per cent (61 of 590); hospital D, 7.1 per cent (55 of 775); and the 12 hospitals in category E, 15.9 per cent (55 of 347) ($p < 0.001$). The use of preoperative MRI gradually increased from 0.3 per cent (1 of 297) in 1997–1998, to 20.9 per cent (131 of 628) in 2009–2010 ($p < 0.001$).

Surgical treatment of screen detected cancers and interval cancers

Of the 2,620 women diagnosed with invasive cancer, 443 were treated by mastectomy and 2,143 underwent BCS; 34 women were not treated surgically. BCS was performed for a significantly larger proportion of screen-detected cancers than interval cancers: 1,569 (85.7 per cent) of 1,830 versus 574 (72.7 per cent) of 790 ($p < 0.001$). Comparable proportions of women in both groups underwent BCS for in situ cancer: 353 (89.6 per cent) of 394 versus 29 (83 per cent) of 35 ($p = 0.221$). The overall mastectomy rate gradually increased from 0.9 per 1000 screened women in 1997–1998, to 1.9 per 1000 screened women in 2009–2010 ($p < 0.001$), with a mean rate of 1.2 per cent. During the study interval, the BCS rate varied between 5.2 per cent (1998–1999) and 7.4 per cent (2009–2010) ($p = 0.099$), with a mean of 6.1 per cent.

The proportion of mastectomies for screen-detected DCIS gradually increased from 0 per cent (1998–1999) to 16.4 per cent (2009–2010) ($P = 0.002$), with a concomitant decrease in the proportion of women treated by BCS (100 per cent in 1998–1999 to 81.8 per cent in 2009–2010; $p = 0.002$). The proportion of mastectomies for screen-detected invasive cancer increased from 12.3 per cent (1997–1998) to 20.2 per cent (2007–2008) and then decreased to 14.9 per cent for women screened in 2009–2010 ($p = 0.001$). The proportion of mastectomies for interval invasive cancer was highest among women screened in 2009–2010; it ranged from 17.9 per cent (2001–2002) to 34.0 per cent (2009–2010) ($p = 0.01$), with a mean of 24.9 per cent (Table 1).

Risk factors for mastectomy

Analysis of the characteristics of women treated surgically for invasive breast cancer, either by BCS or mastectomy, is shown in Table 2. After adjusting for all other variables in a logistic regression analysis, the risk of mastectomy was higher for women with a tumour larger than 20 mm, axillary lymph node metastases, dense breasts, and a mammogram showing microcalcifications or architectural distortion. The risk was also higher if preoperative MRI was performed. Treatment in hospital B was associated with a lower relative risk of mastectomy.

Resection margins

The proportion of positive resection margins following BCS was 12.7 per cent (272 of 2,138) for patients with invasive cancer and 19.1 per cent (73 of 382) for those with DCIS ($p = 0.001$). Among women with invasive cancer and positive resection margins, 32 (11.8 per cent) of 272 underwent no further treatment, 109 (40.1 per cent) a second lumpectomy and 131 (48.2 per cent) a secondary mastectomy. For women with DCIS and positive resection margins, nine (12 per cent) of 73 had no further treatment, 12 (16 per cent) a second lumpectomy and 52 (71 per cent) a secondary mastectomy ($p < 0.001$).

The characteristics of women treated surgically for invasive breast cancer are shown with respect to resection margins in Table 3. The proportion of positive resection margins for patients with invasive cancer was 19.6 per cent in 1997–1998 and 7.6 per cent in 2009–2010 ($p < 0.001$).

For invasive cancer, the factors significantly related to positive resection margins were: interval cancer, tumour size larger than 20 mm, axillary lymph node metastasis, lobular histology and a diagnosis in the earlier years of the study. There was a significant difference between hospitals, with positive resection margin rates varying between 5.8 and 20.3 per cent ($p < 0.001$).

After adjustment for all other variables in a logistic regression analysis, interval cancer, imaging-guided tumour localization, microcalcifications, breast parenchyma asymmetry, tumour size larger than 20 mm, lobular histology, presence of an extensive in situ component, and hospitals C and D were independent risk factors for incomplete tumour resection. Furthermore, grade III tumours were associated with a lower relative risk of tumour-positive margins, with an odds ratio of 0.44 (95 per cent confidence interval (CI) 0.25 to 0.77). Use of preoperative MRI was also associated with a lower risk of positive resections margins, with an odds ratio of 0.42 (95 per cent CI 0.21 to 0.85).

Table 1. **Screening and treatment data for seven consecutive 2-year screening intervals**

	1997–1998	1999–2000	2001–2002	2003–2004
No. of screens	48 721	53 718	53 489	61 251
No. of referred women	537	499	553	985
Referral rate (%)	1.1	0.9	1.0	1.6
Cancer detection rate (per 1000)	4.6	5.1	4.7	5.6
Interval cancer rate (per 1000)	1.5	1.7	2.4	1.8
Sensitivity (%)	75.4	74.5	66.5	75.2
Mastectomy rate (per 1000)	0.9	0.7	0.9	0.9
Breast-conserving treatment rate (per 1000)	5.2	6.0	6.1	6.5
Screen-detected cancer	224	272	252	342
Ductal carcinoma in situ	29	46	35	62
Mastectomy	0 (0)	0 (0)	2 (6)	0 (0)
BCS	29 (100)	46 (100)	33 (94)	62 (100)
No therapy/unknown	0 (0)	0 (0)	0 (0)	0 (0)
Invasive cancers	195	226	217	280
Mastectomy	24 (12.3)	22 (9.7)	24 (11.1)	26 (9.3)
BCS	171 (87.7)	202 (89.4)	192 (88.5)	252 (90.0)
No therapy/unknown	0 (0)	2 (0.9)	1 (0.5)	2 (0.7)
Interval cancer	73	93	127	113
Ductal carcinoma in situ	2	1	4	5
Mastectomy	0 (0)	0 (0)	0 (0)	1 (20)
BCS	2 (100)	1 (100)	4 (100)	4 (80)
No therapy/unknown	0 (0)	0 (0)	0 (0)	0 (0)
Invasive cancers	71	92	123	108
Mastectomy	19 (27)	18 (20)	22 (17.9)	27 (25.0)
BCS	52 (73)	73 (79)	97 (78.9)	78 (72.2)
No therapy/unknown	0 (0)	1 (1)	4 (3.3)	3 (2.8)

Table 1. **Screening and treatment data for seven consecutive 2-year screening intervals** *(continued)*

	2005–2006	2007–2008	2009–2010	Total
No. of screens	66 300	67 530	66 004	417 013
No. of referred women	874	1003	1779	6230
Referral rate (%)	1.3	1.5	2.7	1.5
Cancer detection rate (per 1000)	4.8	5.2	7.0	5.3
Interval cancer rate (per 1000)	2.1	1.8	2.5	2.0
Sensitivity (%)	69.8	74.7	74.0	72.9
Mastectomy rate (per 1000)	1.1	1.5	1.9	1.2
Breast-conserving treatment rate (per 1000)	5.7	5.3	7.4	6.1
Screen-detected cancer	317	352	465	2224
Ductal carcinoma in situ	52	60	110	394
Mastectomy	6 (12)	11 (18)	18 (16.4)	37 (9.4)
BCS	45 (87)	48 (80)	90 (81.8)	353 (89.6)
No therapy/unknown	1 (2)	1 (2)	2 (1.8)	4 (1.0)
Invasive cancers	265	292	355	1830
Mastectomy	38 (14.3)	59 (20.2)	53 (14.9)	246 (13.4)
BCS	226 (85.3)	226 (77.4)	300 (84.5)	1569 (85.7)
No therapy/unknown	1 (0.4)	7 (2.4)	2 (0.6)	15 (0.8)
Interval cancer	137	119	163	825
Ductal carcinoma in situ	7	6	10	35
Mastectomy	1 (14)	1 (17)	3 (30)	6 (17)
BCS	6 (86)	5 (83)	7 (70)	29 (83)
No therapy/unknown	0 (0)	0 (0)	0 (0)	0 (0)
Invasive cancers	130	113	153	790
Mastectomy	28 (21.5)	31 (27.4)	52 (34.0)	197 (24.9)
BCS	98 (75.4)	82 (72.6)	94 (61.4)	574 (72.7)
No therapy/unknown	4 (3.1)	0 (0)	7 (4.6)	19 (2.4)

Values in parentheses are percentages. BCS, breast-conserving surgery

Table 2: **Univariable and multivariable analyses of risk factors for mastectomy in patients with invasive cancers**

		Univariable analysis					Multivariable analysis‡		
		BCS		Mastectomy		P†	Odds ratio*		P
Age (years)	50–69	879	(81.0)	206	(19.0)	0.099	1.00	(reference)	
	60–69	877	(84.4)	162	(15.6)		0.83	(0.61, 1.13)	0.234
	≥ 70	387	(83.8)	75	(16.2)		1.30	(0.87, 1.94)	0.195
Cancer type	Screen-detected	1569	(86.4)	246	(13.6)	< 0.001	1.00	(reference)	
	Interval	574	(74.4)	197	(25.6)		0.98	(0.68, 1.40)	0.899
Family history	No	1755	(82.7)	366	(17.3)	0.718	1.00	(reference)	
	Yes	388	(83.4)	77	(16.6)		1.08	(0.78, 1.51)	0.636
Previous breast surgery	No	1909	(83.6)	374	(16.4)	0.006	1.00	(reference)	
	Yes, benign	234	(77.2)	69	(22.8)		1.07	(0.71, 1.60)	0.760
Use of hormone replacement therapy	No	1941	(83.1)	394	(16.9)	0.290	1.00	(reference)	
	Yes	202	(80.5)	49	(19.5)		0.97	(0.63, 1.49)	0.894
Breast density (%)	≤ 50	1460	(85.6)	245	(14.4)	< 0.001	1.00	(reference)	
	> 50	651	(77.8)	186	(22.2)		1.38	(1.04, 1.81)	0.024
Preoperative MRI	No	1969	(86.4)	309	(13.6)	< 0.001	1.00	(reference)	
	Yes	174	(56.5)	134	(43.5)		4.20	(2.85, 6.18)	< 0.001
Mammographic abnormality	Density	1419	(87.4)	204	(12.6)	< 0.001	1.00	(reference)	
	Microcalcifications	151	(70.6)	63	(29.4)		3.72	(2.34, 5.91)	< 0.001
	Density with microcalcifications	195	(78.6)	53	(21.4)		1.41	(0.90, 2.20)	0.138
	Architectural distortion	18	(47)	20	(53)		2.82	(1.18, 6.74)	0.019
	Breast parenchyma asymmetry	75	(76)	24	(24)		1.20	(0.62, 2.34)	0.587
Tumour size (mm)	≤ 20	1,631	(90.3)	175	(9.7)	< 0.001	1.00	(reference)	
	> 20	501	(67.4)	242	(32.6)		3.39	(2.54, 4.53)	< 0.001
	Unknown	11	(30)	26	(70)		–§		
Lymph node status	N0	1,532	(89.5)	180	(10.5)	< 0.001	1.00	(reference)	
	N+	577	(69.5)	253	(30.5)		2.41	(1.83, 3.18)	< 0.001
	Nx	34	(77)	10	(23)		–§		

Table 2: **Univariable and multivariable analyses of risk factors for mastectomy in patients with invasive cancers** *(continued)***.**

		Univariable analysis					Multivariable analysis‡		
		BCS		Mastectomy		P†	Odds ratio*		P
Tumour histology	Ductal	1,661	(84.5)	304	(15.5)	< 0.001	1.00	(reference)	
	Lobular	249	(73.5)	90	(26.5)		1.44	(1.00, 2.09)	0.051
	Mixed ductal–lobular	102	(75.6)	33	(24.4)		1.41	(0.84, 2.36)	0.200
	Other invasive	124	(89.9)	14	(10.1)		0.90	(0.44, 1.85)	0.769
	Unknown	7	(78)	2	(22)		2.06	(0.22, 19.62)	0.531
Tumour grade	I	719	(85.0)	127	(15.0)	0.003	1.00	(reference)	
	II	718	(81.4)	164	(18.6)		1.04	(0.74, 1.46)	0.818
	III	276	(77.5)	80	(22.5)		1.35	(0.88, 2.07)	0.163
DCIS component	No	1,039	(80.9)	245	(19.1)	0.022	1.00	(reference)	
	Yes	719	(85.5)	122	(14.5)		0.98	(0.71, 1.34)	0.876
	Extensive invasive component	385	(83.5)	76	(16.5)		0.89	(0.61, 1.31)	0.563
Hospital	A	325	(83.3)	65	(16.7)	< 0.001	1.00	(reference)	
	B	654	(88.5)	85	(11.5)		0.63	(0.42, 0.94)	0.024
	C	409	(79.4)	106	(20.6)		1.27	(0.84, 1.90)	0.257
	D	546	(84.0)	104	(16.0)		1.03	(0.69, 1.53)	0.905
	E	209	(71.6)	83	(28.4)		–§		
Year of diagnosis	1997–1998	223	(83.8)	43	(16.2)	< 0.001	1.00	(reference)	
	1999–2000	275	(87.3)	40	(12.7)		0.52	(0.27, 1.02)	0.188
	2001–2002	289	(86.3)	46	(13.7)		0.70	(0.36, 1.33)	0.057
	2003–2004	330	(86.2)	53	(13.8)		0.60	(0.31, 1.15)	0.272
	2005–2006	324	(83.1)	66	(16.9)		0.67	(0.34, 1.32)	0.123
	2007–2008	308	(77.4)	90	(22.6)		0.69	(0.34, 1.40)	0.247
	2009–2010	394	(79.0)	105	(21.0)		0.69	(0.39, 1.20)	0.305

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. MRI, magnetic resonance imaging; DCIS, ductal carcinoma in situ. †χ^2 test; ‡logistic regression analysis, with odds ratios for mastectomy versus breast-conserving surgery; §excluded from multivariable analysis.

Table 3: **Univariable and multivariable analyses of risk factors for positive resection margins in patients with invasive cancers**

		Univariable analysis					Multivariable analysis‡		
		Negative/focal positive		Positive		P†	Odds ratio*		P
Age (years)	50–69	754	(85.9)	124	(14.1)	0.267	1.00	(reference)	
	60–69	770	(88.2)	103	(11.8)		0.75	(0.53, 1.06)	0.102
	≥ 70	342	(88.4)	45	(11.6)		0.88	(0.56, 1.38)	0.575
Cancer type	Screen-detected	1387	(88.7)	177	(11.3)	0.002	1.00	(reference)	
	Interval	479	(83.4)	95	(16.6)		1.83	(1.17, 2.87)	0.009
Family history	No	1522	(87.0)	228	(13.0)	0.367	1.00	(reference)	
	Yes	344	(88.7)	44	(11.3)		0.71	(0.48, 1.06)	0.096
Previous breast surgery	No	1670	(87.7)	235	(12.3)	0.125	1.00	(reference)	
	Yes, benign	196	(84.1)	37	(15.9)		1.11	(0.71, 1.76)	0.643
Use of hormone replacement therapy	No	1964	(89.0)	243	(11.0)	0.446	1.00	(reference)	
	Yes	172	(85.6)	29	(14.4)		0.89	(0.54, 1.47)	0.532
Breast density (%)	≤ 50	1287	(88.3)	170	(11.7)	0.063	1.00	(reference)	
	> 50	550	(84.7)	99	(15.3)		1.32	(0.95, 1.83)	0.105
Preoperative MRI	No	1710	(87.0)	255	(13.0)	0.233	1.00	(reference)	
	Yes	156	(90.2)	17	(9.8)		0.42	(0.21, 0.85)	0.015
Tumour localization	Palpable	719	(87.2)	106	(12.8)	0.890	1.00	(reference)	
	Guided	1147	(87.4)	166	(12.6)		1.96	(1.36, 2.84)	< 0.001
Mammographic abnormality	Density	1281	(90.6)	133	(9.4)	< 0.001	1.00	(reference)	
	Microcalcifications	110	(72.8)	41	(27.2)		2.53	(1.48, 4.33)	0.001
	Density with microcalcifications	164	(84.1)	31	(15.9)		1.98	(1.16, 3.37)	0.012
	Architectural distortion	14	(78)	4	(22)		2.77	(0.71, 10.88)	0.144
	Breast parenchyma asymmetry	56	(80)	14	(20)		2.34	(1.19, 4.59)	0.014
Tumour size (mm)	≤ 20	1456	(89.5)	170	(10.5)	< 0.001	1.00	(reference)	
	> 20	403	(80.4)	98	(19.6)		2.10	(1.47, 3.00)	< 0.001
	Unknown	7	(64)	4	(36)		–§		
Lymph node status	N0	1359	(88.9)	170	(11.1)	< 0.001	1.00	(reference)	
	N+	479	(83.3)	96	(16.7)		1.20	(0.85, 1.68)	0.298
	Nx	28	(82)	6	(18)		–§		

Table 3: **Univariable and multivariable analyses of risk factors for positive resection margins in patients with invasive cancers** ***(continued)*****.**

		Univariable analysis					Multivariable analysis‡		
		Negative/focal positive		Positive		P†	Odds ratio*		P
Tumour histology	Ductal	1481	(89.3)	177	(10.7)	< 0.001	1.00	(reference)	
	Lobular	183	(73.5)	66	(26.5)		3.94	(2.60, 5.96)	< 0.001
	Mixed ductal–lobular	86	(84.3)	16	(15.7)		1.56	(0.82, 2.99)	0.180
	Invasive other	110	(89.4)	13	(10.6)		1.09	(0.53, 2.32)	0.824
	Unknown	6	(100)	0	(0)		–§		
Tumour grade	I	633	(88.0)	86	(12.0)	0.066	1.00	(reference)	
	II	631	(87.9)	87	(12.1)		0.66	(0.45, 0.98)	0.038
	III	247	(89.5)	29	(10.5)		0.44	(0.25, 0.77)	0.005
DCIS component	No	923	(89.3)	111	(10.7)	< 0.001	1.00	(reference)	
	Yes	672	(93.5)	47	(6.5)		0.68	(0.46, 1.03)	0.066
	Extensive invasive component	271	(70.4)	114	(29.6)		4.25	(2.89, 6.27)	< 0.001
Hospital	A	306	(94.2)	19	(5.8)	< 0.001	1.00	(reference)	
	B	596	(91.4)	56	(8.6)		1.51	(0.84, 2.69)	0.167
	C	344	(84.1)	65	(15.9)		3.31	(1.84, 5.94)	< 0.001
	D	435	(79.7)	111	(20.3)		5.00	(2.85, 8.77)	< 0.001
	E	185	(89.8)	21	(10.2)		–§		
Year of diagnosis	1997–1998	176	(80.4)	43	(19.6)	< 0.001	1.00	(reference)	
	1999–2000	233	(84.7)	42	(15.3)		0.50	(0.24, 1.05)	0.132
	2001–2002	250	(86.5)	39	(13.5)		0.29	(0.14, 0.62)	0.068
	2003–2004	299	(90.6)	31	(9.4)		0.54	(0.26, 1.12)	0.001
	2005–2006	281	(87.0)	42	(13.0)		0.80	(0.38, 1.69)	0.097
	2007–2008	263	(85.4)	45	(14.6)		0.42	(0.18, 0.96)	0.559
	2009–2010	364	(92.4)	30	(7.6)		0.65	(0.38, 1.14)	0.039

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. MRI, magnetic resonance imaging; DCIS, ductal carcinoma in situ. †χ^2 test; ‡logistic regression analysis, with odds ratios for positive resection margins versus negative/focal positive margins; §excluded from multivariable analysis.

Discussion

The mastectomy rate doubled over a 14-year screening period, whereas the BCS rate and breast cancer incidence (per 1000 screened women) remained stable. Multivariable analysis showed that patients with microcalcifications, large tumours, lymph node metastasis and those treated in certain hospitals had a higher risk of undergoing mastectomy. The positive resection margin rate declined over time, with wide variation between hospitals. Main independent risk factors for positive resection margins of invasive cancers were tumour size larger than 20 mm, lobular histology and the treating hospital. Preoperative MRI led to a lower risk of positive resection margins, but a substantially higher risk of mastectomy.

As the incidence of smaller tumours detected at screening mammography has increased significantly[24,25], the expectation was that BCS rates would rise in the present study. However, a twofold increase in the mastectomy rate was observed over the 14 years. There are conflicting reports on whether mastectomy rates are increasing[7,8,15], although these studies did not focus specifically on screened populations. Factors behind the increased mastectomy rates could be changes in patients' preferences, a fear of local recurrence and increased use of preoperative MRI[24]. In the present study of women in a screening programme, the use of preoperative MRI was associated with a higher risk of mastectomy and a large variation in the use of MRI was observed between hospitals. Again, there are no data available from studies specifically addressing a screened population, and previous studies[24,25] on symptomatic patients reported conflicting results on the impact of preoperative MRI on the mastectomy rate.

Increased breast density (American College of Radiology category 3 and 4[19]), invasive tumour size larger than 20 mm and axillary lymph node metastasis were also associated with an increased relative risk for mastectomy, in line with previous findings[15,26,27]. An analysis of risk factors for mastectomy in DCIS was not done, owing to the smaller number of mastectomies performed. Nevertheless, a significant increase in the mastectomy rate for DCIS was observed in the last 4 years of the study.

BCS has been one of the major advances in breast cancer management in the second half of the 20th century. Tumour-involved surgical margins are associated with a higher local recurrence rate[28], which is associated with poorer overall survival[29]. Several risk factors have been described for positive resection margins, including lobular histology, tumour size, DCIS and the presence of microcalcifications at mammography[30]. The size of an appropriate tumour-free resection margin is still debated[31,32]. A small tumour-free or microscopically incomplete margin may be acceptable if surgery is followed by radiotherapy to eradicate the tumour cells left behind[33]. In the present study, 13.7 per cent of women had positive resection margins, with wide variation between hospitals. This is in line with previous reports[30,34–37] and the Dutch guidelines[38], which state that a surgeon should strive for a maximum of 20 per cent positive resection margins. Women with DCIS were more likely to have positive resection margins after BCS and more likely to undergo a mastectomy as final type of surgery after positive resection margins than women with invasive breast cancer. This finding is also in line with other studies[30,35,39].

A significant decrease in positive resection margins was observed over time; comparing the rate of positive margins for invasive cancer during the first and last 2-year intervals, an absolute reduction of 12 per cent (from 19.6 per cent to 7.6 per cent) was found. In line with other studies[7,34–36], tumour size greater than 20 mm was an independent risk factor for positive resection margins for invasive cancer. Lobular carcinoma is another known risk factor for positive resection margins, although this does not translate into a higher risk of local recurrence compared with that for invasive ductal carcinoma[40]. The presence of microcalcifications is associated with a DCIS component, and the true size of this lesion is often underestimated by imaging[41]. An extensive in situ component is known to influence the surgical margin status, and so it is important to identify this by preoperative core biopsy, to help in planning resection[42]. Thus the presence of microcalcifications, in situ components on core needle biopsy and lobular histology indicate a risk of positive margins at BCS. Another risk factor for positive resection margins in patients with invasive cancer was the presence of a non-palpable tumour. Improved localization methods for non-palpable breast cancer are needed to reduce the rate of positive margins, as recently emphasized in a study from the USA[43]. Radioactive iodine seed localization of non-palpable tumours seems effective in reducing the risk of positive resection margins[3]. Preoperative use of MRI tended to decrease the risk of positive resection margins in invasive cancer. Finally, histological grade III tumours were associated with a lower risk of tumour-positive resection margins.

The present study has both strengths and limitations. The surgical management and outcome of breast cancer was analysed in a screened population. However, extrapolation of these findings to other screening programmes may be limited, as these may differ from one another in several aspects, including screening interval, age of screened women, reading strategy and referral rate[18,44]. The present findings regarding the impact of preoperative use of MRI on mastectomy rate and margin status cannot be compared easily with previous studies, as information on the indications for MRI in the present population is not available, and other studies were not specifically aimed at asymptomatic, screened women. Furthermore, positive resection margins were used as a surrogate endpoint for local recurrence here, as they are an established risk factor for local recurrence. Monitoring local recurrence itself would require longer follow-up and an even larger numbers of screened women to be useful as a quality indicator of surgery. The 5-year local recurrence rate following BCS was only 2.6 (95 per cent CI 2.2 to 3.1) per cent for patients treated in 2003, based on a study from the Netherlands Cancer Registry[45].

Surgeons performing BCS should try to identify patients at high risk of positive resection margins before surgery, with a special focus on microcalcifications. Furthermore, a continuous effort should be made to improve the quality of excisional biopsies, either by using wire-guided localization or iodine-125-radiolabelled seeds, and to benchmark performance against that of peers.

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Chapter 4

Impact of the introduction of full-field digital mammography screening on screening outcome in the south of the Netherlands

Chapter 4.1

Impact of the transition from screen-film screening mammography to digital screening mammography on screening outcome

Published as: Nederend J, *Duijm LE, Louwman MW, Groenewoud JH, Donkers-van Rossum AB, Voogd AC.* ***Impact of transition from analog screening mammography to digital screening mammography on screening outcome in The Netherlands: a population-based study.*** *Ann Oncol. 2012 Dec;23(12):3098-103. doi: 10.1093/annonc/mds146. Epub 2012 Jun 27.*

Abstract

Background: Full-field digital mammography (FFDM) has replaced screen-film mammography (SFM) in most breast screening programs. We analysed the impact of this replacement on screening outcome.

Methods: The study population consisted of a consecutive series of 60,770 analogue and 63,182 digital screens. During 1-year follow-up, we collected breast imaging reports, biopsy results and surgical reports of all referred women.

Results: Referral rate and cancer detection rate at FFDM were respectively 3.0% and 6.6 per 1,000 screens, compared to 1.5% ($p < 0.001$) and 4.9 ($p < 0.001$) at SFM. Positive predictive values of referral and percutaneous biopsy were lower at FFDM, respectively 21.9% versus 31.6% ($p < 0.001$) and 42.9% versus 62.8% ($p < 0.001$). Per 1,000 screened women, there was a significant increase with FFDM vs. SFM in the detection rate of low- and intermediate grade DCIS (+ 0.7), invasive T1a-c cancers (+ 0.9), invasive ductal cancers (+0.9), low-grade (+1,1), node-negative invasive cancers (+1.2), oestrogen-receptor or progesterone-receptor positive invasive cancers (respectively +0.9 and +1.1) and Her2/Neu negative (+0.8) invasive cancers. Mastectomy rates were stable at 1.1 per 1,000 screens.

Conclusion: FFDM significantly increased the referral rate and cancer detection rate, at the expense of a lower positive predictive value of referral and biopsy. Extra tumours detected at FFDM were mostly low-intermediate grade DCIS and smaller invasive tumours, of more favourable tumour characteristics. Mastectomy rates were not increased in the FFDM population, while increased overdiagnosis cannot be excluded.

Introduction

Many western countries have implemented regional or nation-wide screening mammography programs with the aim to detect breast malignancies at an early stage[1]. High-quality full-field digital mammography (FFDM) has been available now for several years and has replaced screen-film mammography (SFM) in most programs. FFDM improves workflow and is at least as effective as SFM in the detection of breast cancer[2,3]. However, higher cancer detection rates at FFDM may be accompanied by increased referral rates[4,5] and lower positive predictive values of referral for breast cancer[6,7]. Moreover, FFDM especially increases the detection of ductal carcinoma in situ (DCIS), resulting in a larger proportion of breast cancers being over-diagnosed[8].

The Netherlands has a long tradition in screening mammography and transition to digital screening has also resulted in higher referral rates and a significantly enhanced cancer detection rate[6,7]. Although emerging data become available with respect to digital screening accuracy, little is known about the effects of conversion of analogue to digital screening on additional diagnostic tests, tumour stage, histology and biology of screen-detected cancers and surgical treatment of these cancers. In a southern breast cancer screening region of the Netherlands, we therefore performed a comprehensive evaluation of the changes in referral rate, cancer detection rate, utilization of diagnostic tests after referral, characteristics of screen-detected cancers and surgical treatment procedures following the introduction of digital screening mammography.

Methods

Study population

We included a consecutive series of 60,770 analogue screens in 60,770 women (6,851 initial screens and 53,919 subsequent screens) and 63,182 digital screens in 63,182 women (7,019 initial screens and 56,163 subsequent screens), obtained at three specialized screening units in a southern biennial screening mammography region of the Netherlands (BOZ, Bevolkings Onderzoek Zuid) between January 1, 2008 and January 1, 2011. Of the 56,163 women with a subsequent digital screen, 29,649 were also represented in the cohort of 60,770 women who had received an analogue screen between January 1, 2008 and January 1, 2011. Screen-film mammography was replaced by full field digital mammography on respectively May 26, 2009, June 3, 2009 and April 6, 2010 at the three units. To determine the possible presence of a learning curve since the start of digital screening, we divided the total number of digital screens in each screening unit in two equal proportions for which we then separately assessed screening outcome. All women had given written informed consent to use their screening and follow-up data for evaluation purposes. The Central Committee on Research Involving Human Subjects (CCMO) in The Hague, The Netherlands, waived ethical approval for this study.

Screening procedure and referral

Details of our breast cancer screening program, offering biennial screening mammography for women aged 50-75 years, have been described previously[9,10]. In brief, screen-film mammograms were obtained with commercially available units (Performa, Oldelft, Tuusula, Finland). Dedicated mammography screens were utilized (Mamoray MR-R, Agfa, Schroenhausen, Germany). Both dedicated film (Mamoray HDR; Agfa, Mortsel, Belgium), as well as extended-cycle dedicated processing were used. All digital mammograms were acquired with a Lorad Selenia FFDM system (Hologic Inc, Danbury, CT), with a 70 µm pixel size and a 232x286 mm field of view. All mammograms were obtained by specialized screening mammography technologists and double read by a team consisting of eleven certified screening radiologists. Prior screening mammograms were always available for comparison at the time of subsequent screening. To facilitate softcopy reading of subsequent screening examinations at FFDM, the most recent prior screen-film screening mammograms were digitized by using a film scanner and archiver designed for mammography (DigitalNow; R2/Hologic). The original hard copy screen film mammograms were also available for viewing if desired by the screening radiologist. Women with normal or benign mammographic findings, or with a non-specific minimal sign[11], were not referred. If screening mammography showed a suspicious or malignant lesion, the woman was referred to a surgical oncologist or breast clinic for further analysis of the mammographic abnormality. For each referral, the screening radiologists classified the abnormal mammographic findings according to one of five categories: suspicious high density (e.g., spiculated density or density with indistinct borders), suspicious microcalcifications (e.g., pleomorphic, branching, or amorphous/indistinct microcalcifications), density in combination with microcalcifications, architectural distortion, or asymmetry. Women with discrepant readings at screening mammography (only one of the two screening radiologists considered referral necessary) were always referred for further analysis.

Diagnostic workup and surgical treatment of screen-detected cancers

A total of 15 regional and university hospitals were involved in the assessment of screen positive women. After physical examination by the surgeon, additional mammographic views were obtained if necessary. At diagnostic work-up, radiologists classified the radiological findings according to the American College of Radiology BI-RADS12. BI-RADS 4 and BI-RADS 5 lesions were routinely biopsied, whereas BI-RADS 3 lesions were either biopsied of followed-up with mammography. Dependent on the findings at physical examination and mammography and dependent on the diagnostic workup protocols and hospital facilities available, further diagnostic evaluation could include breast ultrasonography, Magnetic Resonance Mammography, percutaneous fine needle aspiration cytology (FNAC) or core biopsy (CB), or open surgical biopsy. During one-year follow-up, we collected data on diagnostic imaging procedures, biopsy specimen and surgical procedures of all referred women. Breast cancers were divided into ductal carcinoma in-situ and invasive cancers; lobular carcinoma in-situ was considered to be a benign lesion. Advanced cancers were defined as invasive cancers with Tumour-Node-

Table 1. **Overall screening results**

	Screen-film mammography	Digital mammography	p-value
Mammograms, n	60,770	63,182	
Initial screens, n (%)	6,851 (11.3)	7,019 (11.1)	0.4
Subsequent screens, n (%)	53,919 (88.7)	56,163 (88.9)	
Age distribution, n (%)			0.9
<50 years	3,870 (6.4)	3,998 (6.3)	
50-69 years	48,999 (80.6)	50,562 980.0)	
≥70 years	7,901 (13.0)	8,622 (13.6)	
Referral, n (%)	941 (1.5)	1,919 (3.0)	<0.001
Initial screens, n (%)	225 (3.3)	447 (6.4)	
Subsequent screens, n (%)	716 (1.3)	1,472 (2.6)	
Mean age of referred women, years (95% CI)	59.9 (59.4-60.4)	59.4 (59.1-59.8)	
Screen detected cancers, n	297	420	
Cancer detection rate*	4.9	6.6	
Initial screens	4.7	7.4	<0.001
Subsequent screens	4.9	6.6	
Positive predictive value of referral, %	31.6	21.9	<0.001
Type of screen detected cancer, n (rate*)			0.003
Ductal carcinoma in situ	44 (0.7)	100 (1.6)	
Invasive cancer	253 (4.2)	320 (5.1)	
Type of surgery, n (rate*)			0.04
Breast conserving treatment	223 (3.7)	348 (5.5)	
Mastectomy	69 (1.1)	68 (1.1)	
No surgical treatment	5 (0.08)	4 (0.06)	

*Per 1,000 screened women. ‡Women are invited in the year they become 50

Table 2. **Lesion characteristics of women referred at screening mammography**

Mammographic abnormality	Screen-film mammography				
	n	Proportion (%)	Referral rate (‰)*	TP (n)	PPV (%)
Density	663	70.5	10.9	205	30.9
Microcalcifications	152	16.2	2.5	53	34.9
Density with microcalcifications	55	5.8	0.9	24	43.6
Asymmetry	46	4.9	0.8	2	4.3
Architectural distortion	24	2.6	0.4	12	50.0
Other	1	0.1	0.0	1	100
Total	941	100	15.5	297	31.6

TP = true positive. PPV = positive predictive value of referral. *Per 1,000 screened women.

Metastases (TNM) stage IIA or higher, i.e. tumour size exceeding 20 mm (T2) and/or presence of lymphatic metastasis in the sentinel node or axillary lymph nodes[13]. Sentinel nodes were classified negative if they harboured isolated tumour cells or sub-micrometastases (<0.2 mm) and were considered positive (N+) if they contained micrometastases (0.2-2 mm) or macro-metastases (>2 mm). For women with bilateral disease, the cancer with the highest stage was retained; multiple foci of cancer in one breast were counted as one cancer.

Statistical analysis

All data were entered into a computerized spreadsheet (Excel; Microsoft, Redmond, WA, USA). Statistics were performed using the SAS program version 9.1.3 (Statistical Analysis Software; SAS/STAT software®, Cary, NC, USA). A double sided t-test was used to test differences between continuous variables, and the χ^2-test to test differences between categorical variables. The significance level was set at 5%.

Results

Overall screening results

Age distribution and the proportion of initial screens were comparable for SFM and FFDM (Table 1). The referral rate and overall cancer detection rate (number of cancers per 1,000 screened women) were significantly higher at FFDM (3.0% versus 1.5% ($p < 0.001$) and 6.6 versus 4.9 ($p < 0.001$), respectively). The cancer detection rate at initial screens was similar to the one observed at subsequent screens (SFM: 4.7 versus 4.9, $p = 0.8$; FFDM: 7.6 versus 6.6, $p = 0.3$).

Table 2. **Lesion characteristics of women referred at screening mammography** *(continued)*

Digital mammography					P-value‡
n	Proportion (%)	Referral rate (‰)*	TP (n)	PPV (%)	
1,068	55.7	16.9	217	20.3	<0.001
580	30.2	9.2	122	21.0	<0.001
120	6.3	1.9	48	40.0	0.7
45	2.3	0.7	2	4.4	0.98
101	5.3	1.6	31	30.7	0.07
5	0.3	0.1	0	0.0	0.01
1,919	100	30.4	420	21.9	< 0.001

‡P-value calculated for PPV at screen-film mammography versus digital mammography

The positive predictive value of referral was significantly lower at FFDM (21.9% versus 31.6%, $p < 0.001$). Per 1,000 screened women, screen-detected DCIS increased from 0.7 at SFM to 1.6 at FFDM ($p < 0.001$) and invasive cancer from 4.2 at SFM to 5.1 at FFDM ($p < 0.001$). The proportion of ductal carcinoma in-situ (DCIS) among women with screen-detected cancers was significantly higher at FFDM (23.8% versus 14.8%, $p = 0.003$). Both the referral rate for suspicious microcalcifications per 1,000 screens and the proportion of women referred for suspicious microcalcifications significantly increased at FFDM (from 2.5 at SFM to 9.2 at FFDM ($p < 0.001$) and from 16.2% at SFM to 30.2% at FFDM ($p < 0.001$), respectively, Table 2). The referral rate for densities was also significantly higher at FFDM (16.9 versus 10.9, $p < 0.001$), but the proportion of women referred for suspicious densities was lower than the one found at SFM (55.7% versus 70.5%, $p < 0.001$). The positive predictive value of referral for densities and for suspicious microcalcifications decreased from 30.9% at SFM to 20.3% at FFDM ($p < 0.001$), and from 34.9% to 21.0% ($p < 0.001$), respectively. Most of the extra cancer detection at FFDM (1.4 out of 1.7 per 1,000 screens) was in cases showing either calcifications alone or calcifications associated with density. Referral rate, cancer detection rate and positive predictive value of referral at digital screening were similar for the first half and the second half of digitally obtained screens in each screening unit (2.9% versus 3.1% ($p = 0.6$), 6.9 per thousand versus 6.5 per thousand ($p = 0.6$) and 23.4% versus 20.8% ($p = 0.7$), respectively).

Diagnostic work-up

Almost half (49.0%) of women referred at SFM or FFDM only received additional breast imaging at diagnostic workup and the number of women who only underwent breast imaging at workup almost doubled from 7.6 at SFM to 14.9 at FFDM per 1,000 screens ($p < 0.001$, Table 3). The other half of referred women underwent biopsy in addition to breast imaging (either percutaneous biopsy, excisional biopsy, or a combination of percutaneous and surgical biopsy). Among the different types of biopsy procedures, the use of stereotactic core needle biopsy most markedly increased after conversion from SFM to FFDM (from 2.2 per 1,000 analogue screens to 7.9 per 1,000 digital screens, $p < 0.001$), the proportion of referred women who underwent stereotactic core needle biopsy increased from 14.9% (140/940) at SFM to 26.4% (506/1,919) at FFDM ($p < 0.001$). The increase in stereotactic core needle biopsy was mainly due to the increase in referral for microcalcifications. The positive predictive value of percutaneous biopsy decreased from 62.8% (297/473) at SFM to 42.9% (418/974) at FFDM ($p < 0.001$) and the highest drop in positive predictive value was found for stereotactic core needle biopsy (from 40.0% (56/140) at SFM to 26.9% (136/506) at FFDM, $p < 0.001$).

Tumour characteristics

Per 1,000 screened women, there was a significant increase with FFDM vs. SFM in the detection rate of low- and intermediate grade DCIS (+ 0.7), invasive T1a-c cancers (+ 0.9), invasive ductal cancers (+0.9), low-grade (+1,1), node-negative invasive cancers (+1.2), oestrogen-receptor or progesterone-receptor positive invasive cancers (respectively +0.9 and +1.1) and Her2/Neu negative (+0.8) invasive cancers (Table 4).

Type of breast cancer surgery

Compared to women screened with SFM, a significantly higher proportion of women screened with FFDM underwent breast conserving surgical treatment of their screen-detected cancer (82.9% versus 75.1%, $p = 0.04$, Table 1). The number of women undergoing breast conserving surgery increased from 3.7 per 1,000 screened women at SFM to 5.5 per 1,000 women at FFDM ($p = 0.04$). A similar mastectomy rate of 1.1 per 1,000 screened women was observed at SFM and FFDM.

Table 3. **Diagnostic work-up of women referred at screening mammography**

Diagnostic work-up	Screen-film mammography			Digital mammography		
	n	Proportion (%)	Rate[§] (‰)	n	Proportion (%)	Rate[§] (‰)
Breast imaging only[*]	461	49.0	7.6	941	49.0	14.9
Breast imaging + US-guided FNAC or CB	325	34.5	5.3	458	23.9	7.2
Breast imaging + SCNB	134	14.2	2.2	499	26.0	7.9
Breast imaging + excisional biopsy	4	0.4	0.1	2	0.1	0.0
Breast imaging + percutaneous biopsy[±] + excisional biopsy	14	1.5	0.2	17	0.9	0.3
None/unknown	3	0.3	0.0	2	0.1	0.0
Total	941		15.5	1,919		30.4

[*]Mammography, breast ultrasonography, Magnetic Resonance Imaging or any combination of these imaging modalities.

[±]US-guided FNAC, US-guided CB, SCNB or any combination of these biopsy procedures.

[§]Per 1,000 screened women.

US = ultrasound. FNAC = fine needle aspiration cytology. CB = core biopsy. SCNB = stereotactic core needle biopsy.

Table 4. **Tumor characteristics of screen-detected cancers**

	Proportion					Rate (per 1,000 screened women)		
	SFM		DM		P-value	SFM	DM	P-value
	N	(%)	N	(%)				
Ductal carcinoma in situ					0.09			
Low grade	7	(15.9)	28	(28.0)		0.1	0.4	0.001
Intermediate grade	15	(31.8)	38	(38.0)		0.2	0.6	0.001
High grade	23	(52.3)	34	(34.0)		0.4	0.5	0.19
Invasive carcinoma					0.4			
Ductal	199	(78.7)	263	(82.2)		3.3	4.2	0.01
Lobular	30	(11.9)	24	(7.5)		0.5	0.4	0.3
Mixed ductal/lobular	10	(4.0)	18	(5.6)		0.2	0.3	0.2
Other	13	(5.1)	14	(4.4)		0.2	0.2	0.9
Unknown	1	(0.4)	1	(0.3)		0.0	0.0	0.9
Size of invasive cancers					0.5			
T1a-c	197	(77.9)	258	(80.6)		3.2	4.1	0.01
T2+	54	(21.3)	58	(18.1)		0.9	0.9	0.9
Unknown	2	(0.8)	4	(1.3)		0.0	0.1	0.4
Lymph-node status					0.001			
Positive	80	(31.6)	59	(18.4)		1.3	0.9	0.04
Negative	171	(67.6)	254	(79.4)		2.8	4.0	<0.001
Unknown	2	(0.8)	7	(2.2)		0.0	0.1	0.1
Tumor stage					<0.001			
Advanced*	105	(41.5)	87	(27.2)		1.7	1.4	0.1
Non-advanced	146	(57.7)	226	(70.6)		2.4	3.6	<0.001
Unknown	2	(0.8)	7	(2.2)		0.0	0.1	0.1
Tumor grade					0.003			
NottinghamI	99	(39.1)	172	(53.8)		1.6	2.7	<0.001
Nottingham II	115	(45.5)	117	(36.6)		1.9	1.9	0.9
Nottingham III	32	(12.6)	22	(6.9)		0.5	0.3	0.1
Unknown	7	(2.8)	9	(2.8)		0.1	0.1	0.7
Estrogen-receptor					0.6			
Positive	224	(89.2)	291	(91.5)		3.7	4.6	0.01
Negative	27	(10.8)	27	(8.5)		0.4	0.4	0.9
Unknown	2	(0.8)	2	(0.6)		0.0	0.0	0.9
Progesterone-receptor					0.007			
Positive	167	(66.0)	237	(74.1)		2.7	3.8	0.002
Negative	76	(30.0)	81	(25.3)		1.3	1.3	0.9
Unknown	10	(4.0)	2	(0.6)		0.2	0.0	0.02
Her2/Neu-receptor					0.9			
Positive	28	(11.1)	33	(10.3)		0.5	0.5	0.6
Negative	221	(87.4)	281	(87.8)		3.6	4.4	0.03
Unknown	4	(1.6)	6	(1.9)		0.1	0.1	0.6
Triple-negative receptor	13	(6.3)	18	(5.6)	0.7	0.3	0.3	0.8

Discussion

To our knowledge, the current population-based study is the first that provides a thorough overview of the impact of transition of SFM to FFDM on screening outcome as well as on diagnostic workup and surgical treatment. This transition resulted in a significantly increased referral rate and detection rate of ductal carcinoma in-situ and invasive cancers, in combination with a significantly decreased positive predictive value of referral and biopsy and an almost fourfold increase in the use of stereotactic core needle biopsy. Invasive cancers at FFDM were more likely to be diagnosed at an earlier tumour stage, showed a more favourable tumour grade and comprised a significantly larger proportion of progesterone-receptor positive cancers. Moreover, cancers detected at FFDM were more likely to be treated by breast conserving surgery, whereas the mastectomy rate was comparable to the rate observed at SFM.

Studies report conflicting results on the effect of implementation of digital mammography on referral rate. Compared to SFM, a significantly higher referral rate[3-5,7,14,15] was observed at FFDM in several European and US studies, whereas others reported a similar or decreased referral rate[16,17] at FFDM. Our three per cent referral rate at FFDM is still lower than the one observed in most other digital screening mammography programs, but it is in accordance with the recommended referral rate in the European guidelines for quality assurance in breast cancer screening and diagnosis[18]. We found a significantly higher overall cancer detection rate at FFDM and most of these extra cases (1.4 out of 1.7 per 1,000 screens) either showed microcalcifications or microcalcifications associated with a density, which is in line with previous studies[3-7,15]. In other study, a higher detection rate at FFDM was only observed for cancers depicted as clustered microcalcifications[4]. Another Dutch study also reported a better depiction of microcalcifications at FFDM leading to a higher SNCB rate7. Finally, several investigators found similar detection rates at FFDM and SFM[17,19].

In our study, the detection rate at screen-film mammography was similar for initial and subsequent screens, whereas a higher detection rate for initial screens was observed in another Dutch study by Fracheboud et al[20]. This contradictory finding may be due to differences in study populations. Many women will have been included several times by Fracheboud et al during their much longer inclusion period, whereas women in our study were included only once in the group of analogue screens. Also, a potentially higher detection rate at initial screens may have been compensated by an increased baseline cancer-risk for women at subsequent screening, as the mean age will be higher for the latter group.

In contrast with most other studies[3-5,14,17,] we observed a significantly lower positive predictive value of referral at FFDM, as compared to SFM. The Dutch nation-wide screen-film mammography program has always been characterized by a very low referral rate of less than 1.5%[5,9] and the referral rate at digital screening of 3.0%, that was observed in our study, has inevitably resulted in a lower positive predictive value. Yet, our positive predictive value of 21.9% is still considerably higher than those reported in other FFDM studies[3,5] and one should try to

minimize false positive referrals as these women may experience considerable and sustained psychological distress[21,22].
In both screening groups, 51% of referred women underwent biopsy in addition to diagnostic breast imaging procedures. The positive predictive value of percutaneous biopsy decreased from 62.8% at SFM to 42.9% at FFDM and the latter percentage is comparable to those reported in other studies[3,5]. The increased overall referral rate at FFDM was mainly due to improved detection of densities and clustered microcalcifications. The increased detection of lesions presenting as microcalcifications resulted in an almost fourfold increase in stereotactic core needle biopsies per thousand screened women and, despite an improved cancer detection rate, in a marked decrease of the positive predictive value of stereotactic biopsies from 40.0% to 26.9%. The increased use of stereotactic core needle biopsy at digital screening will have a great impact on the daily practice of the regional breast clinics as it is much more time consuming than ultrasound guided biopsy.

There are very few data available comparing tumour characteristics of cancers detected at SFM and FFDM. We identified a higher proportion of low- to intermediate-grade DCIS at FFDM. Sparsely available studies on DCIS have shown conflicting results. In accordance with our findings, a US study identified a higher proportion of low- to intermediate-grade DCIS at FFDM4. However, a Scandinavian study found a higher proportion of high-grade cases which approached statistical significance[23]. These discrepancies are interesting as they may reflect differences in screening education and differences in referral guidelines for microcalcifications detected at screening mammography.

The proportion of advanced cancers was significantly lower at FFDM, due to an increase in the detection of smaller, lymph-node negative cancers. In line with an Irish study, we also found a significantly higher proportion of low-grade invasive tumours at FFDM, while more grade 2 and 3 tumours were identified at SFM24. Finally, rates of progesterone-positive, oestrogen-positive and Her2/Neu-negative invasive cancer were increased at FFDM. The rates of triple-negative invasive cancers did not change. We did not find any previously published data on receptor characteristics of cancers detected at FFDM to compare our results with.

To our knowledge, our study is the first that addresses the influence of transition from SFM to FFDM on surgical treatment of screen-detected cancer. There are conflicting reports whether the mastectomy rate is higher in screened than in non-screened women[25,26]. Our data show that tumours detected by FFDM were more likely to be treated with breast-conserving surgery. The mastectomy rate was similar for both groups and transition to FFDM thus not increases a woman's change to undergo mastectomy.

A potential harmful effect of screening is the phenomenon of so-called over-diagnosis of breast cancers, i.e. diagnosis of breast cancers that, if left undiscovered, would never become clinically evident and, thus, would never become lethal. The detection rate of DCIS more than doubled at FFDM (from 0.7 to 1.6), with a significantly larger proportion of low- to intermediate

grade DCIS, whereas the enhanced detection rate of invasive cancers was less profound (from 4.2 to 5.1). Estimates of over-diagnosis vary greatly among studies, from 2-50%, and may be explained by the length of follow-up to allow for lead time, or by the denominator that is used to define the population at risk[26-28]. De Gelder et al. calculated that the proportion of over-diagnosed cancers at the Dutch nation-wide breast screening program will increase from 2.1% at SFM to 2.5% at FFDM, without a further significant reduction in breast cancer mortality[8]. Our findings of a marked increase in small invasive cancers and low to intermediate DCIS at FFDM suggests that the proportion of overdiagnosed cancers is probably higher than the one mentioned by De Gelder et al[8].

Our study has certain limitations. Although all screening radiologists received training on digital screening mammography at the National Expert and Training Centre for Breast cancer screeningprior to implementation of FFDM and all radiologists had more than 5 years experience with working in a digital radiology environment, none of them had experience with the use of FFDM in screening at the start of the study. It is unlikely, however, that our results will have been influenced by a "learning effect", as referral rate, cancer detection date and positive predictive value of referral were similar for the first and second half of the inclusion period for digital screens. The FFDM group was restricted to women who were digitally screened for their first time and we cannot predict the long-term impact of successive digital screening rounds on screening outcome. However, a recent Dutch study found that referral rates at successive digital screening decreased and stabilized at a higher level than in conventional screening, yet with significantly enhanced cancer detection[6]. We could not determine screening sensitivity at FFDM as follow-up should be continued until the next biennial screen in order to detect all interval cancers.

Finally, we are not certain whether the routine comparison of digital screens with previous analogue screens that had been digitized, rather than comparison with the original hard copy analogue screens, may have had some effect on the screening results.
In summary, we conclude that the transition from SFM to FFDM resulted in a significantly enhanced cancer detection rate for DCIS and invasive cancers, at the expense of an increased referral rate and decreased positive predictive value of referral and biopsy. Invasive cancers detected at FFDM were more frequently of low grade, showed less lymph node involvement and were more frequently progesterone-receptor positive. Women with breast cancer detected at FFDM were more likely to be treated by breast conserving surgery, while the mastectomy rate was similar at SFM and FFDM.

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Chapter 4.2

Impact of the transition from screen-film screening mammography to digital screening mammography on interval cancer characteristics and treatment

Published as: Nederend J, *Duijm LE, Louwman MW, Coebergh JW, Roumen RM, Lohle PN, Roukema JA, Rutten MJ, van Steenbergen LN, Ernst MF, Jansen FH, Plaisier ML, Hooijen MJ, Voogd AC.* ***Impact of the transition from screen-film to digital screening mammography on interval cancer characteristics and treatment - A population based study from the Netherlands.*** *Eur J Cancer. 2014 Jan;50(1):31-9. doi: 10.1016/j.ejca.2013.09.018. Epub 2013 Oct 25.*

Abstract

Background: In most breast screening programs screen-film mammography (SFM) has been replaced by full-field digital mammography (FFDM). We compared interval cancer characteristics at SFM and FFDM screening mammography.

Methods: We included all 297 screen-detected and 104 interval cancers in 60,770 SFM examinations and 427 screen-detected and 124 interval cancers in 63,182 FFDM examinations, in women screened in the period 2008-2010. Breast imaging reports, biopsy results and surgical reports of all cancers were collected. Two radiologists reviewed prior and diagnostic mammograms of all interval cancers. They determined breast density, described mammographic abnormalities and classified interval cancers as missed, showing a minimal sign abnormality or true negative.

Results: The referral rate and cancer detection rate at SFM were 1.5% and 4.9‰ respectively, compared to 3.0% ($p<0.001$) and 6.6‰ ($p<0.001$) at FFDM. Screening sensitivity was 74.1% at SFM (297/401, 95%CI=69.8%-78.4%) and 77.5% at FFDM (427/551, 95%CI=74.0%-81.0%). Significantly more interval cancers were true negative at prior FFDM than at prior SFM screening mammography (65.3% (81/124) versus 47.1% (49/104), $p=0.02$). For interval cancers following SFM or FFDM screening mammography, no significant differences were observed in breast density or mammographic abnormalities at the prior screen, tumour size, lymph node status, receptor status, Nottingham tumour grade or surgical treatment (mastectomy versus breast conserving therapy).

Conclusion: FFDM resulted in a significantly higher cancer detection rate, but sensitivity was similar for SFM and FFDM. Interval cancers are more likely to be true negative at prior FFDM than at prior SFM screening mammography, whereas their tumour characteristics and type of surgical treatment are comparable.

Introduction

Full-field digital mammography (FFDM) has gradually replaced screen-film mammography (SFM) in most Western screening mammography programs. Several studies have shown an increased cancer detection rate at FFDM, in combination with higher referral rates and decreased positive predictive values of referral[1-3]. Because of the higher cancer detection rate at digital mammography, a decline in interval cancer rate may be expected. Interval cancers are breast cancers that are diagnosed in women after a screening examination yields negative results, defined as no recommendation for referral, and before any subsequent screen is performed. Furthermore, interval cancers show less favourable pathologic characteristics and a worse prognosis compared to screen-detected cancers[4-9].

Previous analogue screening mammography studies have shown that up to half of interval cancers may be true negative at review of prior mammograms[10-12]. Moreover, a significant portion of advanced interval cancers at SFM screening cannot be prevented through earlier detection at screening[13]. There is, however, very limited data about interval cancers diagnosed after digital screening mammography and it is not yet clear whether the interval cancers found at screen-film mammography are similar to interval cancers found at digital mammography screening. A recent Norwegian study on interval cancers diagnosed after screen-film or digital screening mammography did not find a decline in the interval cancer rate at digital screening and the mammographic features of missed cancers at digital screening were comparable to those missed at screen-film mammography screening[14].

To our knowledge, no data have been published on interval cancers at SFM an FFDM screening mammography in terms of their tumour biology and surgical treatment. In the current study we therefore not only compared the screening sensitivity and mammographic features of interval cancers at screen-film mammography and digital screening mammography, but we also determined tumour biology characteristics, including receptor status and tumour histology grade, and the type of surgical treatment (i.e., breast conserving surgery or mastectomy) of these interval cancers.

Methods

Study population

We included a consecutive series of 60,770 screen-film screened women (6,851 initial screens and 53,919 subsequent screens) and 63,182 digitally screened women (7,019 initial screens and 56,163 subsequent screens). They were screened at three specialized screening units in a southern screening mammography region of the Netherlands (BOZ, Bevolkings Onderzoek Zuid) between January 1, 2008 and January 1, 2011. Of the 56,163 women with a subsequent digital screen, 29,649 were also included in the cohort of screen-film screened women.

Screen-film mammography was replaced by full field digital mammography on respectively May 26, 2009, June 3, 2009 and April 6, 2010 at the three units. All women had given written informed consent to use their screening and follow-up data for evaluation purposes. The Central Committee on Research Involving Human Subjects (CCMO) in The Hague, The Netherlands, waived ethical approval for this study.

Screening procedure and referral

Details of our breast cancer-screening program, offering biennial screening mammography for women aged 50-75 years, have been described previously[15,16]. In brief, screen-film mammograms were obtained with commercially available units (Performa, Oldelft, Tuusula, Finland). Dedicated mammography screens were utilized (Mamoray MR-R, Agfa, Schroenhausen, Germany). Both dedicated film (Mamoray HDR; Agfa, Mortsel, Belgium), as well as extended-cycle dedicated processing was used. All digital mammograms were acquired with a Lorad Selenia FFDM system (Hologic Inc, Danbury, CT), with a 70 µm pixel size and a 232x286 mm field of view. All mammograms were obtained by specialized screening mammography technologists and double read by a team consisting of eleven certified screening radiologists. Prior screening mammograms were always available for comparison at the time of subsequent screening. To facilitate softcopy reading of subsequent screening examinations at FFDM, the most recent prior screen-film screening mammograms were digitized by using a film scanner and archiver designed for mammography (DigitalNow; R2/Hologic). The original hard copy screen film mammograms were also available for viewing if desired by the screening radiologist. Women with normal or benign mammographic findings, or with a non-specific minimal sign[17], were not referred. If screening mammography showed a suspicious or malignant lesion, the woman was referred to a surgical oncologist or breast clinic for further analysis of the mammographic abnormality. For each referral, the screening radiologists classified the abnormal mammographic findings according to one of five categories: suspicious mass (e.g., spiculated density or density with indistinct borders), suspicious microcalcifications (e.g., pleomorphic, branching, or amorphous/indistinct microcalcifications), mass in combination with microcalcifications, architectural distortion, or asymmetry. Women with discrepant readings at screening mammography (only one of the two screening radiologists considered referral necessary) were always referred for further analysis.

Diagnostic workup

A total of 15 regional and university hospitals were involved in the assessment of screen positive women. After physical examination by the surgeon, additional mammographic views were obtained if necessary. At diagnostic work-up, radiologists classified the radiological findings according to the American College of Radiology BI-RADS[18]. BI-RADS 4 and BI-RADS 5 lesions were routinely biopsied, whereas BI-RADS 3 lesions were either biopsied of followed-up with mammography. Dependent on the findings at physical examination and mammography, further diagnostic evaluation could include breast ultrasonography, Magnetic Resonance Mammography, percutaneous fine needle aspiration cytology, core biopsy or open surgical biopsy.

Follow-up

During two-year follow-up, we collected data on diagnostic imaging procedures, biopsy specimen and surgical procedures of all referred women and of interval breast cancers. Interval cancers were defined as breast cancers diagnosed in women after a screening examination yielded negative results (defined as no recommendation for referral) and before a subsequent biennial screen was performed. Procedures for the detection of interval cancers have been described previously[19]. Breast cancers were divided into ductal carcinoma in-situ and invasive cancers; lobular carcinoma in-situ was considered to be a benign lesion. Advanced cancers were defined as invasive cancers with Tumour-Node-Metastases (TNM) stage IIA or higher, i.e. tumour size exceeding 20 mm (T2) and/or presence of lymphatic metastasis in the sentinel node or axillary lymph nodes[20]. Sentinel nodes were classified negative if they harboured isolated tumour cells or sub-micrometastases (<0.2 mm) and were considered positive (N+) if they contained micrometastases (0.2-2 mm) or macrometastases (>2 mm). For women with bilateral disease, the cancer with the highest stage was retained; multiple foci of cancer in one breast were counted as one cancer.

Review of interval cancers

Two experienced screening radiologists (LD, FJ) reviewed the latest screening mammogram of each woman with an interval cancer, as well as the clinical mammogram obtained at the time of interval cancer detection. They categorized mammographic breast density according to the American College of Radiology[18] and the interval cancers were classified as missed, minimal sign[17] or true negative at the previous screen according to the European guidelines[21]. Finally, in case of missed or minimal sign interval cancers, the reviewers classified the mammographic abnormality at the prior screening examination into one of the following categories: mass, microcalcifications, mass in association with microcalcifications, asymmetry, architectural distortion, or other[18]. The two radiologists were blinded to each other's review and performed a consensus reading in case of discrepant findings.

Statistical analysis

All data were entered into a computerized spreadsheet (Excel; Microsoft, Redmond, WA, USA). The analyses were conducted by using statistical software (SPSS, version 20 for Windows; SPSS, Chicago, Ill). The statistical differences in distributions were explored by using the χ^2 test or the Fisher exact test, when appropriate. A t-test for independent samples was used to compare the size of masses. All tests were two sided, and the significance level was set at 5%.

Results

Overall screening results

The referral rate and overall cancer detection rate (number of cancers per 1,000 screened women) were significantly higher at FFDM (3.0% versus 1.5% ($p<0.001$) and 6.6 versus 4.9 ($p<0.001$), respectively, Table 1). The cancer detection rate at initial screens was similar to the one observed at subsequent screens (SFM: 4.7 versus 4.9, $p=0.8$; FFDM: 7.6 versus 6.6, $p=0.3$). The positive predictive value of referral was significantly lower at FFDM (21.9% versus 31.6%, $p<0.001$). Although statistically different, the age distributions of both groups were almost similar when looking at the percentages in each age category.
After SFM, 104 interval breast cancers were diagnosed, compared to 124 interval breast cancers following FFDM. The interval cancer rate per 1,000 screens was similar for SFM and FFDM, namely 1.7 versus 2.0 ($p=0.3$). Screening sensitivity was 74.1% at SFM (95% CI, 69.8-78.4) and 77.5% at FFDM (95% CI, 74.0-81.0). Interval cancers showed comparable proportions of ductal carcinoma in-situ and invasive cancers at SFM and FFDM (respectively 6.7% (7/97) and 93.3% (90/97) versus 7.3% (9/124) and 92.7% (115/124), $p=0.9$). The proportions of interval breast cancers diagnosed within the first year after the latest screen were also similar at SFM and FFDM (36.8% (38/104) versus 35.5% (44/124), $p=0.9$).

Prior visibility and mammographic characteristics of interval cancers

At review, 47.1% (49/104) and 65.3% (81/124) of interval cancers were classified as occult (so-called true interval cancers) at the prior screen-film or digital screening mammogram, respectively. The percentages of missed interval breast cancer and interval breast cancer presenting as a minimal sign on the latest screen were 30.8% (32/104) and 22.1% (23/104) at screen-film mammography screening, and 20.2% (25/124) and 14.5% (18/124) at digital screening ($p=0.02$, Table 1).
A majority of the missed interval breast cancers and interval breast cancers characterized by a minimal sign lesion at the prior screen presented as a mass, both at SFM and FFDM (Table 2). Size distribution, average tumour size and distribution of breast density at the prior screening mammograms of interval cancers (whether missed, true negative or showing a minimal sign at review) were comparable for SFM and FFDM (Table 2). Also the average size of all invasive interval cancers was similar for SFM and FFDM, 23.7 millimetre (range 1-100) and 27.0 millimetre (range 2-90), respectively ($p=0.2$).

Tumour stage and tumour biology characteristics of interval cancers

Table 3 summarizes the tumour stage and tumour biology characteristics of interval breast cancers at SFM and FFDM. At both screening cohorts, a minority of interval cancers was ductal carcinoma in-situ and these cancers showed comparable grade distributions. A majority of the invasive interval breast cancers were of the ductal type, respectively 74.2% (72/97) at SFM and 77.4% (89/115) at FFDM ($p=0.49$). Tumour stage (T1a-c versus T2+), lymph node status and the

proportion of advanced cancers were also comparable for interval cancers following SFM or FFDM screening mammography. We neither observed significant differences in the grading of invasive cancers (Nottingham grade I-III) or receptor status.

Type of breast cancer surgery

Compared to SFM screened women, a significantly higher proportion of FFDM screened women underwent breast conserving surgical treatment of their screen-detected cancer (82.9% versus 75.1%, P = 0.04, Table 1). The number of women treated with breast conserving surgery was 3.7 per 1,000-screened women at SFM and 5.5 per 1,000 women at FFDM (P = 0.04). A similar mastectomy rate of 1.1 per 1,000 screened women was observed at SFM and FFDM. A majority of interval cancer cases were also treated by breast conserving surgery and we found no significant differences in surgical treatment of interval breast cancer in both screening cohorts (p=0.18).

Table 1. **Overall screening results**

	Screen-film mammography		
		Fraction	Rate (‰)
Mammograms, No	60,770		
Referral, No	941	1.5%	
Positive predictive value of referral, %	31.6		
Sensitivity,% (95% CI)	74.1% (69.8-78.4%)		
Breast cancers detected, No	297		4.9
Ductal carcinoma in-situ, No	44	14.8%	0.7
Invasive carcinoma, No	253	85.2%	4.2
Interval cancers detected, No	104		1.7
Ductal carcinoma in-situ, No	7	6.7%	0.1
Invasive carcinoma, No	97	93.3%	1.6
Prior visibility of interval cancers			
Missed, No	32	30.8%	0.5
Minimal Sign, No	23	22.1%	0.4
Occult, No	49	47.1%	0.8
Interval between screen and interval breast cancer			
≤1 year, No	38	36.5%	0.6
>1 year, No	66	63.5%	1.1
Type of surgery			
Screen detected cancer			
Breast conserving treatment, No	223	75.1%	3.7
Mastectomy, No	69	23.2%	1.1
None, No	5	1.7%	0.1
Interval cancer			
Breast conserving treatment, No	67	64.4%	1.1
Mastectomy, No	37	35.6%	0.6
None, No	0	0.0%	0.0

Table 1. **Overall screening results** *(continued)*

	Digital mammography			
		Fraction	Rate (‰)	p-value
Mammograms, No	63,182			
Referral, No	1.919	3.0%		< 0.0001
Positive predictive value of referral, %	22.3			< 0.0001
Sensitivity,% (95% CI)	77.5% (74.0-81.0%)			0.2
Breast cancers detected, No	427		6.8	< 0.0001
Ductal carcinoma in-situ, No	100	23.8%	1.6	0.03
Invasive carcinoma, No	320	76.2%	5.1	
Interval cancers detected, No	124		2.0	0.3
Ductal carcinoma in-situ, No	9	7.3%	0.1	0.9
Invasive carcinoma, No	114	91.9%	1.9	
Prior visibility of interval cancers				
Missed, No	25	20.2%	0.4	0.02
Minimal Sign, No	18	14.5%	0.3	
Occult, No	81	65.3%	1.3	
Interval between screen and interval breast cancer				0.9
≤1 year, No	44	35.5%	0.7	
>1 year, No	80	64.5%	1.3	
Type of surgery				
Screen detected cancer				
Breast conserving treatment, No	348	82.9%	5.5	0.04
Mastectomy, No	68	16.2%	1.1	
None, No	4	1.0%	0.1	
Interval cancer				
Breast conserving treatment, No	78	62.9%	1.3	0.18
Mastectomy, No	42	33.9%	0.7	
None, No	4	3.2%	0.1	

Table 2. **Mammographic features of interval breast cancer**

	Screen-film mammography		Digital mammography		
	No.	Fraction (%)	No.	Fraction (%)	p value
Missed interval cancer					
Mammographic abnormality					
Mass	21	65.6	15	60.0	0.78
Clustered microcalcifications	1	3.1	2	8.0	0.58
Mass and clustered micocalcifications	1	3.1	1	4.0	1
Asymmetry	3	9.4	4	16.0	0.69
Architectural distortion	5	15.6	3	12.0	1
Other	1	3.1	0	0.0	1
Size					
Ductal carcinoma in-situ	1	3.1	2	8.0	0.4
T1a-b	3	9.4	2	8.0	0.9
T1c	10	31.3	6	24.0	0.6
T2+	18	56.3	14	56.0	1
Tx	0	0.0	1	4.0	0.3
Size in mm (range)	27.6 (5-100)		32.2 (7-90)		0.58
Breast density					0.8
ACR I & II	18	56.3	13	52.0	
ACR III & IV	14	43.8	12	48.0	

Table 2. **Mammographic features of interval breast cancer** *(continued)*

	Screen-film mammography		Digital mammography		
	No.	Fraction (%)	No.	Fraction (%)	p value
Interval breast cancer showing a minimal sign					
Mammographic abnormality					
Mass	14	60.9	9	50.0	0.54
Clustered microcalcifications	4	17.4	1	5.6	0.36
Mass and clustered micocalcifications	0	0.0	1	5.6	0.44
Asymmetry	0	0.0	2	11.1	0.19
Architectural distortion	2	8.7	5	27.8	0.21
Other	3	13.0	0	0.0	0.24
Size					
Ductal carcinoma in-situ	1	4.3	3	16.7	0.2
T1a-b	2	8.7	0	0.0	0.2
T1c	6	26.1	6	33.3	0.6
T2+	14	60.9	9	50.0	0.5
Tx	0	0.0	0	0.0	-
Size in mm (range)	26.6 (1-60)		30.2 (7-80)		0.51
Breast density					0.3
ACR I & II	14	60.9	14	77.8	
ACR III & IV	9	39.1	4	22.2	
Occult interval breast cancer					
Size					
Ductal carcinoma in-situ	5	10.2	4	4.9	0.25
T1a-b	9	18.4	10	12.3	0.35
T1c	14	28.6	28	34.6	0.48
T2+	21	42.9	38	46.9	0.65
Tx	0	0.0	1	1.2	0.44
Size in mm (range)	19.1 (2-42)		24.6 (2-80)		0.06
Breast density					0.36
ACR I & II	25	51.0	48	59.3	
ACR III & IV	24	49.0	33	40.7	

ACR = American college of radiology

Table 3. **Tumor characteristics of interval breast cancer**

	Screen-film mammography			Digital mammography			
	No.	Fraction, %	Rate (‰)[±]	No.	Fraction, %	Rate (‰)[±]	p-value
Ductal carcinoma in-situ							
Grade							0.66
Low grade	2	28.6	0.03	3	33.3	0.05	
Intermediate grade	3	42.9	0.05	2	22.2	0.03	
High grade	2	28.6	0.03	4	44.4	0.06	
Invasive Carcinoma							
Type							0.49
Ductal	72	74.2	1.2	89	77.4	1.4	
Lobular	16	16.5	0.3	17	14.8	0.3	
Mixed ductal/lobular	7	7.2	0.1	4	3.5	0.1	
Other	2	2.1	0.03	5	4.3	0.08	
Stage							0.43
T1a-c	44	45.4	0.7	52	45.2	0.8	
T2+	53	54.6	0.9	61	53.0	1.0	
Unknown	0	0.0	0.0	2	1.7	0.0	
Lymph node status							0.42
N+	44	45.4	0.7	50	43.5	0.8	
N0	52	53.6	0.9	63	54.8	1.0	
Nx	1	1.0	0.02	2	1.7	0.03	
Advanced carcinoma							0.73
Advanced	67	69.1	1.1	74	64.3	1.2	
Non-advanced	29	29.9	0.5	39	33.9	0.6	
Unknown	1	1.0	0.02	2	1.7	0.03	

Table 3. **Tumor characteristics of interval breast cancer** *(continued)*

	Screen-film mammography			Digital mammography			
	No.	Fraction, %	Rate (‰)[‡]	No.	Fraction, %	Rate (‰)[‡]	p-value
Nottingham I	34	35.1	0.6	31	27.0	0.5	
Nottingham II	42	43.3	0.7	63	54.8	1.0	
Nottingham III	20	20.6	0.3	18	15.7	0.3	
Unknown	1	1.0	0.02	3	2.6	0.05	
Estrogen receptor							0.87
Positive	75	77.3	1.2	90	78.3	1.4	
Negative	22	22.7	0.4	25	21.7	0.4	
Progesterone receptor							0.24
Positive	60	61.9	1.0	62	53.9	1.0	
Negative	37	38.1	0.6	53	46.1	0.8	
Her2/Neu receptor							0.79
Positive	13	13.4	0.2	14	12.2	0.2	
Negative	84	86.6	1.4	101	87.8	1.6	
Triple receptor- negative	15	15.5	0.2	20	17.4	0.3	0.71

[*]Invasive cancers with Tumor-Node-Metastases (TNM) stage IIA or higher. i.e. tumor size exceeding 20 mm (T2) and/or presence of lymphatic metastasis in the sentinel node or axillary lymph nodes.

[‡] Per 1,000 screened women.

Discussion

We found that the interval breast cancer rate and sensitivity was comparable for SFM and FFDM screening mammography, despite a significantly higher cancer detection rate at FFDM. A significantly larger proportion of interval breast cancers was not visible on prior screens at FFDM than at SFM, whereas mammographic characteristics, tumour stage, tumour biology and surgical treatment were similar for interval cancers diagnosed after SFM or FFDM screening mammography.

In line with our results, the only previous study reporting on interval breast cancer at digital screening also found a similar screening sensitivity and interval breast cancer rate at SFM and FFDM[14]. Previous studies have reported increased cancer detection rates at FFDM screening mammography in the Netherlands[22], Norway[23] and Ireland[24], whereas SFM and FFDM showed similar detection rates in a UK study and Spanish study[25,26]. US studies found comparable overall detection rates for both modalities, with a higher diagnostic accuracy for FFDM in younger women, women with dense breasts and premenopausal women[2,27,28]. In our preceding study[1], we provided a thorough overview of the impact of transition of SFM to FFDM on screening outcome as well as on diagnostic workup and surgical treatment. This transition resulted in a significantly increased referral rate and detection rate of ductal carcinoma in-situ and invasive cancers, in combination with a significantly decreased positive predictive value of referral and biopsy and an almost fourfold increase in the use of stereotactic core needle biopsy. Invasive cancers at FFDM were more likely to be diagnosed at an earlier tumour stage, showed a more favourable tumour grade and comprised a significantly larger proportion of progesterone-receptor positive cancers. Unfortunately, the higher cancer detection rate at FFDM in our study neither improved screening sensitivity nor decreased the interval breast cancer rate. This inevitably leads to the discussion of so called over-diagnosis, i.e. diagnosis of breast cancers that, if left undiscovered, would never become clinically evident and, thus, would never become lethal. Over-diagnosis is more profound at FFDM than at SFM screening mammography, mainly because of the higher detection rate of ductal carcinoma in-situ at digital screening[1,29]. However, as our study only comprised the first digital screening round, the results of future digital screening rounds are necessary to determine the long-term effects of digital screening mammography on cancer detection rate, sensitivity and the true extent of over-diagnosis. Another Dutch study found a decrease in referral rates at subsequent screening rounds and stabilization of the referral rate at a higher level than in conventional screening, yet with significantly enhanced cancer detection[30]. Based on these findings we do not expect to see any difference in interval cancer rate, as these rates are stable despite of the higher cancer detection rate.

Our observation of an unchanged proportion of ductal carcinoma in-situ among interval cancers, accompanied with an improved detection of these early cancers at FFDM, is in line with the results of a recent Norwegian study[14]. We also found that the proportion of interval cancers, diagnosed either within the first or second year after a negative screening examination, was similar for SFM and FFDM and, to our knowledge, we are the first to report on this issue.

Our proportions of missed, minimal sign and true negative interval breast cancers at SFM were comparable to those published in other studies on SFM screening[13,31,32]. A significantly higher proportion of interval breast cancers was not visible at the previous FFDM screen than at the previous SFM screen and the average tumour size of missed interval cancers was comparable for both groups. On the other hand, in a smaller series of 49 and 81 interval cancers diagnosed after respectively FFDM and SFM screening mammography, Hoff et al. observed equal proportions of missed cancers at SFM and FFDM screening mammography and a smaller tumour size for cancers missed at digital FFDM screening[14]. These differences in outcome may be partly explained by differences in study population, reading strategy and screening outcome parameters (including lower referral rates and higher positive predictive value of referral). Moreover, women were included only once in the SFM or FFDM group in our series, whereas they may have been included several times in each group reported by Hoff et al.

We recently reported that the conversion from SFM to FFDM screening mammography significantly increased the detection of low to intermediate grade DCIS and the detection of smaller invasive tumours with more favourable tumour biology characteristics[1]. In the current study, no significant differences in tumour size, lymph node status, proportion of advanced cancers, tumour grade or hormone receptor status were found between interval breast cancers diagnosed after SFM or FFDM screening mammography. Invasive tumour size was comparable for both SFM and FFDM, but the average tumour size of invasive cancers was approximately twice the size reported by Hoff et al. This difference can probably be explained by different methods of measurement. We measured tumour size on the surgical specimen, whereas Hoff et al. measured tumour size on imaging. It is known imaging can be imprecise in measuring tumour size, especially in dens breasts[33]. In contrast to an increased proportion of women treated with breast conserving surgery for their cancer detected at digital screening mammography, the surgical management of interval breast cancer was comparable for SFM and FFDM. Similar to screen-detected cancers, FFDM did not result in an altered mastectomy rate for interval breast cancer.

Our study has certain strengths and limitations. The current study is the second and the largest reporting on interval breast cancer at digital screening mammography. Moreover, we did not limit our analyses to mammographic characteristics of interval cancers and their tumour size, but we also provided insight in tumour biology and surgical management of interval breast cancers. Analysis of subsequent digital screening rounds is mandatory to fully understand the long-term impact of digital mammography on screening outcome. Another limitation lies in the fact that the Dutch screening program may differ from programs offered in other countries[34]. The Dutch nation-wide breast cancer screening program offers free biennial screening to women aged 50-75 years, screening examinations are standardly double read by two screening radiologists and it is characterized by relatively low referral rates and a high positive predictive value of referral. Furthermore, in contrast to Hoff et al[14], we were not able to review screen-detected cancers

for visibility on prior digital screens, as our digitally screened study population only comprised women who had undergone their first round of FFDM screening mammography. Also, comparability of the two groups is very important as slight changes in age distribution can lead to marked changes in cancer incidence, interval cancer rate and biology. Although statistically different, the age distributions of both groups were almost similar when looking at the percentages in each age category. It is very unlikely that these small differences will have affected the results. Finally, an increase in population breast cancer incidence could contribute to the higher cancer detection rate. According to the data of the Netherlands Cancer Registry[35], breast cancer incidence in unscreened age groups did not change significantly in the 3-year period covered by the study, Incidence rates per 100,000 women were 45 in 2008, 41 in 2009 and 44 in 2010 for women aged 30-44 years and 166, 167 and 171 respectively for those aged 75 years or older. It is thus very unlikely that the background incidence will have increased for the screened age group of 50-75 years during these three years.

In summary, FFDM screening mammography resulted in a significantly higher cancer detection rate, but a similar interval cancer rate and sensitivity when compared to SFM screening mammography. Interval breast cancers are more frequently true negative at a prior digital screening mammogram, but show comparable mammographic abnormalities if visible at prior screening. Tumour stage, tumour biology and surgical treatment of interval cancers are similar in women screened with SFM or FFDM.

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Chapter 5

General discussion

General discussion

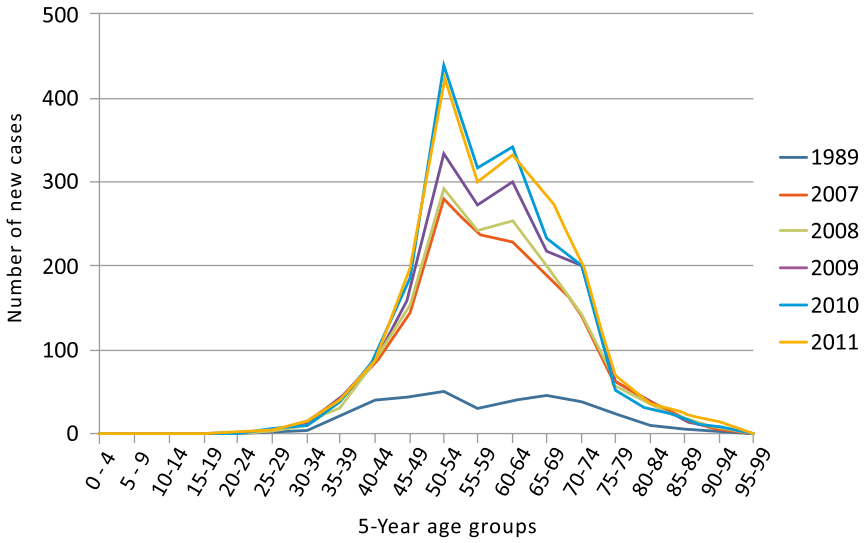
The first randomized trials on breast cancer screening were conducted in the 1960s and 1970s and took place in the United States, Canada, Sweden and the United Kingdom. The results have been summarized in a recently updated Cochrane review[1]. In this review of 8 trials, only the Malmo Trial, the UK age trial, and the Canadian trial were considered adequately randomized and not biased. The early results of these trials, published in the 1980s, were mostly promising and have been the basis to the global introduction of breast cancer screening in industrialized countries[2]. Since the introduction there has been debate about the effectiveness and in the late nineties, the first studies were published that questioned the effectiveness and focused on the side effects of breast cancer screening[3,4]. These studies provoked a fierce debate between those in favour of screening and those opposed. Some opponents of breast cancer screening state screening is obsolete because the lower mortality can mainly be contributed to improved systemic treatment; especially since interval cancer rate remains stable. This debate is still far from over and both parties are to some extent right. The true effect of screening on breast cancer mortality remains uncertain and randomized controlled trials seem no longer feasible due to the worldwide implementation of screening. Because breast cancer screening has become so deeply rooted in society, stopping the programmes is not a realistic option anymore. The only sensible option is to optimize the effectiveness of the on-going screening programmes and to improve the diagnosis and treatment of breast cancer in all screened women. In this discussion these issues will be addressed, as well as the implications of the results of the studies described in this thesis for future research.

In recent years, the debate on breast cancer screening has become more and more polarized. In an attempt to end the discussion, an independent panel convened in the United Kingdom to reach conclusions about the benefits and harms of breast screening on the basis of a review of published work with both oral and written evidence presented by experts in the subject. The panel was assembled by Professor Sir Michael Marmot and consisted of scientific experts who had not previously worked or published on the topic of breast cancer screening. Its conclusions were published in The Lancet in 2012[5]. The panel estimated that screening had decreased breast cancer mortality by 20% in the United Kingdom, whereas overdiagnosis may be present in about 11% of screen-detected cancers. Based on these findings, the panel concluded that breast cancer screening should be continued in the United Kingdom. In response to this overview, a multitude of letters to the editor was published, in which opponents of screening criticized the conclusions. On the other hand, some proponents stated that the panel had underestimated the mortality reduction and overestimated the risk of overdiagnosis resulting from breast cancer screening[6-15]. These strongly opposing reactions again illustrate that the discussion is far from over.

In addition to the previously mentioned panel, a committee of Dutch experts assessed the effectiveness of population screening for breast cancer in the Netherlands in response to a question by Minister of Health[16]. In their report, of January 2014, the committee concluded

that population screening for breast cancer is still worthwhile. They calculated a total of 775 lives saved each year, at the cost of 8% overdiagnosed screen-detected cancers. Furthermore, they explored the potential benefits of tailor-made screening, in which the screening interval and the technique used are adjusted to the individual breast cancer risk of a woman, making screening more efficient. Just like the UK report, the Dutch report leaves room for discussion. Invasive carcinoma and ductal carcinoma in-situ have been considered together when describing the risk of overdiagnosis, whereas the risk is probably much more pronounced for the latter group. The absolute number of in-situ carcinomas in women aged 50-75 has increased six fold since 1989, from 252 to 1554 in 2011 (Figure 1a), while the absolute number of invasive carcinomas doubled in the same period, from 4,066 to 8,387 (Figure 1b)[17]. The introduction of digital mammography screening has led to a further increase in the detection of ductal carcinoma in-situ and treatment involves mastectomy in 40 per cent of cases.

Figure 1a. **Nation wide incidence of in-situ carcinoma in the Netherlands** *Source: www.ikcnet.nl*

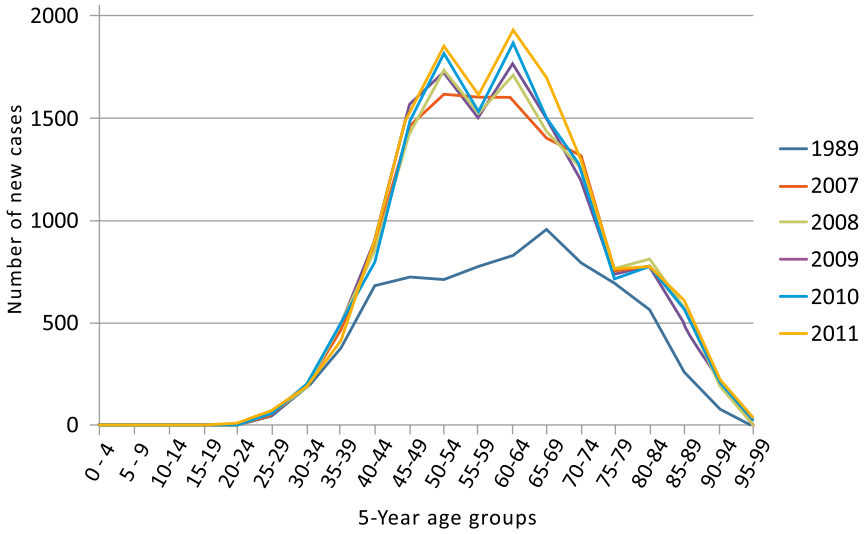


The Swiss Medical Board of uninvolved professionals recently performed a review on screening mammography[18]. The Board advises against introduction of new population breast cancer screening and advises to gradually stop with existing breast cancer screening programmes Switzerland based on three primary considerations:

- results of outdated clinical trials on mammography screening;
- benefits of screening do not clearly outweigh the harms;
- women's perceptions of screening benefits do not match reality.

Non-surprisingly, the report provoked a fierce discussion. A main counterargument is the weighed value of the very out-dated and inadequate Canadian trials on breast cancer screening[19], which are under great debate due to questionable mammographic technology applied in these studies. However, the argument that women's perceptions of mammography benefits do not

Figure 1b. **Nation wide incidence of invasive breast carcinoma in the Netherlands** *Source: www.ikcnet.nl*



match reality seems to be a valid one which has also been stressed in another recent review[20]. It is important to optimize information given on the benefits and harms for women eligible for screening, in order to enable them to decide whether or not they should attend the screening programme. This thesis focuses more on the changing oncologic reality, with improved treatment possibilities of both early and advanced breast cancer[21,22].

As mentioned in the reports by the independent UK panel, the Dutch Health Council committee, and the Swiss Medical Board, each of the available studies has several methodological flaws. To provide irrefutable results, complete data is needed; which will only become available during the process and long term follow-up. So due to the lack of any more randomized trials, prospective data collection is the sole basis of proving the value of mammography screening.

Advanced breast cancer

Most breast cancer deaths occur in women who are diagnosed with breast cancer in an advanced stage. Breast cancer screening aims to detect cancer before it has disseminated to lymph nodes or distant organs. Thus, for breast cancer screening to be effective it will have to lower the incidence of advanced breast cancer. If this assumption is true, the incidence of advanced breast cancer can be used to monitor the benefit of breast cancer screening[23]. Although the incidence of advanced breast cancer may also be affected by other determinants like changing age at first birth[24].

Recent trends

In Chapter 2 we found no decline in the incidence of advanced (T2+ and/or N+) breast cancer at screening mammography. The rates and proportions of advanced breast cancer remained stable over a 12-year time period (1997-2008). As most breast cancer deaths are due to advanced disease, this finding raises the question about the effectiveness of screening. However, it is possible that without breast cancer screening the advanced cancer rate might have been even higher. This possibility is supported by the results of a Danish study, which shows an increase of the mammographic density of the breasts of women in more recent birth cohorts, which could have impaired the detection of smaller tumours. Furthermore, breast cancer incidence has increased significantly in the last decades, due to unfavourable changes in the exposure to risk factors. These risk factors include

- Reproductive history
- Female body composition
- Nutritional factors, such as increased alcohol consumption[24,25].

Finally, the increased proportion of more aggressive tumours, as reflected by a higher mitotic activity index (MAI), might have had a negative effect on the incidence rates of advanced breast cancer[26].

The stable advanced cancer rate in our study can be explained because of the exclusion of the first two years of screening, during which the rates of advanced cancer were higher. An Italian study showed a decrease in late-stage breast cancer from the third year of screening onward[27]. As our published data starts three years after the implementation of screening, this effect might be similar in our population. Another Dutch study, however, showed a decrease in advanced breast cancer incidence the first years after implementation of breast cancer screening, but this decrease was followed by a secular rise after five years[28,29]. Furthermore, as the composition of the group of screening radiologists showed only minor changes during the years and no significant changes in technology were made until the introduction of digital mammography screening in 2009, one can assume that a plateau phase was reached for the performance.

Prevention

In the study described in Chapter 2, two screening radiologists determined whether or not the advanced cancer had been visible at a prior screen, or whether the cancer was associated with so-called minimal sign at the previous screening round. Review showed that at least 59% of the screen-detected advanced cancers could not have been discovered earlier as the cancer had not been visible at the previous screen. The majority of the latter 41% that might have been discovered earlier was visible as a minimal sign (namely 62%, 191/307). These cases could theoretically have been detected earlier if these women had been referred, but adopting such a referral policy would have resulted in recall rates of approximately 10% and, consequently, in a dramatic decrease in the predictive value of a positive screening test[30] and many more women experiencing unnecessary anxiety[31]. The remaining advanced cancers could have been detected at least one screening round before their actual diagnosis, this percentage (16%) is compa-

rable to the percentage reported in other publications[32,33]. Despite quality control programmes and feedback of individual results to the screening radiologists, this rate did not decrease throughout the years. The percentage of missed advanced breast cancers shows that there is room left for improvement. Computer-aided detection might reduce the number of missed carcinomas in the future, but at present the computer cannot improve screening sensitivity without significantly lowering specificity and its contribution to routine screening remains a question of debate[34-36]. However, future improvements in computer software may improve the performance of CAD at screening mammography. Furthermore, digital breast tomosynthesis shows promising results[37,38]. Tomosynthesis is a three-dimensional reconstruction of the breast tissue, which can be viewed as slices through the breast. Recent studies have shown that the combination of conventional mammography and breast tomosynthesis decreases the referral rates, without lowering the cancer detection rate[39-43]. On the downside, one of the main disadvantages of breast tomosynthesis is the extra review time needed by screening radiologists[44] and higher radiation dose[37].
Furthermore, we observed that a prolonged screening interval was associated with a higher risk of advanced breast cancer. To reduce this risk factor, the importance of re-attendance should be emphasised and efforts should be made to convince women to re-attend within a few months of a missed screening round.

Interval cancer

As shown in Chapter 2 the majority of interval cancers are advanced carcinomas. This finding is in line with other studies on interval cancer[32,33,45-51]. The percentage of advanced cancers among women with interval breast cancer was almost twice as high as among women with screen-detected cancer and remained stable throughout our twelve-year screening period. The observation that the distribution of tumour stages of interval cancers was worse than those of screen-detected cancers is expected and also in line with previous reports[33,45]. Similar to advanced cancers detected at screening, half of the advanced interval cancers were mammographically occult at the latest screening and a quarter had been missed, while the last half showed a minimal sign at the latest exam. Especially the 25% of missed interval carcinomas present a challenge for the screening radiologists, as these interval cancers could potentially have been avoided. The finding that a majority of both early stage and advanced interval cancers were diagnosed in the second year after the latest negative screen suggests that shortening of our screening interval may potentially lower the number of advanced interval cancers. Understandably, shortening the interval will compromise the cost-effectiveness of the screening programme and increase the risk of a false positive referral[52].

Trends in the management of referred women

Chapter 3 discusses the trends in the management of referred women. Several factors have influenced the diagnostic and therapeutic management of referred women throughout the years. The introduction of fine needle aspiration cytology and core-biopsy has led to a change in pre-surgical work-up. The implementation of breast-conserving treatment and neo-adjuvant chemotherapy, but also the growing awareness among patients about the available treatment options has led to changes in the surgical management.

Trends in biopsies

Different breast biopsy procedures may be used in the diagnostic work-up of referred women. The choice for a specific procedure is usually made by the radiologist and depends on various factors. Between 1997 and 2011, the use of surgical biopsies for diagnostic work-up of referred women decreased from 37.8% to 1.4%. This dramatic decrease is probably due to the introduction of new national guidelines in 2000, which stated that at least 70% of women with breast cancer should have their cancer proven pre-operatively. In the revised guidelines, which were issued in 2008, this target was increased from 70% to 90%[53]. The decrease in the use of excisional biopsies is especially important for lesions that turn out to be benign, as recent studies have shown that benign surgery decreases future screening sensitivity[54,55.]
Half of the referred women underwent at least one biopsy procedure during diagnostic work-up and this percentage has remained stable throughout the years. However, with increased referral rates at digital mammography screening, substantially more screened women will undergo biopsies for lesions that turn out to be benign. In an attempt to lower the number of unnecessary biopsies, Flowers et al. have suggested a higher threshold for biopsy, as well as the use of a six-month follow-up for low risk BI-RADS IV lesions[56]. This advice would contradict the current Dutch guidelines, stating that a BI-RADS III lesion could be biopsied rather than followed, at discretion of the attending radiologist[57]. This addition to the guideline[58] is made because of the unnecessary anxiety a six-month follow-up might cause, although the difference in anxiety between the two regimes is disputed[59]. The difference in impact on patient anxiety between early intervention with biopsy and regular follow-up visits needs to be investigated and weighed against the risk of higher mortality and morbidity from a longer delay in diagnosis.

Trends in surgical treatment

Between 1997 and 2010 a doubling of the mastectomy rate was observed in the Eindhoven region among women with screen-detected cancer or interval cancer, whereas the breast conserving treatment rate and breast cancer incidence remained stable. Multivariate analysis showed that patients with micro-calcifications, larger tumours, lymph node metastasis and those treated in certain hospitals had an increased risk to undergo mastectomy. Similar variations between hospitals in the surgical treatment of screen-detected as well as clinically detected invasive and non-invasive breast cancers have been described in previous studies[60-63].

They show that not only treatment guidelines, but also surgeon and patient preferences play a major role in the decision-making process.
In Chapter 3.2 a decline in the risk of tumour-positive resection margins was noted, especially for patients with ductal carcinoma in-situ. The most important independent risk factors for tumour-positive resection margins of invasive cancers were

- Tumour size >20 mm,
- Lobular histology
- Hospital where a woman was treated for her breast cancer.

Variations in the proportion of patients with tumour-positive margins of the surgical specimen among hospitals and individual surgeons have also been described in several other studies[64,65]. Feedback about performance to regional hospitals and surgeons treating referred women is important to improve treatment outcome.
Patients undergoing preoperative breast MRI had a lower risk of positive resection margins, but they also had a substantially increased risk to undergo mastectomy (Chapter 3.2). The role of breast MRI in the preoperative work-up is still controversial and various studies have produced conflicting results[66-68]. The lower risk of positive resection margins in women undergoing a pre-operative MRI contradicts an earlier Dutch study in patients with non-palpable breast cancer, which showed a marked increase in positive resection margins after preoperative use of MRI[66]. This contradictory finding may at least be explained partially by smaller resection volumes following pre-operative MRI. Other studies did not find any difference in resection margins between patients with or without pre-operative MRI[68-70]. All these studies were completely or largely based on patients with symptomatic breast cancer. No studies are available on the use of MRI in women with breast cancer detected in a breast-screening programme. Analysis of the indications for the use of MRI in women with screen-detected breast cancer could lead to more clarity on the true risks and benefits of MRI in the pre-operative diagnostic trajectory of referred women.

Impact of digital mammography screening

Screening outcome

The introduction of digital mammography screening resulted in a significantly increased referral rate and detection rate of ductal carcinoma in-situ and invasive cancers, in combination with a significantly decreased positive predictive value of referral and biopsy and an almost fourfold increase in the use of stereotactic core needle biopsy. The negative effects of a lower positive predictive value of referral and biopsy (including patient anxiety and possible lower re-attendance rates) have been addressed in Chapters 1 and 4, however the long-term effects of a lower positive predictive value on screening participation are not yet clear. Still, the positive predictive values of digital mammography screening in the Eindhoven region are well within

European standards and still high compared to other screening programmes[71,72].
The increased detection of ductal carcinoma in-situ at digital mammography intensifies the discussion on overdiagnosis and overtreatment. The current knowledge about the natural course of DCIS is still very limited and is largely based on autopsy studies and randomized studies on the effect of radiotherapy following local excision of DCIS. These trials show that radiotherapy reduces the risk of local relapse by a factor two and that about half of these relapses are invasive disease[73-76]. However, the result of these trials, which were performed in the 1980's and 1990's, do not necessarily reflect the behaviour of the many low-grade lesions found at breast cancer screening nowadays. Confronted with the growing numbers of patients with screen-detected ductal carcinoma in-situ, many clinicians now believe that a randomized clinical trial is urgently needed for patients with low-risk DCIS, in which active monitoring and surgical intervention are compared with regard to the risk of invasive breast cancer and psychological sequelae of diagnosis and treatment[77]. Observational studies should be considered when these trials prove to be infeasible, also taking molecular and pathological characteristics into account. A recently published trial has listed 30 potential research topics on DCIS and identified the top 10 future research priorities, which include the

- validation of risk-stratification,
- comparison of treatment and follow-up strategies
- the assessment of the effect of DCIS management strategies on rates of invasive cancer[78].

A possibility to maximize public support of such trials is to eliminate the term 'carcinoma' from entities that cannot metastasize, in order to reduce confusion among patients and doctors[79].
In Chapter 4.1 it was shown that invasive cancers at digital mammography screening were more likely to be diagnosed at an earlier tumour stage and had a more favourable grade. These findings might point at a greater portion of over-diagnosed cancers at digital screening when compared to screen film screening. Both a Norwegian and a Swedish study raised the possibility that the natural course of some screen-detected invasive breast cancers is to spontaneously regress[80,81]. In these studies, a higher incidence of breast cancer was found in the screened population. This finding leads to the hypothesis that many invasive breast cancers detected by screening mammography would not have persisted to be detected after 6 years of screening, suggesting that the natural course of many of the screen-detected cancers is to spontaneously regress. The authors of these studies suggest that a watchful waiting regime might not only be considered for patients with low grade DCIS but also for patients with small invasive cancers[82].
Despite the higher cancer detection rate at digital mammography, Chapter 4.2 described an equal interval breast cancer rate and sensitivity for screen-film mammography and digital mammography screening. Because of its recent introduction, only limited data is available on interval cancers in women undergoing digital mammography screening, and thus the effects of digital mammography on screening sensitivity are not yet clear. An overview of digital mammography screening outcome in different countries is shown in Table 1, which shows a summary of studies comparing screen-film and digital mammography screening outcome that include interval cancer data[83-91].

Table 1. **Main results of the studies evaluating SFM and FFDM and reporting on sensitivity**

	First Author	Lewin	Skaane	Skaane	Pisano	Juel	Kerlikowske	Hoff	Nederend
	Year of publication	2001	2003	2004	2005	2009	2011	2012	2013
	Country	USA	Norway	Norway	USA	Norway	USA	Norway	Netherlands
	Age group	>40 years	50-69	50-69	>45 years	50-69	40-79	50-69	50-75
	Follow up	1 year	1 year	2 years	1 year	1 year	1 year	2 years	2 years
SFM	Women screened, No	4945	3683	9903	42760	7442	638252	55435	60770
	Women reffered, No	685	128	229	3765	174	63463	1402	941
	Referral rate, No	13.9%	3.5%	2.3%	8.8%	2.3%	9.3%	2.5%	1.5%
	SD, No	22	28	50	174	29	-*	258	297
	CDR, ‰	4.4	7.6	5.0	4.1	3.9	4.5	4.7	4.9
	IC, No	17	13	30	161	12	-*	126	104
	ICR, ‰	3.4	3.5	3.0	3.8	1.6	0.8	2.3	1.7
	Cancer incidence, ‰	7.9	11.1	8.1	7.8	5.5	4.6	6.9	6.6
	Sensitivity	56.4%	68.3%	62.5%	51.9%	70.7%	81.9%	67.2%	74.1%
	Specificity	86.5%	97.3%	98.2%	91.6%	98.0%	91.0%	97.9%	98.9%
	PPV of referral	3.2%	21.9%	21.8%	4.6%	16.7%	4.0%	18.4%	31.6%
FFDM	Women screened, No	4945	3683	4009	42760	6932	231034	37977	63182
	Women reffered, No	568	128	173	3648	168	26833	1312	1919
	Referral rate	11.5%	3.5%	4.3%	8.5%	2.4%	10.0%	3.5%	3.0%
	SD, No	21	23	32	185	33	-*	257	427
	CDR, ‰	4.2	6.2	8.0	4.3	4.8	3.8	6.8	6.8
	IC, No	18	18	10	150	7	-*	92	124
	ICR, ‰	3.6	4.9	2.5	3.5	1.0	0.7	2.4	2.0
	Cancer incidence, ‰	7.9	11.1	10.5	7.8	5.8	4.6	9.2	8.7
	Sensitivity	53.8%	56.1%	76.2%	55.2%	82.5%	84.0%	73.6%	77.5%
	Specificity	88.9%	97.1%	96.5%	91.9%	98.0%	90.4%	97.2%	97.6%
	PPV of referral	3.7%	18.0%	18.5%	5.1%	19.6%	3.8%	19.6%	22.3%

* not mentioned in the publication

All studies only include one screening round of follow-up. Several more screening rounds are needed before the true effect of digital mammography on interval cancer rate and mortality would become apparent.
The study in Chapter 4.2 is the second report on interval cancers at digital mammography screening. A significantly higher proportion of interval breast cancers were not visible at pre digital mammography screens compared to screen-film mammography. Further monitoring of subsequent screening rounds is needed to determine whether interval cancer detected at digital mammography really exhibits different prior visibility than those diagnosed after screen-film mammography.

How to proceed with breast cancer screening?

With more knowledge about the potential harms of breast cancer screening a different strategy for breast cancer screening should be considered. Perhaps a personalized risk-based approach could optimize the effectiveness of breast cancer screening and reduce the risk of overdiagnosis, as is currently investigated by a Dutch study: "Breast cancer screening - from one-size-fits-all to a personalised risk-based approach[92]".
This thesis shows the majority of interval cancers present in the second year after screening. A shortening of the screening interval for women at higher risk (i.e. high breast density, younger age) can possibly lower (advanced) interval cancer rate and improve mortality[93,94].
The amount of data available in Eindhoven region to evaluate the quality and the outcome of the screening programme is significantly higher than in other regions in the Netherlands but incomplete data impedes the proper evaluation of the screening programme. For a proper evaluation not only information on the screening process is needed but also on diagnostic procedures and treatment of women referred after a positive screening test. Also, more effort should be put in to the identification of the determinants of interval cancers to reduce their risk and improve the prognosis of this particular group of patients.

Quality control and extended data collection

This thesis stresses the need for quality control programs, both for the breast cancer screening programme and for the hospitals involved in the work-up and treatment of referred women. In the Netherlands, every regional screening group is visited once every three years and both the rates of cancer detection and interval cancer are evaluated, including the percentage of 'missed' interval and ≥T2 cancers. Furthermore, interval cancers are reviewed on a regular basis with the complete group of screening radiologists and they receive a review of screening performance at an individual level twice a year. Also, strict rules apply for screening radiologists with respect to extra training and CME-credits in breast radiology. Despite these efforts, a substantial proportion of interval cancers and screen-detected were missed. Even though the proportion of missed cancers in the Eindhoven region remained well within acceptable limits set in the national guidelines, improvements can still be made[95]. It has well been documented that screening results significantly vary among screening radiologists[96,97] and continuous efforts should be made to improve the performance of individual screening radiologists.

The digital era provides more opportunities for quality control, as more data is now digitalized and therefore easily accessible for analysis. Also, the linkage of different registries, hospitals and administrations offers many possibilities for quality improvement. However, in practice, making such linkages between registries appears to be harder than it looks, as proven by the lack of data on interval cancers in many countries, including the Netherlands[98]. Individual training programmes, focusing on personal weak spots in cancer detection and referral behaviour can improve the performance of screening radiologists[99,100].

A more user friendly individualized feedback system might be more effective, as much can be learned from errors[101]. The current software used in the breast cancer screening programme unfortunately does not provide a tailored quality control system, as there are very few possibilities for a radiologist to review his or her referrals or interval cancers. This review can only be done in a very time-consuming way, as the screening patient database does not contain any information on follow-up, pathological results and does not contain the clinical mammogram in case of an interval carcinoma. This time-consuming review method raises the threshold to actively learn from ones mistakes and/or experience. Ideally, the software would have the possibility to automatically reproduce work-lists, which include information about screening outcome. To facilitate such an extensive patient record, extended data collection is mandatory. Currently the following data are routinely collected by the regional screening organizations:

- Number of invitations
- Number of screening rounds
- Non-participants
- Non-responders
- Referrals
- False-positive referrals
- Work-up (invasive or non-invasive)
- Tumour histology and stage
- Client reactions.

The main objective of this extra data collection must be the screened woman; she should benefit most of the collected data, ideally with improved survival and as little overdiagnosis as possible. For quality control and scientific purposes we suggest the collection of more parameters, as shown in table 2. Improvements in screening on a basis of more efficient quality control can be achieved with relevant research questions, which can be answered using this extended data collection. Also, developing and testing a tailor-made screening design would become a lot easier with extended data available in the screening patient database. However, the complexity, multi-disciplinarity and pitfalls of creating, using and updating such an extensive database should not be underestimated i.e. becoming a victim of big data. Ultimately, the wellbeing of the screened woman is at stake.

Finally, we found substantial differences among hospitals with respect to the workup and treatment of referred women. Regular feedback on performance and comparison with other hospitals is mandatory to ensure an optimal quality of diagnostic procedures and treatment outcome of referred women.

Table 2. **Recommendations for extended data collection in breast screenees and patients with early breast cancer**

Indicators		Data collection through	Purpose
Dates	*Date of diagnosis of screen detected cancer or interval cancer*	Screening programme	QC
Risk factors	*Family history of breast cancer, type of previous breast surgery, hormone use*	Screening programme	
Prior mammographic visibility	*Both screen-detected and interval cancer, occult, minimal sign and missed lesions*	Radiologist	QC + Sc
Breast density	*Screening mammogram*	Radiologist	Sc
BI-RADS classification	*Screening mammogram and clinical mammogram of referred women and interval cancers*	Radiologist	Sc
Referral advice	Discrepancies at double reading among screening radiologists	Screening programme	QC
Work-up	*- Imaging type and outcome: Mammography, digital breast tomosynthesis, ultrasound, MRI* *- Biopsy procedures: FNAC, CB, vacuum assisted biopsy, surgical excision*	Radiologist, in combination with screening programme	Sc
Tumour biology	*Tumour grade and receptor status*	Pathologist	Sc + PR
Type of breast cancer treatment	*Surgery (breast conserving surgery, mastectomy), radiotherapy, systemic therapy (adjuvant, palliative)*	Combined effort of surgeon, radiotherapist and oncologist	QC + Sc + PR
Surgical characteristics	*Specimen margin status, lumpectomy volume*	Pathologist	Sc + PR
Screening re-attendance after false positive referral		Screening programme	QC
Clinical mammograms outside screening programme	*Breast imaging outcome, indications for clinical mammography*	Screening programme	Sc
Questionnaire	*Quality of Life assessment after referral, psychological impact on referral, work-up and/or treatment*	Epidemiologist-psychologist	Sc + PR
Breast cancer incidence	*Background incidence, cancer detection rate, interval cancer rate*	Epidemiologist	PH
Breast cancer mortality		Epidemiologist	PH + QC

QC = Quality control; Sc = Scientific; PR = Prognostic parameter PH = public health;
FNAC = Fine Needle AspirationCytology; CB = Core Biopsy

Conclusions

A substantial proportion of cancers in women participating in screening programmes still present as interval cancers, most often as a palpable localised mass, but sometimes even as symptomatic metastatic disease. The interval cancer rate was stable throughout the years and the rate did not decline, not even after the introduction of digital screening. Patients with interval cancers have a worse prognosis when compared to screen-detected cancers and it is therefore important to minimize the interval cancer rate in screening programmes, preferably without a shortening of the screening interval. Monitoring interval cancers is important in the assessment of the quality of the breast cancer screening programme and interval cancers should be used in quality assessments of screening programmes with the aim to improve screening sensitivity, as is common practice in the Dutch setting.

The higher false-positive rate has become of greater concern in the current era of digital mammography screening. In the Netherlands, the positive predictive value of referral is still high when compared to screening programmes in other countries. Still, efforts should be made to reduce the number of false positives. We have shown that advanced breast cancer is inevitable in a breast cancer-screening programme, but possibilities exist to reduce the advanced breast cancer rate, also in the current setting of full-field digital mammography.

In order to improve the benefits to harms ratio of breast cancer screening, future digital mammography related research should focus on the (simultaneous) reduction of the following three problems:

- The rate and management of advanced breast cancers among screened women
- The risk of a false positive screening test in screened women
- The overdiagnosis of (low grade) DCIS.

Such wide-ranging research may end the polarizing discussion between adversaries and supporters of breast cancer screening and the start of a constructive discussion. With the changing oncologic reality and improved treatment, there might be a time where stage does not influence mortality anymore[102]. However, as long as breast cancer stage influences mortality, breast cancer screening will remain indispensable and efforts should be made to optimize breast-cancer screening for a maximal beneficiary outcome for women at risk for breast cancer.

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Chapter 6

Summary and Acknowledgements

Chapter 6.1

Summary

Introduction

Despite a steady decrease of mortality from breast cancer, the incidence of breast cancer is still increasing. The incidence in the Netherlands is among the highest in Europe. Breast cancer is the leading cause of cancer death in women aged 35-64 worldwide. Early detection of breast cancer has become an important aspect of current breast cancer management, as most breast cancer related deaths are due to advanced disease. In the Netherlands, organized breast cancer screening was introduced around 1990 and a more than 30% decrease in breast cancer mortality has been established since then, probably as a result of early cancer detection in combination with improved therapeutic options.

Despite the positive outcomes of several trials and population-based studies, the effectiveness of breast cancer screening has been under discussion for more than two decades now. The simultaneous and equal decrease of the mortality rate in unscreened women is a frequently used argument against screening, as well as possible harmful effects of breast cancer screening. One of the potential side-effects is so-called overdiagnosis, which is the diagnosis of cancer that will never cause symptoms or lead to death during a patient's lifetime. Without breast cancer screening, such cancers would not have been discovered and treated. Estimates of the amount of screening induced overdiagnosis vary widely, from 2% in a Dutch study to 52% in an international systematic review. However, it still remains unclear which part of the diagnosed cancers can be monitored rather than treated surgically. Another subject of debate are the false positive referrals, which are women referred for a benign lesion. The psychological distress in these women can be substantial and is an important issue to be acknowledged as false positive referral may negatively influence screening re-attendance.

Digital mammography has been available for several years now and has proven its value in the clinical setting. Digital mammography has been introduced in most screening programmes. In many countries, the introduction of digital mammography in breast cancer screening resulted in higher cancer detection rates, especially in women with radiographically dense breasts. Data on interval cancers in the setting of digital mammography are sparse and data on the impact on breast cancer mortality are lacking.

Aims

In the South of the Netherlands, the Eindhoven Cancer Registry is a long-standing, population-based registry, which was started in 1955 as part of a programme for nation-wide cancer registration. Since the introduction of mammography screening in our region in 1995, data of the cancer registry have been combined with additional data on screening outcome collected by one of the screening radiologists, resulting in a unique database with extensive information on screening outcome. This database allowed the performance of the studies presented in this

thesis. Data collected over a period of more than 15 years enabled evaluation of classification and surgical treatment of breast cancer detected and missed by mammography screening.
The specific aims of this thesis are to describe the trends in the diagnosis of advanced breast cancer (Chapter 2), the trends in the use of biopsies and surgical management (Chapter 3) and to explore the effects of the introduction of digital mammography in breast cancer screening (Chapter 4).

Methods

The Dutch breast cancer-screening programme offers biennial mammography screening to women aged 50-75 years of age. The screening region of Eindhoven comprises about a third of the South of the Netherlands. Here, the breast cancer screening programme was implemented in 1995. Between May 2009 and April 2010, screen-film mammography was gradually replaced by digital mammography. Since the start of the programme over 700,000 screens have been performed, over 14,000 women have been referred to the regional hospitals and more than 3,500 cancers have been detected. Currently 13 certified screening radiologists double read 60,000 screens annually. Screening outcome has been closely monitored and registered for all screened women. One radiologist (L.E.M. Duijm, MD, PhD) visits the regional hospitals on a regular basis to collect data on imaging procedures, type of breast biopsy and treatment of each referred woman. These data were combined with the data of the regional screening organization (Breast Cancer Screening South) and the Eindhoven Cancer Registry.

Interval cancers are breast cancers diagnosed in women after a screening mammogram has yielded negative results (defined as no recommendation for referral). Efforts were made by the screening office and L.E.M. Duijm to trace as many women with interval cancers as possible.

Two experienced screening radiologists (L.E.M. Duijm and F.H. Jansen) reviewed the latest screening mammogram of all screen-detected cancers and interval cancers, as well as the clinical mammogram obtained at the time of interval cancer detection. They categorised mammographic breast density and the cancers were classified as missed, minimal sign or true negative at the previous screen. Finally the reviewers classified the mammographic abnormality at the prior screening examination.

Results

Advanced cancer in breast cancer screening

Most breast cancer deaths occur in women who are diagnosed with breast cancer in an advanced stage, i.e. with lymph node metastasis or distant metastases. Breast cancer screening aims to detect cancer when it is small, and not disseminated to lymph nodes or distant organs.

Several studies have shown that screening mammography is effective in reducing breast cancer mortality. These studies were carried out in an era before the use of anti-hormonal therapies and other adjuvant therapies. It remains a question of debate which part of mortality reduction can be attributed to screening and which part to adjuvant systemic treatment. If a mortality reduction were due to screening, one would expect that this reduction is preceded by a decrease in the risk of a diagnosis of advanced breast cancer.

This study determined the trends in the incidence of advanced breast cancer in 351,009 consecutive screens, during 1997-2011 (Chapter 2). Advanced breast cancers were defined as cancers with TNM stage IIA or higher, i.e. tumour size exceeding 20 mm (T2) and/or the presence of lymphatic metastasis in the sentinel node or axillary lymph nodes.

In the South of the Netherlands we found no decline in the incidence of advanced screen detected cancers and advanced interval cancers during twelve years of screening mammography. Advanced breast cancer comprised around one-third of screen-detected cancers and two-thirds of all interval carcinomas. Two experienced radiologists determined whether or not these advanced cancers were visible at the prior screening study. After review of this prior visibility, they concluded that the majority of these advanced cancers were not visible at a prior mammogram, or showed a minimal sign that did not warrant a recall. Multivariate analysis showed that a screening interval of 30 months or more significantly increased the risk of detecting breast cancer in an advanced stage.

Biopsy use and surgical management

The aim of these studies was to determine trends in breast biopsies used for the work-up of abnormalities detected at screening mammography (Chapter 3.1) and to determine trends in surgical management of both screen-detected and interval cancer (Chapter 3.2).

Screened women with a mammographic abnormality are referred to a hospital for further diagnostic workup and, if necessary, treatment. There are various breast biopsy procedures, including

- Percutaneous fine-needle aspiration cytology,
- Percutaneous core-needle biopsy (ultrasound-guided or stereotactic vacuum-assisted)
- invasive surgical biopsy.

Surgical biopsies for diagnostic purposes should be avoided, as they increase unnecessary psychological distress in false-positive referrals and benign breast surgery complicates interpretation of subsequent mammograms due to postoperative changes. All women screened in our screening region from 1997-2011 were included and time trends in types of breast biopsies for abnormalities detected at screening mammography were determined. Also, the proportion of referred women who experienced a delay in breast cancer diagnosis and the causes of these delays were determined. A delay was defined as a diagnosis of breast cancer more than three months after referral.

Regarding surgical treatment, patient and tumour characteristics were compared between women who underwent mastectomy or breast conserving surgery for their screen-detected or interval cancer and between women with a negative or positive resection margin after breast conserving surgery.

We found that in our screening region diagnostic surgical biopsy for the workup of a screening mammography abnormality has become very uncommon. Diagnostic surgical biopsies have mostly been replaced by percutaneous core biopsies. The replacement of surgical biopsies by percutaneous core biopsies did not increase the percentage of women who experienced a delay in breast cancer diagnosis.

During a 14-year screening period we observed a doubling of the mastectomy rate (per 1,000 screened women), whereas the breast conserving surgery rate and breast cancer incidence remained stable. Multivariable analysis showed that patients with microcalcifications, large tumours, lymph node metastasis and those treated in certain hospitals had a higher risk to undergo mastectomy. Furthermore, we observed a decline over time in positive resection margins, with variation among hospitals. Main independent risk factors for the presence of positive resection margins of invasive cancers were

- Tumour size >20 mm,
- Lobular histology
- Non-palpable tumour
- The hospital where a woman was treated for breast cancer.

Having had a pre-operative MRI lowered the risk of positive resection margins, but resulted in a substantially higher risk to undergo mastectomy. Women with Interval cancers were not more likely to be treated with mastectomy when taking into account their less favourable tumour stage. The proportion of tumour positive resection margins decreased over time. However, substantial differences were seen among hospitals (6-20%).

Digital mammography screening

In recent years, full-field digital mammography has replaced screen-film mammography in most breast screening programmes. Digital mammography has several advantages. It improves workflow and it is as least as effective as screen-film mammography in the detection of breast cancer. However, higher cancer detection rates at digital mammography may be accompanied by increased referral rates. In our region, screen-film mammography was gradually replaced by digital mammography between May 2009 and April 2010. We evaluated 60,770 screen-film screens and 63,182 digital screens from 2008-2011. The studies in Chapter 4.1 and Chapter 4.2 describe the impact of the introduction of digital mammography screening on diagnostic workup, tumour characteristics and surgical treatment of screen-detected and interval cancers in our region.

The transition of screen-film mammography to digital mammography has resulted in an increased referral rate and a significantly increased detection rate ductal carcinoma in-situ and invasive cancers, at the expense of a decreased positive predictive value of referral and biopsy. An almost fourfold increase in the use of stereotactic core needle biopsy was observed, which has a great impact on the daily practice of the regional breast clinics as it is much more time consuming than ultrasound guided biopsy.

Invasive cancers at digital mammography were more likely to

- be diagnosed at an earlier tumour stage,
- show a more favourable tumour grade,
- show less lymph node involvement
- and comprised a significantly larger proportion of progesterone-receptor positive cancers.

Women with breast cancer detected at digital mammography were more likely to be treated by breast-conserving surgery, whereas the mastectomy rate was similar at screen-film mammography and digital mammography.

The interval breast cancer rate and sensitivity were comparable for screen-film and digital screening mammography, despite a significantly higher cancer detection rate at digital mammography. A significantly larger proportion of interval breast cancers was not visible on prior screens at digital mammography compared to screen-film mammography, whereas mammographic characteristics, tumour stage, tumour biology and surgical treatment were similar for interval cancers in both groups.

Conclusions

The majority of the advanced breast cancers detected at biennial screening cannot be prevented. In order to obtain a modest reduction of the risk of detecting breast cancer in an advanced stage, efforts are needed to minimize the number of women with an extended screening interval.

Quality control in hospitals treating breast cancer patients is important in order to ensure optimal care for women diagnosed with breast cancer, with special attention to cancers found in women referred by a breast cancer screening programme as these cancers differ from clinically detected cancers. Surgeons performing breast conserving surgery should try to pre-operatively identify patients with a high risk of positive resection margins, especially focusing on the role of microcalcifications since these are more commonly encountered in a screened population. Furthermore, continuous efforts should be made to improve the quality of the excision of non-palpable tumours, either by using wire-guided localisation or iodine-125-radiolabelled seeds, and to benchmark the performance against that of peers.
In the South of the Netherlands, digital mammography significantly increased the referral rate and cancer detection rate, at the expense of a lower positive predictive value of referral and biopsy. Additional tumours detected at digital mammography are mostly low to intermediate grade ductal carcinoma in-situ and smaller invasive tumours, with more favourable tumour characteristics. Mastectomy rates did not increase. Digital mammography results in a significantly higher cancer detection rate, but programme sensitivity was similar for both screen-film and digital mammography screening. Interval cancers are more likely to be true negative at prior digital mammography than at prior screen-film mammography, whereas their tumour characteristics and type of surgical treatment are comparable.

The quality of the screening programme and the performance of screening radiologists should be closely monitored, with the aim to continuously improve breast cancer screening results. Future research should focus on the following three issues in order to try to improve the benefits to harms ratio by reduction of:

- The proportion of advanced breast cancers among screened women
- The risk of a false positive screening test
- The risk of overdiagnosis.

Such wide-ranging research initiatives may put an end to the polarizing discussion between adversaries and supporters of breast cancer screening and be the start of a constructive discussion. As long as breast cancer stage influences mortality, breast cancer screening will remain indispensable and efforts should be made to optimize breast-cancer screening for a maximal beneficiary outcome for women at risk for breast cancer.

Chapter 6.2

Samenvatting

Achtergrond

Borstkankerscreening is niet meer weg te denken uit de Nederlandse maatschappij. Borstkanker is een van de meest voorkomende maligniteiten bij vrouwen in de westerse wereld en de incidentie neemt nog steeds toe. In Nederland is in 2013 bij 14,600 vrouwen borstkanker vastgesteld en de kans voor een vrouw om borstkanker te ontwikkelen is inmiddels 1 op 7. Borstkanker is wereldwijd de meest voorkomende oorzaak van sterfte door kanker bij vrouwen. Vroege detectie van borstkanker is belangrijk, omdat de sterfte aan borstkanker meestal het gevolg is van detectie van de ziekte in een te ver gevorderd stadium. De toename van het aantal vrouwen met borstkanker is toe te schrijven aan verschillende factoren. Eén daarvan is de invoering van borstkankerscreening, een andere is een toegenomen blootstelling aan risicofactoren. Ook speelt een groeiende bewustwording van het risico op borstkanker bij Nederlandse vrouwen een prominente rol.

Ondanks de positieve conclusies van diverse studies is er al meer dan 20 jaar discussie over de effectiviteit van borstkankerscreening. De gedocumenteerde afname in mortaliteit van 30% wordt namelijk ook gezien in de leeftijdsgroepen die niet gescreend worden. Dit is voor critici reden om te beweren dat de gecostateerde daling van de mortaliteit geheel en al te danken is aan een betere behandeling en niet aan de screening. Het is nu niet meer mogelijk om de exacte bijdrage van screening en behandeling op sterfte te bepalen, omdat beide veranderingen min of meer gelijktijdig zijn ingetreden. Een ander nadelig effect van borstkankerscreening zijn de verwijzingen van vrouwen die bij verdere analyse in het ziekenhuis geen borstkanker blijken te hebben, de zogenaamde fout-positieve verwijzingen. Uit nationaal en internationaal onderzoek is gebleken dat een dergelijke verwijzing leidt tot veel onnodige en mogelijk langdurige stress bij de vrouw. Bovendien zijn er aanwijzingen dat een dergelijke onterechte verwijzing kan leiden tot een lager opkomstpercentage in volgende rondes. Tenslotte wordt de zogenaamde overdiagnose als potentieel nadeel van de screening genoemd. Overdiagnose betekent dat borstkanker wordt gediagnosticeerd welke, indien niet ontdekt, niet tot het overlijden van de vrouw zou leiden. Zonder screening zouden deze kankers niet gediagnosticeerd en niet behandeld worden. De schattingen van het aandeel overdiagnosticeerde borstkankers lopen erg uiteen; van 2,5% in een Nederlandse studie tot 52% in een internationale review. Vooralsnog blijft het onduidelijk welke van de tumoren in de borstkankerscreening niet (direct) chirurgisch behandeld dienen te worden.

Digitale mammografie heeft zich bewezen in de klinische setting. De goede resultaten in de kliniek en de screening, alsmede de voortdurende technische ontwikkelingen, hebben geleid tot de vervanging van analoge mammografie door digitale mammografie in de meeste screeningsprogramma's . Digitale mammografie verbetert de workflow en verhoogt het kankerdetectiecijfer. Data over intervalkankers bij digitale mammografie zijn nauwelijks voorhanden. Een intervalkanker is een kanker welke ontdekt wordt bij een vrouw tussen twee screeningsronden in, zonder dat zij bij de voorgaande screeningsronde verwezen is.

Onderzoeksdoel

In het zuiden van Nederland is er sinds 1955 een kankerregistratie en sinds 1989 is deze kankerregistratie een onderdeel van een programma voor landelijke kankerregistratie. Parallel aan deze registratie zijn er sinds de invoering van borstkankerscreening in 1995 in de regio Eindhoven gegevens verzameld over de gescreende vrouwen. In een systematisch opgezette databank werden door een van de screeeningsradiologen (Dr. L.E.M. Duijm) alle relevante gegevens van de gescreende vrouwen verzameld. In deze databank werd onder meer het diagnostisch- en eventueel behandeltraject van de verwezen vrouwen in kaart gebracht, alsmede informatie over de vrouwen die een intervalkanker bleken te hebben. Data verzameld over een periode van meer dan 15 jaar hebben evaluatie van trends in classificatie en chirurgische behandeling van borstkanker mogelijk gemaakt. Specifieke doelen van het proefschrift zijn het beschrijven van:

- Trends in het voorkomen van gevorderde borstkanker (Hoofdstuk 2)
- Trends in het gebruik van diagnostiek en behandeling van borstkanker (Hoofdstuk 3)
- De effecten van de introductie van digitale mammografie in de borstkankerscreening (Hoofdstuk 4)

Materiaal en methode

Het Nederlandse screeningsprogramma bestaat uit een tweejaarlijkse screening van vrouwen tussen de 50 en 75 jaar. De screeningsregio rond Eindhoven omvat ongeveer een derde van Zuid-Nederland. In deze regio werd borstkankerscreening geïmplementeerd in 1995, als een van de laatste regio's in Nederland. Tussen mei 2009 en april 2010 zijn de analoge mammografen gefaseerd vervangen door digitale mammografen. Sinds de start van de screening in deze regio zijn er meer dan 700.000 screeningsonderzoeken verricht, meer dan 14.000 vrouwen verwezen naar regionale ziekenhuizen en is bij meer dan 3.000 vrouwen invasief borstkanker vastgesteld en bij meer dan 700 in-situ kanker. Anno 2014 zijn 13 gecertificeerde screeningsradiologen werkzaam bij het Bevolkingsonderzoek Zuid, die tezamen jaarlijks ruim 60.000 screeningsonderzoeken beoordelen. De uitkomsten van screening worden nauwgezet gemonitord. De eerder genoemde screeningsradioloog bezoekt met regelmaat de regionale ziekenhuizen om data te verzamelen van de verwezen vrouwen, met betrekking tot verrichte diagnostische onderzoeken, biopsie procedures en type behandeling. Ook worden de intervalkankers opgespoord en toegevoegd aan de databank. Deze data zijn gecombineerd met die van de screeningsorganisatie en het Integraal Kankercentrum Zuid (IKZ, thans onderdeel van het IKNL) en vormden daarmee de basis van dit proefschrift.

Twee ervaren radiologen (Dr. L.E.M. Duijm en Drs. F.H. Jansen) herbeoordeelden het laatste screeningsonderzoek van alle vrouwen bij wie borstkanker was vastgesteld, zowel intervalkankers als kankers ontdekt tijdens een vervolg screeningsronde.

De densiteit van het mammogram werd toegevoegd aan de databank en per kanker werd bepaald of deze gemist was op het voorgaande screeningsmammogram, of er minimale tekenen van kanker zichtbaar waren, of dat de betreffende kanker niet eerder zichtbaar was. Tenslotte werd het type afwijking op het mammogram geclassificeerd.

Bevindingen

Hoofdstuk 2: trends in de detectie en incidentie van gevorderd borstkanker

De meeste vrouwen overlijden aan borstkanker nadat deze ziekte in een gevorderd stadium is vastgesteld. Een gevorderd stadium is kanker welke is uitgezaaid naar lymfklieren of andere organen. Het doel van borstkankerscreening is het ontdekken van tumoren wanneer deze klein zijn en nog beperkt zijn gebleven tot de borst. Studies hebben aangetoond dat borstkankerscreening de mortaliteit van borstkanker verlaagt. Het blijft echter een discussie welk deel van de sterftereductie toe te wijzen is aan betere behandeling en welk deel aan de screening. Als de sterftedaling het gevolg is van de screening zou men verwachten dat de afname van de sterfte voorafgegaan wordt door een daling in het risico op gevorderde borstkanker. Eerdere studies hebben aangetoond dat screening kan leiden tot een afname van het aantal borstkankers welke in een gevorderd stadium wordt gediagnosticeerd.

In hoofdstuk twee bestudeerden wij in een retrospectief onderzoek de trends in de incidentie van deze gevorderde kankers, gedefinieerd als kankers groter dan 2 centimeter en/of borstkankers met lymfkliermetastasen.
Gedurende een periode van 12 jaar bepaalden we bij 351.009 screeningsonderzoeken de incidentie van deze gevorderde kankers. Ook onderzochten we welk percentage van deze tumoren potentieel bij een eerdere screeningsronde hadden kunnen worden gedetecteerd. Tenslotte bepaalden we risicofactoren voor de diagnose van gevorderde kankers.
In tegenstelling tot andere studies vonden we gedurende de studieperiode 1997-2008 geen afname in het percentage gevorderde kankers. Bij ongeveer een derde van de bij screening ontdekte kankers betrof het kanker in een gevorderd stadium. Van de intervalkankers bleek twee derde gevorderd. Tevens bleek dat het merendeel van de gevorderde kankers (59%) niet in een vroeger stadium ontdekt had kunnen worden bij de tweejaarlijkse screening. Veel van deze kankers waren namelijk niet zichtbaar bij een eerdere screeningsronde of ze werden vastgesteld bij de eerste screeningsronde. Multivariate analyse toonde aan dat een screeningsinterval van meer dan 2 jaar een risicofactor blijkt te zijn voor gevorderde borstkanker.

Hoofdstuk 3: trends in diagnostiek en behandeling van verwezen vrouwen

Het doel van deze studies was om trends in het diagnostisch traject van verwezen vrouwen in kaart te brengen. Ook wilden we trends beschrijven in de chirurgische behandeling van zowel borstkankers gevonden in de screening als van intervalkankers.

Gescreende vrouwen met een afwijkend screeningsmammogram worden verwezen naar een ziekenhuis voor verdere diagnostiek en, indien nodig, behandeling. Ongeveer de helft van de verwezen vrouwen krijgt alleen aanvullende beeldvorming, welke kan bestaan uit een aanvullende mammografische opnames, tomosynthese, echografie en/of MRI. Bij de andere helft is (minimaal) invasieve diagnostiek nodig om de diagnose te stellen. Er zijn verschillende biopsie procedures: percutane dunne naald aspiratie cytologie, percutane holle naald biopsie, percutane vacuüm-biopsie (echogeleid of stereotactisch) en invasieve chirurgische biopsie. Chirurgische biopten voor diagnostische doeleinden dienen zoveel mogelijk vermeden te worden, omdat ze voor meer onnodige stress zorgen bij vrouwen die zijn verwezen vanwege een benigne afwijking en omdat chirurgie de beoordeling van latere mammografische onderzoeken bemoeilijkt.

Alle vrouwen die hebben deelgenomen aan de borstkankerscreening tussen 1997 en 2011 zijn geïncludeerd in deze studie. Veranderingen in die periode in het gebruik van biopsieprocedures werden bepaald. Tevens werd vastgesteld welk deel van de verwezen vrouwen met borstkanker een vertraging opliep in de diagnose, gedefinieerd als een diagnose meer dan drie maanden na verwijzing vanuit de screening.

We concludeerden dat vrouwen tegenwoordig nauwelijks meer (ca. 1%) geconfronteerd worden met een diagnostisch chirurgisch excisiebiopt in het diagnostisch traject na verwijzing. Deze excisiebiopten zijn nagenoeg allemaal vervangen door percutane biopten. De vervanging heeft niet gezorgd voor een toename in het percentage vrouwen dat vertraging opliep in het stellen van de diagnose borstkanker.

Wat betreft de chirurgische behandeling werden patiënt- en tumorkarakteristieken vergeleken tussen vrouwen die een mastectomie dan wel borstsparende behandeling ondergingen en vrouwen met met positieve dan wel negatieve snijranden na een borstsparende behandeling voor borstkanker.

Gedurende dezelfde 14 jaren (1997-2011) is (uitgedrukt per 1000 gescreende vrouwen) het aandeel dat een mastectomie ondergaat verdubbeld, terwijl het aandeel vrouwen dat borstsparend behandeld werd en de borstkanker incidentie gelijk bleven. Multivariate analyse toonde aan dat vrouwen met microcalcificaties op het mammogram, grote tumoren, lymfkliermetastasen en vrouwen behandeld in bepaalde ziekenhuizen een hoger risico hadden op een mastectomie.

Verder observeerden wij in de loop der tijd een afname in het aantal tumoren met tumorpositieve snijranden, met een grote variatie tussen de verschillende ziekenhuizen. De belangrijkste onafhankelijke risicofactoren voor tumorpositieve snijranden waren: een tumorgrootte van meer dan 20 millimeter, lobulaire histologie en het ziekenhuis waar de behandeling heeft plaats gevonden. Het verrichten van een preoperatieve MRI verlaagde het risico op tumorpositieve snijranden, maar verhoogde het risico op een mastectomie. Vrouwen met een intervalkanker hadden geen hoger risico op een mastectomie, wanneer rekening werd gehouden met het gemiddeld ongunstiger stadium van deze tumoren.

Hoofdstuk 4: impact van de introductie van digitale mammografie in de screening

In het afgelopen decennium is in de meeste borstkankerscreening programma's analoge mammografie vervangen door digitale mammografie. Digitale mammografie heeft verschillende voordelen. Het verbetert de workflow en is minstens zo effectief in de detectie van borstkanker en waarschijnlijk zelfs beter. De hogere borstkankerdetectie bij digitale mammografie heeft echter ook een prijs, namelijk een hoger verwijspercentage. In onze screeningsregio is analoge mammografie gefaseerd vervangen door digitale mammografie tussen mei 2009 en april 2010. Wij onderzochten 60.770 analoge en 63.182 digitale screeningsonderzoeken tussen 2008 en 2011. De studies in hoofdstuk 4 beschrijven de impact van de introductie van digitale mammografie op het diagnostisch natraject, tumorkarakteristieken en chirurgische behandeling van zowel door screening ontdekte borstkanker als intervalkankers.

De implementatie van digitale mammografie leidde tot een significant hoger kankerdetectiecijfer van zowel invasieve tumoren als in-situ tumoren. Dit ging ten koste van een hoger verwijscijfer en een lagere positief voorspellende waarde van verwijzing en biopsie. Het gebruik van stereotactische biopten in het natraject is bijna verviervoudigd, met grote consequenties voor de regionale ziekenhuizen die het natraject verzorgen. Deze biopten kosten namelijk veel tijd.

Invasieve tumoren gedetecteerd bij digitale mammografie waren vaker kleinere kankers, met een lage tumorgraad, zonder positieve okselklieren en met positieve progesteron receptoren. Vrouwen met borstkanker, vastgesteld met digitale mammografie, hadden een hogere kans om een borstsparende behandeling te ondergaan, terwijl het aantal vrouwen dat een mastectomie onderging, per 1000 gescreende vrouwen, gelijk blijft.

Het aandeel intervalkankers en de sensitiviteit van het screeningsprogramma waren vergelijkbaar voor analoge en digitale mammografie, ondanks het significant hogere kankerdetectiecijfer bij digitale screening. Hierbij was een groter aandeel van de intervalkankers niet zichtbaar op het laatste screeningsonderzoek. Mammografische kenmerken, tumor stadium, tumor biologie en chirurgische behandeling van de intervalkankers waren gelijk in beide groepen.

Conclusie

Het merendeel van de gevorderde borstkanker kan niet worden voorkomen met een tweejaarlijkse screening. Om een bescheiden reductie van het aantal vrouwen met gevorderde borstkanker te bewerkstelligen moet moeite gedaan worden om het aantal vrouwen met een screeningsinterval van meer dan twee jaar te verminderen. Kwaliteitscontrole binnen ziekenhuizen, die betrokken zijn in de diagnostiek en behandeling van verwezen vrouwen, is belangrijk om optimale zorg voor de gescreende vrouwen te waarborgen. Chirurgen die borstsparende behandelingen uitvoeren moeten vooraf rekening houden met factoren die het risico op tumorpositieve snijranden vergroten, met een speciaal focus op micro-calcificaties. Er moet meer aandacht komen voor de kwaliteit van röntgen-geleide excisies om de resultaten hiervan tussen oncologische centra onderling te kunnen vergelijken

De introductie van digitale mammografie in de screening heeft geleid tot een 35 procent hoger kanker detectiecijfer en een verdubbeling van het verwijscijfer, ten koste van een 10 procent lagere positief voorspellende waarde van verwijzing en een 20 procent lagere voorspellende waarde van biopsie. De extra tumoren, ontdekt bij digitale mammografie, waren grotendeels laag- tot intermediair-gradige in-situ tumoren en kleine invasieve tumoren, met gunstigere tumorkarakteristieken. Ondanks het hogere kankerdetectiecijfer bleef de sensitiviteit (de "gevoeligheid") van het screeningsprogramma gelijk. Intervalkankers waren bij digitale mammografie 20 procent vaker niet zichtbaar op het laatste screeningsmammogram, terwijl karakteristieken als tumorgrootte, tumorstadium, lymfklierstatus en chirurgische behandelingen gelijk waren.

De kwaliteit van de borstkankerscreening en de prestaties van screeningsradiologen moeten gemonitord worden, teneinde de screeningsresultaten te verbeteren en daarmee uiteindelijk de mortaliteit te verminderen. Om de voordelen en nadelen van de screening beter in kaart te brengen zou toekomstig onderzoek moeten focussen op het verminderen van:

- het aandeel gevorderde borstkankers bij vrouwen die deelnemen aan de screening
- het risico op een fout-positieve verwijzing
- het risico op overdiagnose.

Hierbij kan gedacht worden aan onderzoek naar nieuwe technieken als tomosynthese, hiermee kunnen als het ware driedimensionale foto's van de borst gemaakt worden. Dit zou het risico op een fout-positieve verwijzing kunnen verminderen en wellicht ook bijdragen aan het verlagen van het aandeel gevorderde kankers. Het minder- of niet-invasief behandelen van in-situ kankers en kleine invasieve kankers kan een oplossing zijn voor de overdiagnose. Dergelijk onderzoek kan een einde betekenen van de gepolariseerde discussie tussen voor- en tegenstanders van de borstkankerscreening en het begin van een constructieve discussie.

Zolang het stadium waarin borstkanker verkeert invloed heeft op de mortaliteit, zal de noodzaak voor vroege detectie van borstkanker blijven bestaan. Dit rechtvaardigt het bestaansrecht van borstkankerscreening. Het verder optimaliseren van de borstkanker screening is noodzakelijk om het voordeel voor de gescreende vrouw te maximaliseren.

Chapter 6.3

Dankwoord

Veel dank ben ik verschuldigd aan allen die hebben meegewerkt aan de totstandkoming van dit proefschrift. De volgende personen wil ik in het bijzonder bedanken.

Mijn promotor, professor J.W. Coebergh, na enkele minuten al Jan Willem. Hoewel je pas halverwege bij mijn onderzoek betrokken bent geraakt, heb ik veel gehad aan je enthousiasme, kennis en betrokkenheid. Dank voor je doortastendheid in het afronden van dit boekwerk.

Dr. Lucien Duijm, mijn copromotor. Jij hebt me enthousiast gemaakt voor wetenschappelijk onderzoek en zonder jou was het waarschijnlijk bij een half-af manuscript ergens op een harde schijf thuis gebleven. Ik bewonder met name je ongelooflijke gedrevenheid, en ik wil je van harte bedanken voor alle tijd die je in ons onderzoek hebt gestoken. Je opmerkingen en verbeteringen zorgden meer dan eens voor een volledig roodgekleurd manuscript, gelukkig werd dit naarmate het traject vorderde steeds iets minder. Ik ben blij dat ik nu af en toe ook iets terug kan doen.

Dr. Adri Voogd, ook copromotor. Wij hebben elkaar leren kennen via Lucien en ik heb altijd genoten van je snelle reacties op mails en ook van de altijd zeer uitgebreide commentaren op de artikelen. Waar een radioloog in een oogopslag een afwijking ziet, zie jij die in een manuscript. Nadat Lucien het artikel al onderste boven had gekeerd wist jij toch altijd weer met scherpe opmerkingen en talloze extra referenties te komen.

De leden van de kleine commissie, Prof. van den Bosch, Dr. Broeders, en Prof. Verhoef hebben allen tijd genomen voor de inhoudelijke beoordeling van mijn proefschrift, waarvoor ik allen hartelijk wil danken.

Tom en Joep, fijn dat jullie mijn paranimfen willen zijn. Tom, broertje en vriend. Bedankt voor je tekstuele hulp bij het Nederlands deel van dit proefschrift. Joep, begonnen als teamgenoten, nu als tegenstanders in het water, maar vrienden buiten het water. Veel mooie herinneringen met jullie beiden. Dat er nog maar vele mogen volgen.

Vivian, jij was de eerste van 'ons' drietal die promoveerde en plaveide daarmee vast de weg. Jouw betrokkenheid en doorzettingsvermogen zorgden ervoor dat ik ook verder ging, want als jij kan promoveren en tegelijk twee kinderen opvoeden, dan moest ik dat zeker ook kunnen! Verder ben je altijd beschikbaar voor discussie en steun, bedankt!

Wikke, collega en mede-promovenda. Jij staat altijd voor iedereen klaar met een ongelooflijke inzet. Klagen hoor ik jou zelden doen, zelfs niet tijdens de afronding van je eigen proefschrift. Ik heb heel veel bewondering voor je.

Lisa, jij maakt een kwartet promovendi onder de vleugels van Lucien. Je bent altijd eigenwijs en dat waardeer ik aan je. Met kritische vragen liet je me meer dan eens twijfelen aan mezelf. Bedankt voor de kritische noot en succes met je eigen promotie.

Dr. Marieke Louwman. Jouw statistiek kennis is onmisbaar geweest bij de totstandkoming van mijn proefschrift. De afstand tussen Eindhoven en het Franse platteland en dagelijkse sores op de boerderij zorgden soms voor wat vertraging, maar uiteindelijk zijn alle ingewikkelde analyses afgerond, met een zeer fraai resultaat. Mijn dank daarvoor!

Frits Jansen, jij hebt een ongelooflijke hoeveelheid mammogrammen opnieuw beoordeeld en hebt daarmee een aanzienlijke bijdrage geleverd aan mijn proefschrift. Toch is jouw bijdrage aan het plezier op de werkvloer ontzettend veel belangrijker. Jij bent een fantastische collega en opleider, maar bovenal altijd een vrolijke noot.

Harrie van de Bosch, mijn vice-opleider, collega, vriend en eeuwig promovendus. Min of meer door jouw toedoen ben ik in Eindhoven beland, maar ook op vele andere mooie plaatsen over de wereld, waarvoor ik je hartelijk wil bedanken. Ik kan nog veel van je leren!

Philip Jurgens, het gelach op de gang zal nog lang doorklinken. Ik heb veel van je geleerd, radiologie maar nog meer over alles wat er bij een afdeling radiologie en het leven komt kijken. Bewust of onbewust heb jij ook gezorgd voor de inspiratie voor de kaft.

Matt Holland, dear friend. Thank you for the necessary grammatical corrections of the introduction, discussion and summary.

Mijn dank gaat ook uit naar de overige coauteurs van dit proefschrift, Astrid Donkers, Hannie Groenewoud, Jan Roukema, Liza van Steenbergen, Marianne Hooijen, Matthieu Rutten, Menno Plaisier, Mike van Beek, Miranda Ernst, Paul Lohle en Rudi Roumen.

De overige leden van de maatschap radiologie van het Catharina Ziekenhuis wil ik ook graag bedanken voor de mogelijkheid om de opleiding radiologie te combineren met een promotietraject. Zonder jullie steun en bijdragen was het niet mogelijk geweest om dit proefschrift af te krijgen of de bijbehorende voordrachten te houden. Hartelijk dank voor jullie enthousiasme en steun.

Henk Swinkels, bedankt voor de fantastische vormgeving van zowel kaft als inhoud.

Teamgenoten, bedankt voor het begrip wanneer ik door 'het werk' weer eens niet op kom opdagen voor een training. (Bijna) dagelijks geniet ik van jullie gezelschap, jullie houden me jong!

Lieve schoonfamilie, bedankt voor jullie oprechte interesse.

Lieve ouders, dank voor een stevig fundament. De laatste jaren kom ik niet meer zo vaak in het ouderlijk huis als ik zou willen. Jullie betekenen ontzettend veel voor me.

Ineke, Annelies en Marieke, ook jullie zie ik veel minder. Toch is onze band hecht als altijd. Als het stil is in huis denk ik vaak terug aan ons oude 'huishouden van Jan Steen'.

Mijn allerliefste Veronie, iedere dag met jou samen is weer een feest.
Jouw steun, vrolijkheid en begrip zijn onmisbaar geweest bij het schrijven van dit proefschrift.

Chapter 6.4

Curriculum Vitae

Curriculum Vitae

Joost Nederend werd geboren op 21 november 1984 te 's-Gravenhage.
In 2002 behaalde hij zijn atheneum diploma aan het Sint-Antonius College te Gouda. Hij werd direct ingeloot voor de studie geneeskunde aan de Universiteit Leiden. Tijdens deze studie liep hij co-schappen in verschillende ziekenhuizen, waaronder het Leids Universitair Medisch Centrum, het Groene Hart Ziekenhuis te Gouda en het Rijnland Ziekenhuis te Leiderdorp.
Zijn afstudeeronderzoek (retrospectief onderzoek naar atherosclerose te zien op PET-CT) werd verricht op de afdeling radiologie van het Leids Universitair Medisch Centrum, in samenwerking met het Catharina ziekenhuis Eindhoven.
Na het behalen van het arts-examen in augustus 2008 is hij op 1 oktober van dat jaar, na een kort intermezzo als arts-assistent interne geneeskunde in het Groene Hart Ziekenhuis, begonnen aan de opleiding tot radioloog in het Catharina Ziekenhuis (opleider dr. A.V. Tielbeek).
Tijdens deze opleiding werd in 2010 gestart met wetenschappelijk onderzoek, dat resulteerde in dit proefschrift.
De opleiding radiologie is in oktober 2013 afgerond en momenteel is hij als fellow abdominale radiologie werkzaam in het Catharina Ziekenhuis.

Chapter 6.5

Portfolio

List of publications

Maarten van Leeuwen JN, Robin Smithuis. Liver-incidentalomas. What to do with incidentally found lesions in the liver? *The Radiology Assistant* 2007.

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van Breest Smallenburg V, Nederend J, Voogd AC, et al. Trends in breast biopsies for abnormalities detected at screening mammography: a population-based study in the Netherlands. *British Journal of Cancer* 2013; 109(1): 242-248.

Klompenhouwer EG, Duijm LE, Voogd AC, den Heeten GJ, Nederend J, Jansen FH, Broeders MJ. Variations in screening outcome among pairs of screening radiologists at non-blinded double reading of screening mammograms: a population based study. *Eur Radiol* 2014; 24(5):1097-104.

Nederend J, Duijm LE, Louwman MW, Coebergh JW, Roumen RM, Lohle PN, Roukema JA, Rutten MJ, van Steenbergen LN, Ernst MF, Jansen FH, Plaisier ML, Hooijen MJ, Voogd AC. Impact of the transition from screen-film to digital screening mammography on interval cancer characteristics and treatment – A population based study from the Netherlands. *European Journal of Cancer* 2014; 50(1): 31-39.

Nederend J, Duijm LE, Louwman MW, Jansen FH, Voogd AC. Trends in the surgical management of screen detected cancers and interval cancers in a Dutch screening mammography program and risk factors for positive tumour positive resection margins after breast conserving treatment. *Br J Surg* 2014; 101(8):949-58.

Attended courses

2014	**IDKD Abdominal Imaging Course,** *Davos*
2013	**Breast cancer screening course LRCB,** *Nijmegen*
	RSNA 2013, *Chicago*
	ESMRB Advanced MRI Abdomen, *Bruges*
2012	**AIRP,** *Washington*
	Course pancreatic tumours, *UMC Utrecht*
	MR-physics course*, Philips Healthcare, Hilvarenbeek*
	ECR 2012, *Vienna*
	Musculoskeletal Radiology of the upper limb, *Den Bosch*
2011	**MRI Liver course,** *UMC Utrecht*
	Acute Abdomen, *MCH Westeinde, The Hague*
	Scientific writing course, *Eindhoven*
	ECR 2011, *Vienna*
2011-2012	**Imaging techniques, BVT-1 en BVT-2,** *NVvR*
2009	**Radiation protection for radiologists, 3M,** *Interuniversitair Instituut voor Radiopathologie en Stralenbescherming (IRS), Leiden*
2008 – 2014	**Radiologendagen**, **Sandwichcourses,** *Nederlandse Vereniging voor Radiologie (NVvR)*

Oral presentations

Imaging van lymfklieren bij prostaatcarcinoom. Regionale refereeravond Urologie 2014. Eindhoven [in Dutch].

Impact of the transition from screen-film to digital screening mammography on interval cancer characteristics and treatment - A population based study from the Netherlands. RSNA 2013. Chicago.

Defaecografie. Vergadering Abdomensectie. Apeldoorn [in Dutch].

mRadiology, de toekomst van de radiologie. Vergadering Abdomensectie. Lieshout [in Dutch].

mRadiology, de radioloog mobiel. Congres PACS anywhere. Papendal [in Dutch].

Impact of transition from analogue screening mammography to digital screening mammography on screening outcome in The Netherlands: a population-based study. Radiologendagen 2012. Den Bosch [in Dutch].

De thuiswerkende radioloog. Congres Apps4Health, Mobiel in de Zorg. Oegstgeest [in Dutch].

Dramatic increase in stereotactic core needle biopsy rate and ductal carcinoma in-situ detection after conversion from analogue to digital screening mammography. ECR 2012. Vienna.

Conversion from analogue to digital screening mammography results in a more favorable tumour stage and tumour biology of screen detected cancers. ECR 2012. Vienna.

Variations in screening outcome among pairs of radiologists at independent double reading of screening mammograms: a population-based study ECR 2012. Vienna.

Trends in incidence and detection of advanced breast cancers at biennial screening mammography: a population based cohort study. Radiologendagen 2011. Maastricht [in Dutch].

Effect of previous benign breast surgery on cancer detection at screening mammography. ECR 2011. Vienna.

Schildkliercarcinoom: de rol van de radioloog in diagnostiek en follow-up. Bijscholingsavond NVMBR januari 2011. Eindhoven [in Dutch].

Biennial breast cancer screening in the Netherlands: trends in the use of excisional biopsy in women with benign follow-up at recall. Radiologendagen 2010. Veldhoven [in Dutch].