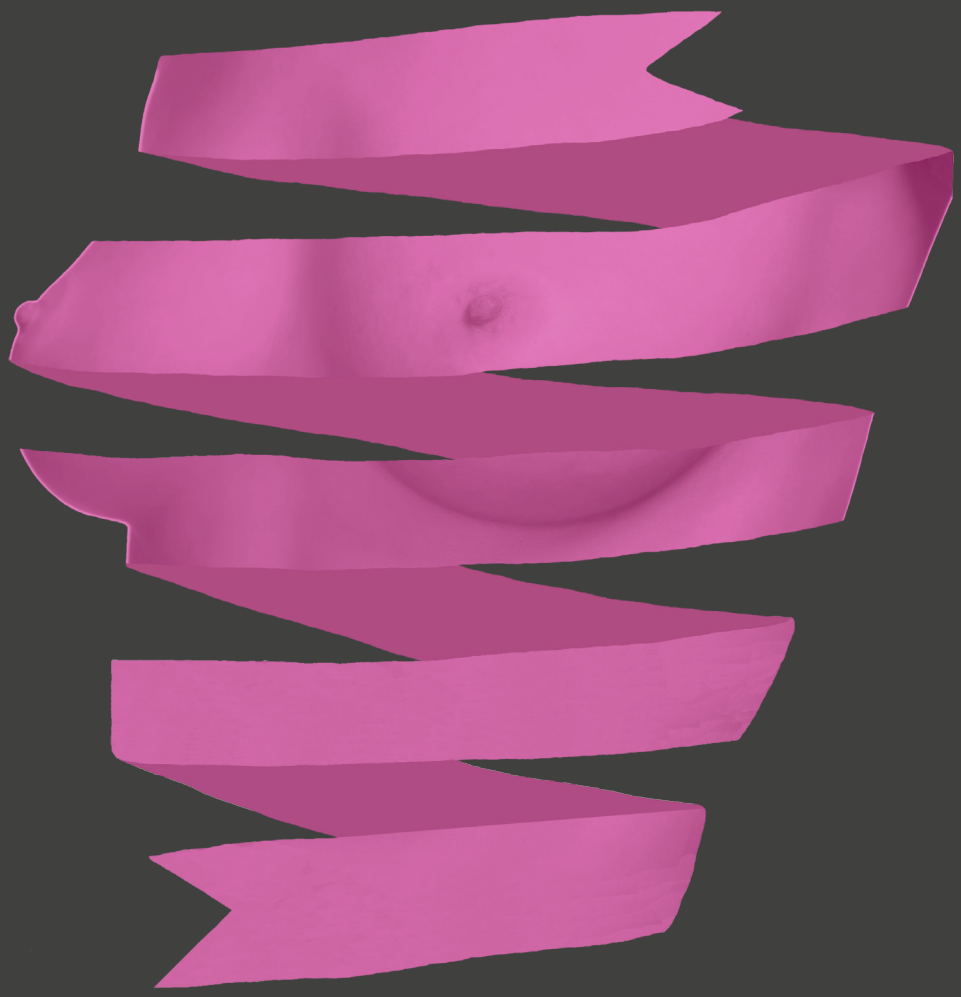
Improving the sensitivity of screening mammography in the south of the Netherlands



Vivian van Breest Smallenburg

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Improving the Sensitivity of Screening Mammography in the South of the Netherlands

Het verbeteren van de sensitiviteit van screenings mammografie in het zuiden van Nederland

Proefschrift

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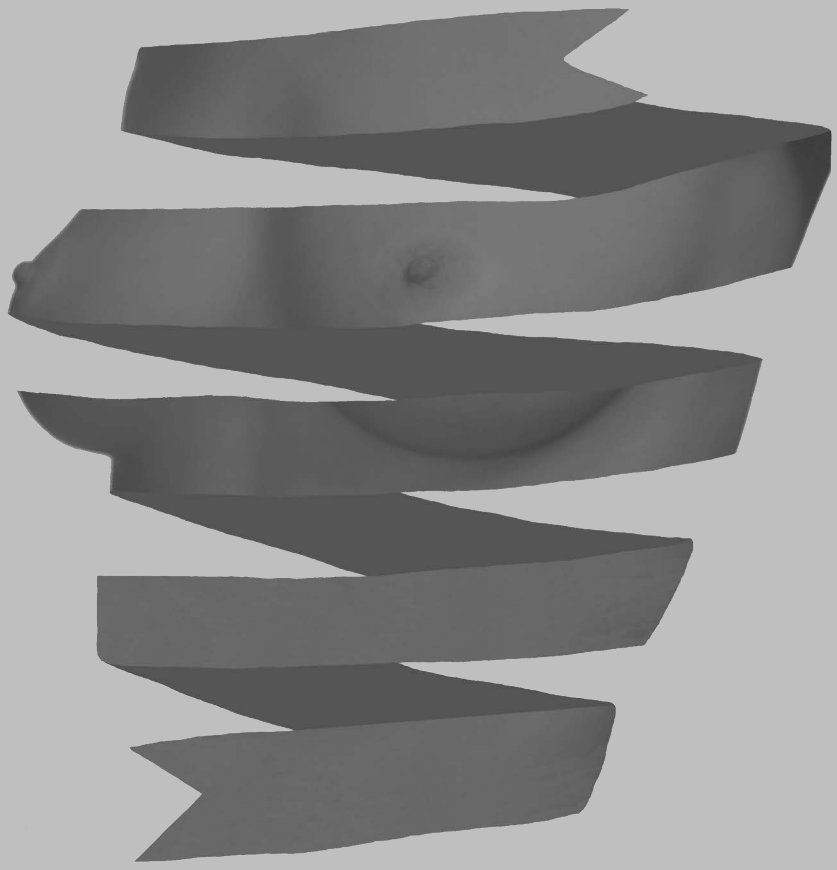
General Introduction



In this thesis I explore several factors that influence the sensitivity of screening mammography, with the aim to improve screening outcome in the southern breast cancer screening region of the Netherlands.

This general introduction describes:
- the background and implementation of mass breast cancer screening
- trends of breast cancer incidence and mortality
- the debate on screening
- the relevance of this thesis
- screening mammography sensitivity
- methods and population
- the outline of this thesis

Mass screening for breast cancer

Around the world every day thousands of women are diagnosed with breast cancer. 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. It is, after lung cancer, the most important cause of cancer death among women and it has especially impact on the lives of middle-aged women, as it is responsible for over 25% of cancer deaths of women aged 30-59.[2]

Early detection of breast cancer is important, as increasing tumour size and lymph node invasion decrease long-term survival.[3,4] Identifying breast cancer at an early stage is most effectively done by screening mammography and during the 1970s and 1980s evidence came for establishing breast screening programmes. The very first breast cancer screening trial was initiated in 1963 within the Health Insurance Plan (HIP) of Greater New York. Their first results showed that just 31 breast cancer deaths emerged in the study group of 30,000 screened women, compared to 52 cancer deaths in the equally sized non-screened control group.[5] The benefit persisted, as after 18 years of follow-up the researchers reported a 25% reduction in breast cancer related mortality among the group of screened women.[6] In the 1980s these results were supported by the Swedish Two-County Trial which demonstrated a 31% reduction in mortality due to breast cancer screening and also several other randomised controlled trials reported benefits of mammographic screening.[7-9] These promising outcomes initiated the introduction of breast cancer screening programmes in most western countries.

Despite the favourable outcomes of international studies, the Dutch Health Council did not decide on the implementation of a breast screening programme immediately. Only after the demonstration of the effectiveness of mammographic screening by two Dutch pilot studies from Utrecht and Nijmegen[10,11] and the reasonable outcome from a cost-effectiveness analysis with the MISCAN micro-simulation model,[12] the Dutch Health Council advised the implementation of a nationwide breast screening programme. The Dutch government approved and during 1990-1997 the Dutch breast cancer screening programme was gradually introduced. The programme offers women aged 50-69 years (and from 1998 also women aged 70-75 years) biennial mammography screening[13] and is offered as a freely available public health policy. Since 2006 the National Institute for Public Health and the Environment

(RIVM) is responsible for the coordination of the Dutch breast cancer screening programme and the screening programme is continuously being monitored and evaluated by several institutions (Figure 1). At present, every year around 1,000,000 women are invited to participate in the Dutch breast cancer screening programme. Participation has always been high; the attendance rate of invited women was approximately 75% in earlier years and currently over 80% of invited women undergo screening.[14]

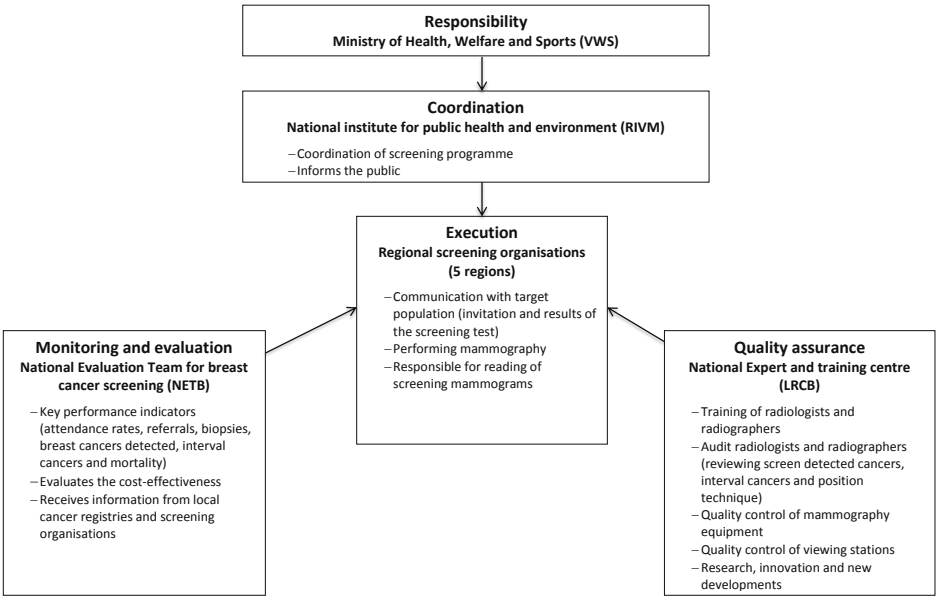


Figure 1. *Organisation of breast cancer screening in the Netherlands. Source: www.lrcb.nl and www.rivm.nl (accessed October 29, 2012)*

Breast cancer incidence and mortality

In many western countries breast cancer incidence increased during the late 20th century, and in various countries, including the Netherlands, incidence is still increasing (Figure 2).[1,15] Several factors are thought to be responsible for the rising breast cancer incidence; changes in risk factors, the improved detection of (early) breast cancer due to the increased use of mammography and cytology since the 1980s and the introduction of nationwide breast screening programmes.[1,15,16]

Known risk factors for breast cancer include factors related to hormones such as nulliparity, later age at first birth, shorter lactation period, use of oral contraceptives and postmenopausal hormone therapy.[17,18] Since the late 1960s most of these factors have changed in adverse ways. For example, the age at first birth of Dutch women increased from 24 (1970) to 29 years (currently).[2] Also adverse changes in lifestyle factors, like obesity, smoking, low physical activity and alcohol consumption, almost certainly play a role in the increasing incidence of breast cancer.[18,19,20] The incidence of breast cancer in the Netherlands is currently among

the highest in the world, with around 36 new breast cancer patients every day and the age-standardised rate being 128/100,000 person years (European Standardised Rate, ESR).[2,21]

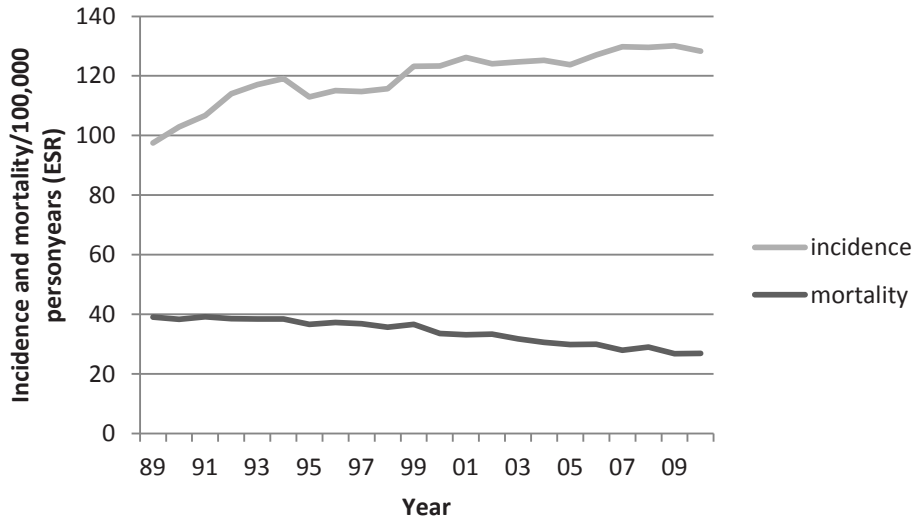


Figure 2. *Breast cancer incidence and mortality in The Netherlands, 1989-2009. Source: www.ikcnet.nl (accessed August 29, 2012)*

In contrast to the increasing breast cancer incidence, breast cancer death rates have been decreasing since the 1990s.[2] Improved breast cancer awareness, the introduction of mammography screening and improvements of systemic and (neo)adjuvant therapy are thought to be responsible for this better survival.[22-24]

Debate on screening

Mortality

Despite of the positive outcomes of several trials and population based studies, the effectiveness of breast cancer screening has been under debate for more than 10 years now. Improved breast cancer awareness, screening and improved treatment probably all contributed to the decrease in breast cancer mortality, however, the exact contribution of each factor is difficult to determine. Criticizing of the breast cancer screening trials started in 2000 from the Nordic Cochrane Centre in Denmark.[25] In a review article Gøtsche et al. discussed 8 large randomized breast cancer screening trials[5,7-9,26-29] and the conclusion was that most of the screening trials, especially the Swedish, had poor internal validity. These negative conclusions from the Cochrane Review caused doubt on the effectiveness of screening and the Dutch minister of Health, Welfare and Sports asked the Dutch Health Counsil (advisory body for the government) to investigate the validity of the Cochrane Review. In 2002 the Dutch Health Counsil concluded in a report that the arguments forthcoming from the Cochrane Review were not persuading enough for deciding to stop breast cancer screening.[30] Several other studies also refuted the conclusions of the Nordic Cochrane centre; researchers of a long term follow-up study of the Swedish trials found a 21% breast cancer

mortality reduction for women aged 40-70 years and concluded that "The recent criticism against the Swedish randomised controlled trials is misleading and scientifically unfounded".[31] In a Dutch study, de Koning concluded that the outcomes of several screening trials, including the Swedish, were based on reliable methodological methods and that "there is 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".[32] Nevertheless, the criticizing of the Swedish trials and the effectiveness of screening continues. Autier et al. recently analysed Swedish data and mortality trends[33] and they concluded that the decline in breast cancer mortality in Sweden was not due to breast cancer screening. The authors argued that breast cancer mortality rates in Swedish women had started to decrease before the introduction of mammography, and had continued to decline at a rate similar to that in the prescreening period. Autier et al. can, however, not exclude that breast cancer mortality would have increased in concordance with incidence, when screening had not been available.

The best way to stop the debate on screening would be a new randomized trial. It would, however, be unethical to withheld women who currently have access to the screening programme from screening mammography, and therefore a new trial is not an option. The different views on the methodology of the 'old' breast cancer screening trials will continue to exist and it is thus unlikely that the debate will be settled in the near future.

Besides the effect of mass screening on breast cancer mortality, also potential disadvantages caused by radiation, overdiagnosis and false-positive referrals are repeatedly under discussion.

Radiation

In mammography low energy X-rays are used to examine the breast. Breast tissue is known to be very sensitive to radiation exposure and frequent mammography could therefore cause radiation induced breast cancer. In the Netherlands, however, radiation exposure is kept to a minimum. Women in the Netherlands undergo screening mammography on a biennial base (in contrast to the US where women are screened annually) and, until recently, two-view mammography was only performed in the first screening rounds. Furthermore, Zoetelief et al. reported that the average glandular dose was 1.3 mGy per view for Dutch analogue screening mammography.[34] This dose is low compared to the 2-2.4 mGy dose reported in studies from the United States (US) and the United Kingdom (UK).[35-37] Finally, the recent conversion of the Dutch breast screening programme from analogue to digital mammography is expected to result in a further decrease of radiation exposure.[36]

Overdiagnosis

Overdiagnosis is the diagnosis of cancer that will never cause symtoms or death during a woman's lifetime. Without screening these cancers would not have been detected and treated. In a systematic review of countries with organised screening programmes, Jørgensen et al. found an overdiagnosis rate of 52%.[38] Several other studies also report high overdiagnosis rates, ranging between 15 and 42%.[39,40] On the other hand, a study from the UK estimated that at least two lives are saved for every overdiagnosed case and that the benefits thus outweight the harms.[41] Also the European Screening Network working group

(EUROSCREEN) recently concluded that the benefits of screening in terms of lives saved outweigh the harms caused by overdiagnosis.[42] Their conclusion was based on a review of breast cancer screening services in Europe. The working group reported a mortality reduction of 38-48% in screened women and found that for every 1,000 women screened every two years from the age of 50 to the age of about 68-69, between 7 and 9 lives would be saved, and 4 cases would be overdiagnosed. Finally, a recent study from Denmark estimated the overdiagnosis rate among screened Danish women to be only 2.3%.[43] Also in the Netherlands researchers estimate the overdiagnosis rate to be low, around 8-10% for the screened population and 2-3% for all women.[44-46] De Gelder et al. argued that the huge differences with other studies on estimated overdiagnosis rates are the result of methodological differences, lack of sufficient follow-up by other studies and differences in screening characteristics and performance.[45]

A special concern in the discussion on overdiagnosis is DCIS (ductal carcinoma in situ). DCIS is a precursor to invasive carcinoma, although many DCIS lesions will never progress to invasive cancer. Worldwide the incidence of DCIS has increased substantially and this is attributed to screening.[47,48] In the Netherlands during 1989-2010 the incidence increased from 5/100,000 to 21/100,000 (ESR),[2] meaning that DCIS represents approximately 16% of all new breast cancers in the Netherlands. DCIS is usually excised when detected because it is impossible to determine which particular DCIS will progress to (a symptomatic) invasive cancer and which will not. DCIS can be treated by mastectomy or breast conserving therapy (lumpectomy combined with radiotherapy) and currently an increasing proportion of women diagnosed with DCIS is treated by breast conserving therapy.[46,49] Early detection of DCIS by screening also seems to have benefits. In the Netherlands, women with screen-detected DCIS are more often treated by breast conserving therapy than women with clinically diagnosed DCIS[49]. Furthermore, screen-detected DCIS seems to be biologically more aggressive than interval DCIS and therefore early detection is favourable.[50]

False-positives

False-positive referral is the final potential harm of mass breast cancer screening. Studies have shown that a false-positive referral causes unnecessary stress and anxiety and could negatively influence re-attendance to the screening programme.[51,52] Furthermore, false positive referral increases screen-related costs due to unnecessary diagnostics. The researchers of EUROSCREEN found that for every 1,000 women screened, 170 women would have at least one referral followed by a non-invasive assessment before absence of breast cancer could be confirmed. A total of 30 women would have at least one recall followed by invasive procedures, such as a biopsy, before confirming a negative result.[42] False-positive referral rates have a close relationship with the specificity of the screening test and positive predictive value (PPV). The PPV of screening in the Netherlands is with approximately 49% among the highest in the world.[53] However, with a screening mammography specificity of around 90% false-positive referrals are unfortunately unavoidable.

The relevance of this thesis

From the former we can conclude that the Dutch breast cancer screening programme is characterized by low radiation exposures and that the overdiagnosis rate is likely to be much

lower than those reported in most international screening studies. Furthermore, multiple Dutch studies have concluded that breast cancer screening in the Netherlands indeed reduces the risk of breast cancer death (Table 1). The careful monitoring and evaluation by the National Evaluation Team for breast cancer screening (NETB, this is a cooperation between the department of Public Health of the Erasmus university of Rotterdam and the department of Epidemiology, Biostatistics and HTA of the St. Radboud university of Nijmegen) and the quality assurance programmes of the National Expert and Training Centre (LRCB), attribute to the quality of the Dutch breast cancer screening programme. Both the high attendance rates and high quality of screening are likely to explain the good screening results in the Netherlands. Finally, when taking into account the increase of breast cancer awareness and the major developments in the detection and treatment of breast cancer due to the implementation of mass breast cancer screening, the influence of screening on breast cancer mortality could even be larger than assumed.

Table 1. *Recent Dutch studies reporting a mortality reduction by breast cancer screening.*

Year	First author	Study design	Setting	Mortality reduction
2003	Otto[54]	Retrospective data analysis	The Netherlands	1.2% per year
2004	Vervoort[55]	Simulation analysis	The southern region of the Netherlands and the Netherlands	28-30%
2008	Otten[56]	Retrospective data analysis	The Netherlands	2.3% (55–64 years), 2.8% (65-74) and 4.8% (70-74) per year
2010	Paap[57]	Case-control study	Limburg	70%
2011	Van Schoor[58]	Case-control study	Nijmegen	65%
2012	Otto[59]	Case-control study	The southwest region of the Netherlands	56%

In spite of the favourable Dutch screening results, there is, however, still room for improvements. The Dutch breast screening programme has been running for more than 2 decades now, and on a yearly base approximately 5,000 tumours are detected by screening (screen detected cancers, SDC). However, approximately 1 out of 3 breast cancers is detected between screening rounds and presents itself thus as an interval cancer (IC). ICs are cancers diagnosed after a negative screening examination, but before the next screening round. They are known to have a less favourable tumour stage distribution than SDCs and they have a worse prognosis.[60,61] The Malmo mammographic screening trial (MMST) for example reported that the death rate during 9 years of follow-up was 2.3 times higher for women with an IC than it was for women with a SDC.[62] Furthermore, Shen et al. found that women with ICs had a 53% higher risk of dying from breast cancer than women with a SDC.[63] ICs are mainly detected by linkage of data from regional screening organisations and local cancer registries. According to national data, published by the NETB, IC rates in the Netherlands remained more or less stable over time.[14] Incidence varied between 1.0 and 1.3/1,000 woman-years follow-up (FU) during the period 1998-2004. The national data are, however,

incomplete because data linkage between screening organisations and cancer registries is not a systematic procedure yet. Therefore most screening units do not have their data on ICs up-to-date. In the part of the southern breast cancer screening region where the studies of this thesis were performed, the incidence of ICs fluctuated between 1.1 and 2.3/1,000 woman-years FU (Figure 3). The figure shows that also at a local level the incidence of ICs did not decrease over the past years.

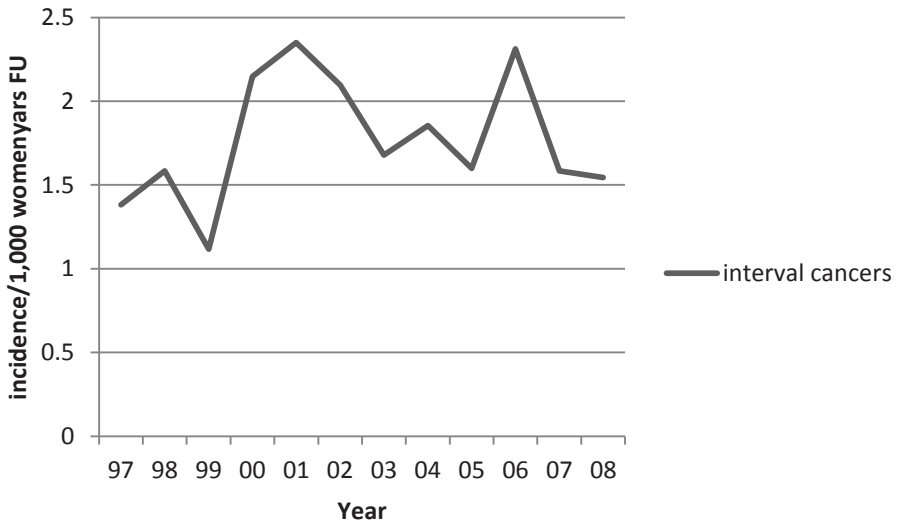


Figure 3. *Trends in IC incidence in the south of the Netherlands.*

Confident with the effectiveness of the Dutch breast cancer screening programme and confronted with the IC rates I decided to focus on further improvements of screening results. Furthermore, because missed cancers can result in malpractice claims, a small part of this thesis pays attention to screen related malpractice claims.

IC rates have a close relationship with screening sensitivity and because of the moderate breast screening sensitivity of 70-80%[14,64,65] there is a potential for further improvements. A higher screening sensitivity will reduce IC rates and will probably further decrease breast cancer related mortality. Furthermore, a high rate of attendance is essential for the success of the breast cancer screening programme, and the debate on screening could have caused confusion among women about attending for breast cancer screening. Optimisation of screening results will hopefully remove these doubts.

Screening mammography sensitivity

Screening-programme sensitivity measures the proportion of breast cancers that are detected within the breast screening programme out of all breast cancers (ICs plus SDCs) diagnosed in screened women in the 2-year screening interval. Screening-programme sensitivity depends on the screening-test sensitivity (this is the proportion of breast cancers

detected when breast cancer is present) and breast cancer tumour growth (doubling time) of the various breast cancer types. A low mammographic tumour detectability and fast tumour growth result in a low sensitivity of the screening programme because of high IC rates. A high screening-test sensitivity is essential for the detection of small cancers and for limiting the number of ICs.

Combination of screening mammography with other modalities

Although the cost of mammography is relatively low, its moderate sensitivity for breast cancer detection does not make mammography a perfect screening test. Combinations of mammography with other modalities, including palpation, ultrasonography, Magnetic Resonance Imaging (MRI) or breast tomosynthesis, have been investigated with the purpose to increase breast screening sensitivity. Clinical breast examination by palpation, in addition to mammography, results in a 4% increase of the sensitivity. However, the specificity of the screening test decreases with 2.8% and the PPV of referral decreases even with 23.8%. Therefore, a combination of mammography and breast palpation is probably not cost-effective in a screening setting.[66] The addition of breast ultrasound to screening mammography will yield an additional 1.1 to 7.2 cancers per 1,000 screened high-risk women, but it also substantially increases the number of false positives among average risk women. Besides, an addition of breast ultrasound to each screening mammography examination will be very time consuming and far too expensive for large scale screening programmes.[67,68] It is well known that breast MRI yields a higher sensitivity for breast cancer detection than conventional mammography. For example, Kuhl et al. found an overall sensitivity of breast MRI for cancer detection of 93%.[69] However, due to the high cost of MRI and limited availability of MRI scan time, breast MRI for screening purposes is currently reserved for young women who are at high risk for breast cancer.[69,70] Finally, adding tomosynthesis to screening mammography will probably reduce the number of false-positive referrals, as tomosynthesis improves specificity. Again, adding this examination to standard screening mammography will increase screening costs and will also increase radiation exposure. There are no large screening studies available yet in which the additional value of tomosynthesis to standard screening mammography has been evaluated. Therefore, at present, only mammography seems to be an appropriate modality for routine breast cancer screening.

Patient-related factors and mammography sensitivity

Mammography sensitivity is influenced by several factors (Table 2), including patient characteristics. Breasts consist of fibroglandular and fat tissue and breast density is lower in fatty breasts. Increased density of the breast tissue may obscure breast tumours and makes interpretation more difficult, resulting in a decreased sensitivity. A lower Body Mass Index, the use of hormone replacement therapy and younger age are all correlated with increased breast density.[71-73] Also intrinsic changes of the fibroglandular tissue, such as fibrocystic changes (FCC), result in a higher breast density. FCC is a common, non-cancerous condition and is related to the response of the breast tissue to monthly hormonal changes.[74] Furthermore, previous breast conserving therapy for breast cancer decreases mammographic sensitivity, as surgery and radiation therapy may cause rigorous mammographic changes. These changes hamper mammographic interpretation and result in a lower sensitivity for breast cancer detection.[75,76] The effect of prior benign breast surgery on screening

mammography sensitivity has barely been investigated, although mammographic changes have been described in 45-50% of women with prior benign breast surgery and a negative effect on mammography sensitivity has been reported.[71,77,78] Finally, breast implants decrease the sensitivity of subsequent mammography.[79]

Image-related factors and mammography sensitivity

In addition to patient characteristics, also various image-related factors determine mammography sensitivity. A good overall image quality is obviously important and the number of views and the availability of prior mammograms for comparison are significant factors as well. Several studies have demonstrated that standard two-view mammography results in a higher cancer detection rate compared to single-view mammography, both for initial and subsequent screens.[80,81] Having a prior mammogram for comparison is also associated with increased sensitivity, as evaluating previous screens may help the radiologist to detect new lesions.[82] Finally, digital mammography has been shown to have a higher sensitivity than conventional mammography, especially for premenopausal women.[83-85] Digitisation of the Dutch breast cancer screening programme started in 2006 and was completed in 2010.

Table 2. *Determinants of the sensitivity of screening mammography.*

Determinant category	Determinant	Related to
Patient related	Breast density	BMI, FCC, hormone therapy, age
	Breast conserving surgery	Surgery, radiotherapy
	Benign breast surgery	Excision of benign lesion, abscess drainage, breast reduction surgery
	Breast augmentation	
Image related	Image quality Number of views Prior mammogram for comparison Analogue versus digital	
Screening situation related	Breast cancer prevalence	
	Radiologist performance	Experience, certainty
	Screening method	Single reading vs. double reading, addition of mammography technician for reading mammograms, Computer Aided Detection (CAD)

Screening situation-related factors and mammography sensitivity

Several researchers describe the 'prevalence effect' as a possible explanation for a relatively low detection rate of breast cancers. The prevalence of abnormalities in visual search tasks influences observer performance (prevalence effect) and the low prevalence of breast cancers in the screened population (approximately 7.5/1,000 screens) could therefore negatively influence the breast cancer detection rate.[86,87] Furthermore, studies have shown substantial variability in interpretation and reading accuracy among radiologists.[88] Accuracy of mammographic interpretation depends on experience at interpreting mammograms and on the radiologist's certainty of interpretation. Training improves the results of inexperienced screening radiologists[89] and to optimize the radiologist assessment of screening mammograms in the Netherlands, all screening radiologists are trained and certified by the LRCB. Since the implementation of digital screening in the Netherlands, the LRCB also organises refresher courses on digital screening. Furthermore, as part of a national quality assurance programme, screening radiologists review the screening mammograms of ICs and advanced SDCs at regular intervals. These measures may all help radiologists to improve their cancer detection rates. Mammography sensitivity also depends on the used screening method. Studies have shown that the accuracy of mammographic interpretation increases when a mammogram is evaluated by two radiologists,[90-92] which is the standard protocol in the Netherlands. Sensitivity also increases when a screening mammography technician examines the screening mammograms in addition to two screening radiologists.[93] Whether Computer Aided Detection (CAD), in addition to single reading, yields better detection performances than radiologist double reading is not clear, as conflicting results have been reported on this issue.[94,95] The recent digitization of the Dutch screening programme makes the use of CAD easier to apply, and as adding CAD to the current practice of double reading could improve screening sensitivity, it may be introduced in the Dutch screening programme in the near future.[96]

Methods and population

Monitoring screening outcome is essential, as the effect of screening on breast cancer mortality will only become apparent in the long-term. The NETB carefully monitors the breast screening programme annually by collecting data on screening outcomes; regional cancer registries and screening organisations provide regional data. In this thesis I focussed on the breast cancer screening programme in the south of the Netherlands. Data from Breast Cancer Screening South, the Eindhoven Cancer Registry and regional hospitals enabled the studies in this thesis.

Breast Cancer Screening South

Breast Cancer Screening South (BOZ) is one of five regional screening organisations in the Netherlands. This organisation provides screening for cervical cancer and breast cancer in the provinces of Brabant and Limburg. BOZ started breast cancer screening in 1991 and at the end of 1995 the first screening round of the southern screening region was completed. A total of 160,580 women were invited to attend this first screening round and 131,127 women actually underwent screening (attendance rate, 82%). Altogether 1,877 (1.4%) women were referred for further evaluation of a mammographic abnormality and in 806 of these women breast cancer was diagnosed, yielding a cancer detection rate of 6.1/1,000 screens (Table 3).[97]

The number of women who underwent biannual screening mammography at BOZ gradually increased over the years and, conform the national screening policy, analogue screening was replaced by full-field digital screening in 2009. In 2010, a total of 253,602 women were invited and 211,684 women (84%) actually underwent screening mammography. The screening radiologists referred 4,370 (2.1%) women for further diagnostic workup and 1,227 of these women had breast cancer (cancer detection rate 5.8/1,000 screens).[98] These screening results are comparable with the Dutch national screening results from 2010 (Table 3, in parentheses).[99]

Table 3. *Main results from Breast Cancer Screening South of 1995 and 2010 (and national results of 2010).*

	1995	**2010**
Invitations (No)	160,580	253,602 (1,193,413)
Screen examinations (No)	131,127	211,684 (961,765)
Attendance rate	82%	84% (81%)
Referred women (No)	1,877	4,370 (19,406)
Referral rate	1.4%	2.1% (2.0%)
Screen detected cancers (No)	806	1,227 (5,646)
Cancer detection rate per 1,000 screens	6.1	5.8 (5.9)

The studies in this thesis are based on the screening results of a group of 12 certified screening radiologists that work for BOZ. They asses approximately 32,000 screening mammograms on an annual base, meaning that each of these screening radiologists evaluates at least 5,000 screening mammograms yearly.

Eindhoven Cancer Registry

The Eindhoven Cancer Registry, being part of or hosted by the Comprehensive Cancer Centre South (IKZ, founded in 1982), started in 1955 as part of a programme for nationwide cancer registration. The registry started in three hospitals in the city of Eindhoven and gradually expanded. It now includes the province of North Brabant and the northern part of the province of Limburg with 2.4 million inhabitants, 10 general hospitals, 6 regional pathology laboratories and two radiotherapy institutes. Data on newly diagnosed malignancies are collected from the national pathology archive (PALGA), national registry of hospital discharge, laboratories and radiotherapy institutes. Additional data on diagnosis, stage and treatment are collected from hospital records by trained registry personnel. Also information on co-morbidities and lifestyle factors are collected. Completeness of data is estimated to be at least 95%.[100]

The Eindhoven Cancer Registry not only collects data, but is also closely linked with the regional Breast Cancer Study Group. This study group has been responsible for the development of guidelines for the management of breast cancer since 1978. The study group initiated several projects to improve local breast cancer management. This included the

introduction and fine tuning of breast conserving therapy at a time that mastectomy was the standard and the introduction of the sentinel node biopsy technique.[101,102]

The Eindhoven Cancer Registry regularly publishes data on cancer incidence and mortality trends in the south of the Netherlands. Breast cancer incidence in the south of the Netherlands increased during 1960-2008 (Figure 4 and 5).[15,103-105] Incidence especially increased after the implementation of breast cancer screening in age groups targeted by the screening programme. Breast cancer mortality decreased in the past decades, corresponding with the nationwide mortality trend in The Netherlands. Several local researchers attributed the increased survival from breast cancer to the implementation of screening.[15,105,106] However, in a study from 2004, other local researchers questioned mortality reduction by screening, as the majority of invasive breast cancers in their study was detected between screening rounds or in patients who did not participate in the screening programme.[107] Furthermore, Nederend et al. recently found no decline in the risk of advanced breast cancer during 12 years of screening mammography.[108] Though, perhaps the latter could be explained by an increasing incidence of advanced breast cancers in the general population.[109] These publications implicate that not only at an international and national level, but also at a local level, the effectiveness of screening is under discussion.

Outline

The objectives of the studies in this thesis were:

1. To determine the current sensitivity of screening mammography, the rate of missed cancers and related malpractice claims.
2. To examine the effect of replacing single-view by two-view mammography in subsequent screening rounds on screening outcome.
3. To investigate the impact of prior benign breast surgery on screening mammography sensitivity and to examine trends in the use of biopsies for (benign) screen detected breast lesions.

The sensitivity of screening, the rate of missed cancers at screening mammography and related malpractice claims are described in chapter 2. In chapter 3 the Dutch breast screening policy regarding two-view mammography and consequences of an implementation of standard two-view mammography on screening outcome are described. This chapter also provides information on additional costs for implementation of standard two-view mammography in the Dutch breast cancer screening programme. We determined the impact of prior benign breast surgery on screening mammography sensitivity in chapter 4.1, and in chapter 4.2 the relation between prior benign breast surgery and the decreased sensitivity of screening mammography is further investigated. In chapter 4.3 trends in the use of (surgical) biopsies for (benign) screen detected breast lesions are presented. Finally, in chapter 5.0, the main results of the studies in this thesis are discussed as well as their significance for the current en future breast cancer screening programme in (the south of) the Netherlands.

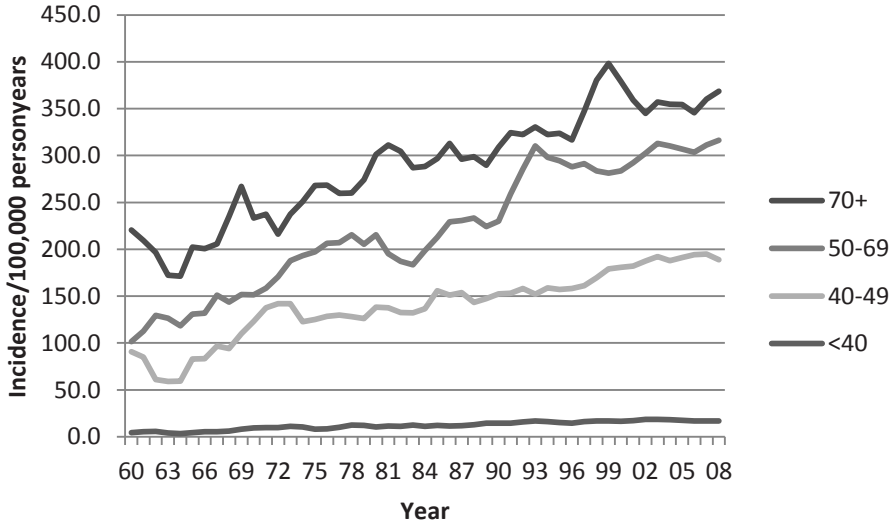


Figure 4. *Breast cancer incidence in the south of the Netherlands.*
Source: WJ Louwman, JWW Coebergh[103]

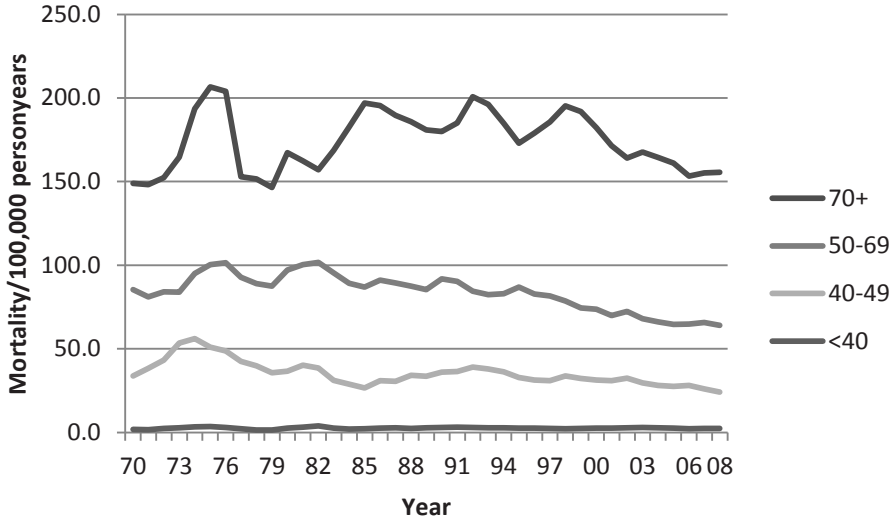


Figure 5. *Breast cancer mortality in the south of the Netherlands.*
Source: WJ Louwman, JWW Coebergh[103]

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. IKCnet. www.ikcnet.nl (accessed August 29, 2012)
3. Tabár L, Vitak B, Chen HH, Duffy SW, Yen MF, Chiang CF, Krusemo UB, Tot T, Smith RA. The Swedish Two-County Trial twenty years later. Updated mortality results and new insights from long-term follow-up. Radiol Clin North Am 2000;38:625-51.
4. Soerjomataram I, Louwman MW, Ribot JG, Roukema JA, Coebergh JW. An overview of prognostic factors for long-term survivors of breast cancer. Breast Cancer Res Treat 2008;107:309-30.
5. Shapiro S, Strax P, Venet L. Periodic breast cancer screening in reducing mortality from breast cancer. JAMA 1971;215:1777-85.
6. Shapiro S.Periodic screening for breast cancer: the HIP Randomized Controlled Trial. Health Insurance Plan. J Natl Cancer Inst Monogr 1997;22:27-30.
7. Tabár L, Fagerberg CJ, Gad A, Baldetorp L, Holmberg LH, Gröntoft O, Ljungquist U, Lundström B, Månson JC, Eklund G, et al. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. Lancet 1985;1:829-32.
8. Frisell J, Eklund G, Hellström L, Lidbrink E, Rutqvist LE, Somell A. Randomized study of mammography screening--preliminary report on mortality in the Stockholm trial. Breast Cancer Res Treat 1991;18:49-56.
9. Andersson I, Aspegren K, Janzon L, Landberg T, Lindholm K, Linell F, Ljungberg O, Ranstam J, Sigfússon B. Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial. BMJ 1988;297:943-8.
10. Collette HJ, Day NE, Rombach JJ, de Waard F. Evaluation of breast cancer in a non-randomised study (the DOM project) by means of a case-control study. Lancet 1984;1:1224-6.
11. Verbeek ALM, Hendriks JHCL, Holland R, Mravunac M, Sturmans F, Day NE. Reduction of breast cancer mortality through mass screening with modern mammography. First results of the Nijmegen project, 1975-1981. Lancet 1984;1:1222-4.
12. van der Maas PJ, de Koning HJ, van Ineveld BM, van Oortmarssen GJ, Habbema JD, Lubbe KT, Geerts AT, Collette HJ, Verbeek AL, Hendriks JH, Rombach JJ. The cost-effectiveness of breast cancer screening. Int J Cancer 1989;43:1055-60.
13. Fracheboud J, de Koning HJ, Boer R, Groenewoud JH, Verbeek AL, Broeders MJ, van Ineveld BM, Hendriks JH, de Bruyn AE, Holland R, van der Maas PJ; National Evaluation Team for Breast cancer screening in The Netherlands. Nationwide breast cancer screening programme fully implemented in The Netherlands. Breast 2001;10:6-11.
14. National Evaluation Team for Breast Cancer Screening (NETB). National evaluation of breast cancer in the Netherlands 1990-2007, twelfth evaluation report. Rotterdam: Erasmus MC Rotterdam, Radboud University Nijmegen Medical Centre; 2009.
15. Louwman WJ, Voogd AC, van Dijck JA, Nieuwenhuijzen GA, Ribot J, Pruijt JF, Coebergh JW. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: a long-term population-based study in southeastern Netherlands. Cancer Causes Control 2008;19:97-106.
16. Althuis MD, Dozier JD, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973-1997. Int J Epidemiol 2005;34:405-12.
17. Soerjomataram I, Pukkala E, Brenner H, Coebergh JW. On the avoidability of breast cancer in industrialized societies: older mean age at first birth as an indicator of excess breast cancer risk. Breast Cancer Res Treat 2008;111:297-302.
18. Hulka BS, Moorman PG. Breast cancer: hormones and other risk factors. Maturitas 2001;38:103-113;disc ussion113-16.
19. Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Altieri A, Cogliano V; WHO International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of alcoholic beverages. Lancet Oncol 2007; 8: 292-93.

20. Luo J, Margolis KL, Wactawski-Wende J, Horn K, Messina C, Stefanick ML, Tindle HA, Tong E, Rohan TE. Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study. BMJ 2011;342:d1016.

21. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer 2008;44:1345-89.

22. Baum M. The changing face of breast cancer-past, present and future perspectives. Breast Cancer Res Treat 2002;75suppl1:S1-5;discussionS33-5.

23. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, Mandelblatt JS, Yakovlev AY, Habbema JD, Feuer EJ; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784-92.

24. Jones AL. Reduction in mortality from breast cancer: screening and increased use of adjuvants are responsible—adjuvants more so. BMJ 2005;330:205-6.

25. Gøtsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? Lancet 2000;355:129–34.

26. Alexander FE, Anderson TJ, Brown HK, Forrest AP, Hepburn W, Kirkpatrick AE, Muir BB, Prescott RJ, Smith A. 14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. Lancet 1999;353:1903-08.

27. Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1-breast cancer detection and death rates among women aged 40–49 years. Can Med Assoc J 1992; 147:1459-76.

28. Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2-breast cancer detection and death rates among women aged 50 to 59 years. Can Med Assoc J 1992;147:1477-88.

29. Bjurstam N, Bjorneld L, Duffy SW, Smith TC, Cahlin E, Eriksson O, Hafström LO, Lingaas H, Mattsson J, Persson S, Rudenstam CM, Säve-Söderbergh J. The Gothenburg breast screening trial: first results on mortality, incidence, and mode of detection for women ages 39–49 years at randomization. Cancer 1997;80:2091-99.

30. Gezondheidsraad. Het nut van bevolkingsonderzoek naar borstkanker. Publicatie nr 2002/03. Den Haag: Gezondheidsraad; 2002. (In Dutch)

31. Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002;359:909-19.

32. HJ De Koning Mammographic screening: evidence from randomised controlled trials. Ann Oncol 2003;14:1185-89.

33. Autier P, Koechlin A, Smans M, Vatten L, Boniol M. Mammography screening and breast cancer mortality in Sweden. J Natl Cancer Inst 2012;104:1080-93.

34. Zoetelief J, Thijssen MAO, de Koning HJ. Eindrapport CVZ project "Stralingsbelasting bij het bevolkingsonderzoek naar borstkanker in Nederland". Diemen: CVZ; 2005. (In Dutch)

35. Thierry-Chef I, Simon SL, Weinstock RM, Kwon D, Linet MS. Reconstruction of absorbed doses to fibroglandular tissue of the breast of women undergoing mammography (1960 to the present). Radiat Res 2012;177:92-108.

36. Hendrick RE, Pisano ED, Averbukh A, Moran C, Berns EA, Yaffe MJ, Herman B, Acharyya S, Gatsonis C. Comparison of acquisition parameters and breast dose in digital mammography and screen-film mammography in the American College of Radiology Imaging Network digital mammographic imaging screening trial. AJR 2010;194:362-9.

37. Law J, Faulkner K. Radiation benefit and risk at the assessment stage of the UK Breast Screening Programme. Br J Radiol 2006; 79:479-82.

38. Jørgensen KJ, Gøtzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. BMJ 2009;339:b2587.

39. Morrell S, Barratt A, Irwig L, Howard K, Biesheuvel C, Armstrong B. Estimates of overdiagnosis of invasive breast cancer associated with screening mammography. Cancer Causes Control 2010;21:275-82.

40. Kalager M, Adami HO, Bretthauer M, Tamimi RM. Overdiagnosis of invasive breast cancer due to mammography screening: results from the Norwegian screening program. Ann Intern Med 2012;156:491-9.

41. Duffy SW, Tabar L, Olsen AH, Vitak B, Allgood PC, Chen TH, Yen AM, Smith RA. Absolute numbers of lives saved and overdiagnosis in breast cancer screening, from a randomized trial and from the Breast Screening Programme in England. J Med Screen 2010;17:25-30.

42. Paci E. Summary of the evidence of breast cancer service screening outcomes in Europe and first estimate of the benefit and harm balance sheet. J Med Screen 2012;19 suppl 1:5-13.

43. Njor SH, Olsen AH, Blichert-Toft M, Schwartz W, Vejborg I, Lynge E. Overdiagnosis in screening mammography in Denmark: population based cohort study. BMJ 2013;346:f1064.

44. Verbeek AL, Broeders MJ, Otto SJ, Frachebou J, Otten JD, Holland R, den Heeten GJ, de Koning HJ. Effects of the population screening into breast cancer. Ned Tijdschr Geneeskd 2013;157:A5218. (in Dutch)

45. de Gelder R, Heijnsdijk EA, van Ravesteyn NT, Fracheboud J, Draisma G, de Koning HJ. Interpreting overdiagnosis estimates in population-based mammography screening. Epidemiol Rev 2011;33:111-21.

46. de Koning HJ, Draisma G, Fracheboud J, de Bruijn A. Overdiagnosis based and overtreatment of breast cancer: Microsimulation modelling estimates on observed screen and clinical data. Breast Cancer Res 2006;8:202.

47. van Steenbergen LN, Voogd AC, Roukema JA, Louwman WJ, Duijm LE, Coebergh JW, van de Poll-Franse LV. Screening caused rising incidence rates of ductal carcinoma in situ of the breast. Breast Cancer Res Treat 2009;115:181-3.

48. Kerlikowske K. Epidemiology of ductal carcinoma in situ. J Natl Cancer Inst Monogr 2010;2010:139-41.

49. Lee RJ, Vallow LA, McLaughlin SA, Tzou KS, Hines SL, Peterson JL. Ductal carcinoma in situ of the breast. Int J Surg Oncol. 2012;2012:123549.

50. de Roos MA, van der Vegt B, de Vries J, Wesseling J, de Bock GH. Pathological and biological differences between screen-detected and interval ductal carcinoma in situ of the breast. Ann Surg Oncol 2007;14:2097-104.

51. Bond M, Pavey T, Welch K, Cooper C, Garside R, Dean S, Hyde CJ. Psychological consequences of false-positive screening mammograms in the UK. Evid Based Med 2012. doi: 10.1136/eb-2012-100608 (in press)

52. Brett J, Austoker J. Women who are recalled for further investigation for breast screening: psychological consequences 3 years after recall and factors affecting re-attendance. J Public Health Med 2001;23:292-300.

53. Elmore JG, Nakano CY, Koepsell TD, Desnick LM, D'Orsi CJ, Ransohoff DF. International variation in screening mammography interpretations in community-based programs. J Natl Cancer Inst 2003;95:1384-93.

54. Otto SJ, Fracheboud J, Looman CW, Broeders MJ, Boer R, Hendriks JH, Verbeek AL, de Koning HJ; National Evaluation Team for Breast Cancer Screening. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003;361:1411-7.

55. Vervoort MM, Draisma G, Fracheboud J, van de Poll-Franse LV, de Koning HJ. Trends in the usage of adjuvant systemic therapy for breast cancer in the Netherlands and its effect on mortality. Br J Cancer 2004;91:242-7.

56. Otten JD, Broeders MJ, Fracheboud J, Otto SJ, de Koning HJ, Verbeek AL. Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975-2006. Int J Cancer 2008;123:1929-34.

57. Paap E, Holland R, den Heeten GJ, van Schoor G, Botterweck AA, Verbeek AL, Broeders MJ. A remarkable reduction of breast cancer deaths in screened versus unscreened women: a case-referent study. Cancer Causes Control 2010;21:1569-73.

58. van Schoor G, Moss SM, Otten JD, Donders R, Paap E, den Heeten GJ, Holland R, Broeders MJ, Verbeek AL. Increasingly strong reduction in breast cancer mortality due to screening. Br J Cancer 2011;104:910-4.

59. Otto SJ, Fracheboud J, Verbeek AL, Boer R, Reijerink-Verheij JC, Otten JD, Broeders MJ, de Koning HJ; National Evaluation Team for Breast Cancer Screening. Mammography screening and risk of breast cancer death: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2012;21:66-73.

60. Cowan WK, Angus B, Gray JC, Lunt LG, al-Tamimi SR. A study of interval breast cancer within the NHS breast screening programme. J Clin Pathol 2000;53:140-6.

61. Duijm LE, Groenewoud JH, de Koning HJ, Coebergh JW, van Beek M, Hooijen MJ, van de Poll-Franse LV. Delayed diagnosis of breast cancer in women recalled for suspicious screening mammography. Eur J Cancer 2009;45:774-81.

62. Andersson I, Aspegren K, Janzon L, Landberg T, Lindholm K, Linell F, Ljungberg O, Ranstam J, Sigfússon B. Mammographic screening and mortality from breast cancer: the Malmo Mammographic Screening Trial. BMJ 1988;297:943-8.

63. Shen Y, Yang Y, Inoue LY, Munsell MF, Miller AB, Berry DA. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. J Natl Cancer Inst 2005;97:1195-203.

64. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of the factors that influence them: an analysis of 27,825 patient evaluations. Radiology 2002;225:165-75.

65. Yankaskas BC, Cleveland RJ, Schell MJ, Kozar R. Association of recall rates with sensitivity and positive predictive values of screening mammography. AJR 2001;177:543-49.

66. Oestreicher N, Lehman CD, Seger DJ, Buist DS, White E. The incremental contribution of clinical breast examination to invasive cancer detection in a mammography screening program. AJR 2005;184:428-32.

67. Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Böhm-Vélez M, Pisano ED, Jong RA, Evans WP, Morton MJ, Mahoney MC, Larsen LH, Barr RG, Farria DM, Marques HS, Boparai K; ACRIN 6666 Investigators. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA 2008;299:2151-63.

68. Nationaal Borstkanker Overleg Nederland. CBO richtlijn mammacarcinoom. Amsterdam: NABON; 2008. (in Dutch)

69. Kuhl CK, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, Kuhn W, Schild HH. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 2005; 23: 8469-76.

70. Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, Manoliu RA, Kok T, Peterse H, Tilanus-Linthorst MM, Muller SH, Meijer S, Oosterwijk JC, Beex LV, Tollenaar RA, de Koning HJ, Rutgers EJ, Klijn JG; Magnetic Resonance Imaging Screening Study Group. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004;351:427-37.

71. Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, Hilton E, Bailey S, Barrett N, Briers P, English R, Jackson A, Kutt E, Lavelle J, Rockall L, Wallis MG, Wilson M, Patnick J. Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study. BMJ 2004;329:477.

72. Checka CM, Chun JE, Schnabel FR, Lee J, Toth H. The relationship of mammographic density and age: implications for breast cancer screening. AJR 2012;198:W292-5.

73. Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, Geller BM, Abraham LA, Taplin SH, Dignan M, Cutter G, Ballard-Barbash R. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med 2003;138:168-75.

74. Vorherr H. Fibrocystic breast disease:pathophysiology, pathomorphology, clinical picture and management. Am J Obstet Gynecol 1986;154:161-79.

75. Holli K, Saaristo R, Isola J, Hyöty M, Hakama M. Effect of radiotherapy on the interpretation of routine follow-up mammography after conservative breast surgery: a randomized study. Br J Cancer 1998;78:542-5.

76. Dershaw DD. Mammography in patients with breast cancer treated by breast conservation (lumpectomy with or without radiation). AJR 1995;164:309-16.

77. Brenner RJ, Pfaff JM. Mammographic changes after excisional breast biopsy for benign disease. AJR 1996;167:1047-52.

78. Taplin SH, Abraham L, Geller BM, Yankaskas BC, Buist DS, Smith-Bindman R, Lehman C, Weaver D, Carney PA, Barlow WE. Effect of previous benign breast biopsy on the interpretive performance of subsequent screening mammography. J Natl Cancer Inst 2010;102:1040-51.

79. Miglioretti DL, Rutter CM, Gellar BM, Cutter G, Barlow WE, Rosenberg R, Weaver DL, Taplin SH, Ballard-Barbash R, Carney PA, Yankaskas BC, Kerlikowske K. Effect of breast augmentation on the accuracy of mammography and cancer characteristics. JAMA 2004;291:442–50.

80. Wald NJ, Murphy P, Major P, Parkes C, Townsend J, Frost C. UKCCCR multicentre randomised controlled trial of one and two view mammography in breast cancer screening. BMJ 1995;311:1189-93.

81. Blanks RG, Bennett RL, Patnick J, Cush S, Davison C, Moss SM. The effect of changing from one to two views at incident (subsequent) screens in the NHS breast screening programme in England: impact on cancer detection and recall rates. Clin Radiol 2005;60:674-80.

82. Roelofs AA, Karssemeijer N, Wedekind N, Beck C, van Woudenberg S, Snoeren PR, Hendriks JH, Rosselli del Turco M, Bjurstam N, Junkermann H, Beijerinck D, Séradour B, Evertsz CJ. Importance of comparison of current and prior mammograms in breast cancer screening. Radiology 2007;242:70-7.

83. Pisano ED, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, Conant EF, Fajardo LL, Bassett L, D'Orsi C, Jong R, Rebner M; Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group.Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med 2005;353:1773-83.

84. Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population-based screening program: follow-up and final results of Oslo II study. Radiology 2007;244:708-17.

85. 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;23:3098-103.

86. Van Wert MJ, Horowitz TS, Wolfe JM. Even in correctable search, some types of rare targets are frequently missed. Atten Percept Psychophys 2009;71:541-53.

87. Wolfe JM, Horowitz TS, Van Wert MJ, Kenner NM, Place SS, Kibbi N. Low target prevalence is a stubborn source of errors in visual search tasks. J Exp Psychol Gen 2007;136:623-38.

88. Elmore JG, Jackson SL, Abraham L, Miglioretti DL, Carney PA, Geller BM, Yankaskas BC, Kerlikowske K, Onega T, Rosenberg RD, Sickles EA, Buist DS. Variability in interpretive performance at screening mammography and radiologists' characteristics associated with accuracy. Radiology 2009;253:641-51.

89. Timmers JM, van Doorne-Nagtegaal HJ, Verbeek AL, den Heeten GJ, Broeders MJ. A dedicated BI-RADS training programme: effect on the inter-observer variation among screening radiologists. Eur J Radiol 2012;81:2184-8.

90. Warren RM, Duffy SW. Comparison of single reading with double reading of mammograms, and change in effectiveness with experience. Br J Radiol 1995;68:958 -62.

91. Kopans DB. Double reading. Radiol Clin North Am 2000;38:719 -24.

92. Duijm LE, Louwman MW, Groenewoud JH, van de Poll-Franse LV, Fracheboud J, Coebergh JW. Inter-observer variability in mammography screening and effect of type and number of readers on screening outcome. Br J Cancer 2009;100:901-7.

93. Duijm LE, Groenewoud JH, Fracheboud J, de Koning HJ. Additional double reading of screening mammograms by radiologic technologists: impact on screening performance parameters. J Natl Cancer Inst 2007;99:1162-70.

94. Karssemeijer N, Otten JD, Verbeek AL, Groenewoud JH, de Koning HJ, Hendriks JH, Holland R. Computer-aided detection versus independent double reading of masses on mammograms. Radiology 2003;227:192-200.

95. Fenton JJ, Taplin SH, Carney PA, Abraham L, Sickles EA, D'Orsi C, Berns EA, Cutter G, Hendrick RE, Barlow WE, Elmore JG. Influence of computer-aided detection on performance of screening mammography. N Engl J Med 2007;356:1399-409.

96. den Heeten GJ, Karssemeijer N. Computerised assessment of screening mammograms. Ned Tijdschr Geneeskd 2011;155:A3035. (in Dutch)

97. Van Bon-Martens MJH, Klingenberg H, Dijkstra HAJ, Peeters PHM. Borstklachten ten tijde van bevolkingsonderzoek naar borstkanker: grotere kans op verwijzing en op borstkanker. Ned Tijdschr Geneeskd 2001;145:1067-71. (in Dutch)

98. Jaarbericht 2010 Bevolkingsonderzoek Zuid. http://www.bevolkingsonderzoekzuid.nl/page3344/Jaarverslag (accessed July 25, 2011)

99. National Evaluation Team for Breast Cancer Screening (NETB). NETB report 2012, main results 2010 breast cancer screening programme in the Netherlands. Rotterdam: Erasmus MC Rotterdam, Radboud University Nijmegen Medical Centre; 2012.

100. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. Int J Epidemiology 1993;22:369-76.

101. Voogd AC, van Beek MW, Crommelin MA, Kluck HM, Repelaer van Driel OJ, Coebergh JW. Management of early breast cancer in southeast Netherlands since 1984. A population-based study. Regional Breast Cancer Study Group. Acta Oncol 1994;33:753-7.

102. Roumen RM, Kuijt GP, Liem IH, van Beek MW. Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection. Br J Surg 2001;88:1639-43.

103. Louwman WJ, Coebergh JWW. 55 jaar kankerregistratie, trends in incidentie en sterfte. Integraal Kankercentrum Zuid: Eindhoven, 2010. (in Dutch)

104. Coebergh JW, Crommelin MA, Kluck HM, van Beek M, van der Horst F, Verhagen-Teulings MT. Breast cancer in southeast North Brabant and in North Limburg; trends in incidence and earlier diagnosis in an unscreened female population, 1975-1986. Ned Tijdschr Geneeskd 1990;134:760-5. (in Dutch)

105. Louwman WJ, van de Poll-Franse LV, Fracheboud J, Roukema JA, Coebergh JW. Impact of a programme of mass mammography screening for breast cancer on socio-economic variation in survival: a population-based study. Breast Cancer Res Treat 2007;105:369-75.

106. Aarts MJ, Voogd AC, Duijm LE, Coebergh JW, Louwman WJ. Socioeconomic inequalities in attending the mass screening for breast cancer in the south of the Netherlands--associations with stage at diagnosis and survival. Breast Cancer Res Treat 2011;128:517-25.

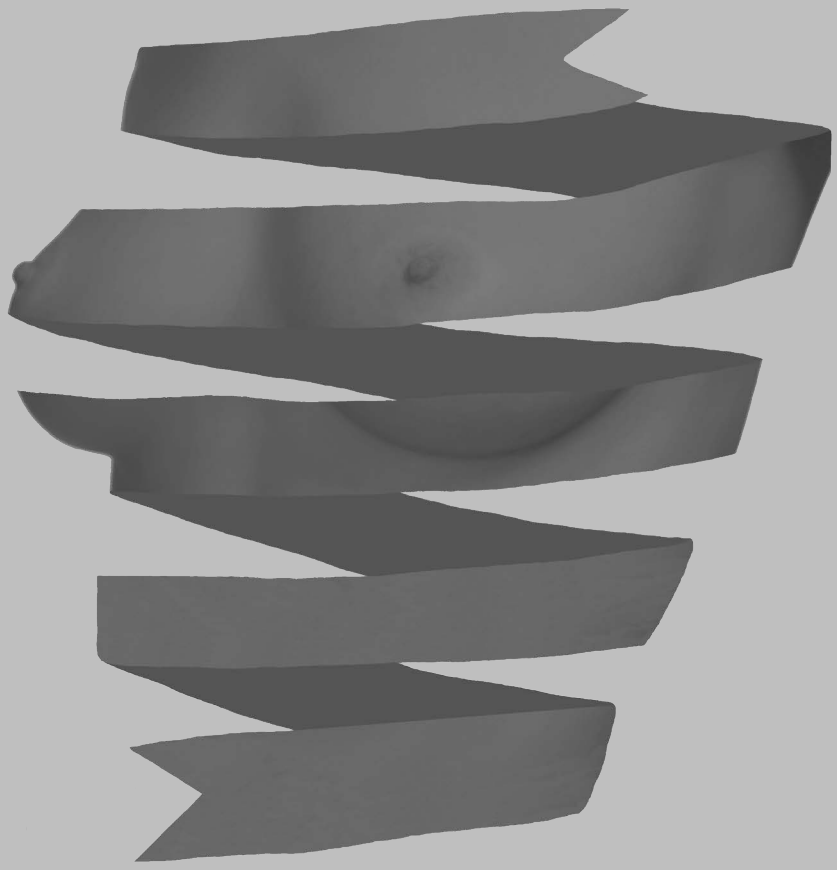
107. Ernst MF, Voogd AC, Coebergh JW, Roukema JA. Breast carcinoma diagnosis, treatment, and prognosis before and after the introduction of mass mammographic screening. Cancer 2004;100:1337-44.

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

109. Louwman WJ, van Diest PJ, van Beek MW, Schapers RF, Nolthenius-Puylaert MB, Baak JP, Coebergh JW. Trends in breast cancer aggressiveness before the introduction of mass screening in southeastern Netherlands 1975-1989. Breast Cancer Res Treat 2002;73:199-206.

Chapter 2

Current sensitivity of breast cancer screening, missed cancers and malpractice claims



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Malpractice claims following screening mammography in The Netherlands
van Breest Smallenburg V, Setz-Pels W, Groenewoud JH, Voogd AC, Jansen FH, Louwman WJ, Tielbeek AV, Duijm LEM

Abstract

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

Introduction

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

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

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

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

Materials and methods

Study population

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

Screening procedure and referral

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

Follow-up procedure

For each referred woman, we collected data on radiology, pathology and surgical procedures at the hospitals where the mammographic screening abnormalities of referred women were evaluated, with 2-year follow-up. A majority of interval cancers (interval cancers are breast cancers that are diagnosed in women after a negative screening examination, defined as no recommendation for referral) were identified by linking the records of screened women to those of the regional cancer registry and radiotherapy laboratory. Some interval cancers were traced by the occasional reports on interval cancers provided by general practitioners or medical specialists to the screening centre, whereas other interval cancers were identified by inquiry about pathology specimens at the various regional pathology laboratories, some months after a hospital had requested the screening mammograms of a screening participant who had not been referred. Communications between the screening organization and screened women that were related to screening procedures, screening outcome or diagnostic procedures after referral were routinely recorded by the organization.

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

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

of those women who had undergone more than one breast biopsy procedure needed for breast cancer confirmation.

Communication between the coordinating screening radiologist and screened women

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

Results

Overall screening results

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

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

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

A total of 670 interval cancers had been diagnosed among the screened population (Figure 1). The reviewers reported that 163 (24.3%) of these cancers had been missed at the latest

screening mammogram, 164 (24.5%) had been visible as a minimal sign and 343 (51.2%) were not visible at the latest screen.

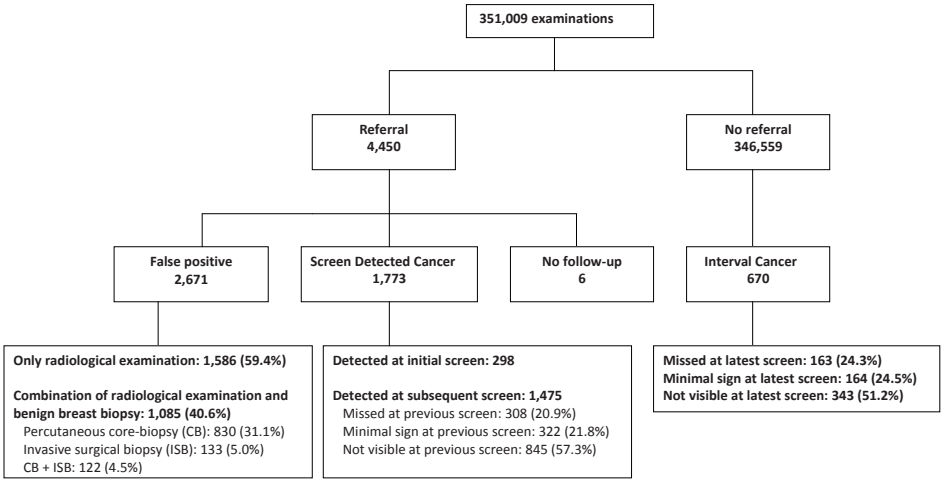


Figure 1. *Mammography screening outcome from January 1997 - January 2009.*

Requests for additional information and malpractice claims

Between January 1997 and September 2011, a total of 19 screened women had contacted the screening organization for questions related to their cancer detected at screening (8 women) or interval cancer (11 women) (Figure 2). Of these 19 women, 2 had been screened between 1997-2001 (102,439 screens, including 498 screen detected cancers and 169 interval cancers), 6 between 2001-2005 (114,740 screens, including 599 screen detected cancers and 244 interval cancers) and 11 between 2005-2009 (133,830 screens, including 676 screen detected cancers and 257 interval cancers). The resulting contact between the women and the coordinating radiologist was limited to conversation by telephone in 5 cases and comprised 3 screen detected cancers (previous screen: 2 minimal sign lesions, 1 not visible) and 2 interval cancers (latest screen: 1 minimal lesion, 1 not visible). Additional face to face contact occurred in 14 women, of whom 5 had advanced cancer detected at subsequent screening (previous screen: 1 missed, 3 minimal sign lesions, 1 not visible) and 9 had a diagnosis of advanced interval cancer (latest screen: 2 missed, 5 minimal sign lesions, 2 not visible). In these patients advanced cancer was defined as invasive cancer >20 mm. and/or lymph node positive cancer. None of the 19 women started a malpractice lawsuit or insurance claim for financial compensation.

Apart from the 19 women mentioned above, another 3 women directly initiated an insurance claim for financial compensation of their interval cancer without previously having contacted the screening organization (Figure 2). The time span between the latest screen and the start of the claim in these 3 cases was 14, 25 and 40 months, respectively. One claim was rejected (latest screen: minimal sign lesion), whereas the verdicts of the other 2 claims (two interval cancers that had been missed at the latest screen) still have to be finalized.

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

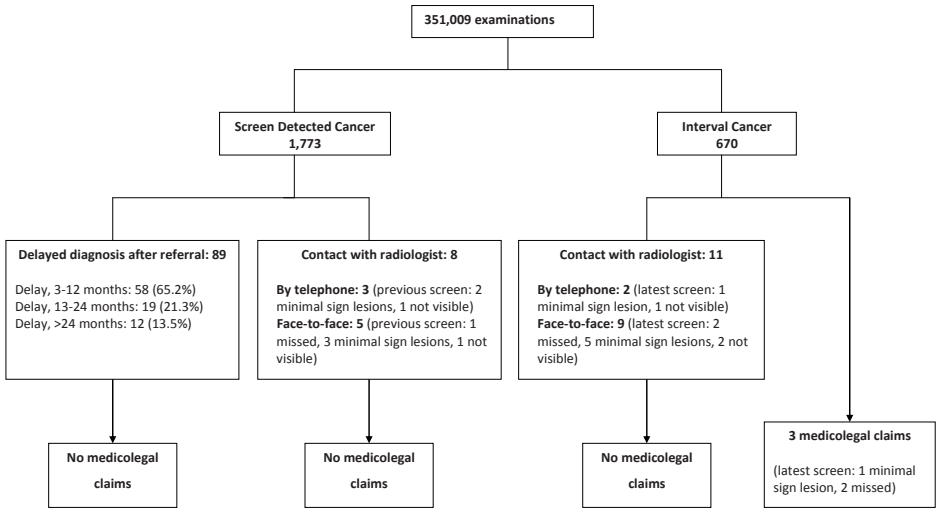


Figure 2. *Malpractice claims at screening mommography.*

Delayed cancer diagnosis after referral

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

Discussion

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

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

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

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

So far, only 3 women have filed a claim for financial compensation of their interval cancer and they did so without first contacting the coordinating screening radiologist. Apart from

the open communication, several other factors may also partly explain the very low number of contacts between the screening organization and screening participants and sporadic claims in our study. With each invitation, women receive written information that breast cancer may be missed at screening mammography and they should always seek medical attention in case of breast complaints following a negative screen. Although data about payouts for missed and delayed breast cancer diagnoses in the Netherlands are lacking, these payouts may probably be much lower when compared to the US. Moreover, Dutch lawyers are not allowed to practice a no-win no-fee policy. Finally, women may have refrained from contacting the coordinating screening radiologist and starting malpractice claims after having received satisfactory information from their physicians in the hospitals to which they had been referred.

False positive referral negatively affects quality of life[26] and almost 1 out of every 10 referred women in our study (9.5%, 255/2,671) with benign follow-up underwent invasive surgical biopsy. Surgical biopsy harbours the risk of infection, cosmetic drawbacks and may decrease the accuracy of future screening mammography.[20] Nevertheless, only one referred woman complained about her false positive referral and she wanted the screening organization to compensate her for the costs of clinical mammography and breast ultrasonography. The Dutch nation-wide screening mammography programme provides free screening mammography, but it does not cover any costs related to additional diagnostic procedures. An addition of this information to the screening invitation letter probably prevents invited women to be confronted with unexpected financial expenses in case not all hospital related costs are covered by their medical insurance.

Although the screening organization is not responsible for the quality of clinical assessment of referred women, we also determined whether any of the referred women with a delay in breast cancer diagnosis filed a claim. About 5% of women in our screened population experienced a diagnostic delay of more than 3 months after their referral and we previously found that this delay is most frequently due to erroneous interpretation or classification of breast lesions at clinical breast imaging.[23,24] To our surprise, none of the women filed a malpractice claim, not even when they were diagnosed with advanced cancer 2 years after referral.

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

Our study has certain limitations. We realize that the eagerness of patients to start a lawsuit will be influenced by national legislation and the beforehand probability and height of insurance payouts. Furthermore, the Dutch nation-wide breast screening programme differs in several aspects from other European programmes and US programmes. For example, the referral rate in the Netherlands is very low when compared to a 3-6% referral rate in other European countries and a 10% referral rate in the US.[1,15] In the Netherlands, all mammograms are routinely double read by two screening radiologists, which may not be standard practice in other screening programmes.[7,27] Also, many European programmes, including the Dutch one, offer biennial screening for women aged 50-75 years. In contrast, women are screened every 3 years in the United Kingdom and US programmes usually offer annual screening from the age of 45. Screening interval length may influence screening outcome parameters such as screening sensitivity and tumour size of screen detected cancers and interval cancers.[28,29] Furthermore it was not possible to compare the low number of claims in our screening region with a nation-wide number of claims following breast cancer screening. Details of claims are not routinely registered by screening organizations in the Netherlands. We found, however, one published claim, regarding a woman with interval cancer.[30] Her claim was rejected after concluding that both screening radiologists had made the right decision by not referring the woman for her minimal sign lesion. Despite the absence of a national registry of claims, we have no reason to believe that the frequency of claims in our region differs from those in other parts of the Netherlands.

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

Finally, only mammograms obtained with analogue units were included in the current study, whereas most mammography units are now digital. Digitization of the breast cancer screening programme in the Netherlands has recently been completed and the proportion of cancers missed at a previous screen may hopefully decrease in the future as digital screening tends to yield higher cancer detection rates when compared to analogue screening.[32,33]

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

References

1. Dowling EC, Klabunde C, Patnick J, Ballard-Barbash R; International Cancer Screening Network (ICSN). Breast and cervical cancer screening programme implementation in 16 countries. J Med Screen 2010;17:139-46.
2. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay in survival in patients with breast cancer: a systematic review. Lancet 1999;353:1119–26.
3. Richards MA, Smith P, Ramirez AJ, Fentiman IS, Rubens RD. The influence on survival of delay in the presentation and treatment of symptomatic breast cancer. Br J Cancer 1999;79:858-64.
4. Yankaskas BC, Schell MJ, Bird RE, Desrochers DA. Reassessment of breast cancers missed during routine screening mammography: a community-based study. AJR 2001;177:535-41.
5. Warren Burhenne LJ, Wood SA, D'Orsi CJ, Feig SA, Kopans DB, O'Shaughnessy KF, Sickles EA, Tabar L, Vyborny CJ, Castellino RA. Potential contribution of computer-aided detection to the sensitivity of screening mammography. Radiology 2000;215:554-62.
6. Duijm LEM, Groenewoud JH, Fracheboud J, de Koning HJ. Additional double reading of screening mammograms by radiologic technologists: Impact on screening performance parameters. J Natl Cancer Inst 2007;99:1162-70.
7. Fenton JJ, Abraham L, Taplin SH, Geller BM, Carney PA, D'Orsi C, Elmore JG, Barlow WE; for the Breast Cancer Surveillance Consortium. Effectiveness of computer-aided detection in community mammography practice. J Natl Cancer Inst 2011;103:1152-61.
8. Fileni A, Magnavita N, Pescarini L. Analysis of malpractice claims in mammography: a complex issue. Radiol Med 2009;114:636-44.
9. Physician Insurers Association of America. Breast cancer study. Rockville: PIAA; 2002.
10. Berlin L. Breast cancer, mammography, and malpractice litigation: the controversies continue. AJR 2003;180:1229–37.
11. Kopans DB. Mammography screening is saving thousands of lives, but will it survive medical malpractice? Radiology 2004;230:20-4.
12. Bassett LW, Monsees BS, Smith RA, Wang L, Hooshi P, Farria DM, Sayre JW, Feig SA, Jackson VP. Survey of radiology residents: breast imaging training and attitudes. Radiology 2003;227:862-9.
13. Wing P, Langelier MH. Workforce shortages in breast imaging: impact on mammography utilization. AJR 2009;192:370-8.
14. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann Oncol 2008;19:614-22.
15. Smith-Bindman R, Chu PW, Miglioretti DL, Sickles EA, Blanks R, Ballard-Barbash R, Bobo JK, Lee NC, Wallis MG, Patnick J, Kerlikowske K. Comparison of screening mammography in the United States and the United Kingdom. JAMA 2003;290:2129-37.
16. Carney PA, Yi JP, Abraham LA, Miglioretti DL, Aiello EJ, Gerrity MS, Reisch L, Berns EA, Sickles EA, Elmore JG. Reactions to uncertainty and the accuracy of diagnostic mammography. J Gen Intern Med 2007;22:234-41.
17. Gallagher TH, Cook AJ, Brenner RJ, Carney PA, Miglioretti DL, Geller BM, Kerlikowske K, Onega TL, Rosenberg RD, Yankaskas BC, Lehman CD, Elmore JG. Disclosing harmful mammography errors to patients. Radiology 2009;253:443-52.
18. Robinson AR, Hohmann KB, Rifkin JI, Topp D, Gilroy CM, Pickard JA, Anderson RG. Physician and public opinions on quality of health care and the problem of medical errors. Arch Intern Med 2002;162:2186-90.
19. Duijm LEM, Groenewoud JH, Hendriks JHCL, de Koning HJ. Independent double reading of screening mammograms in the Netherlands: effect of arbitration following reader disagreements. Radiology 2004;231:564-70.

20. Van Breest Smallenburg V, Duijm LEM, Voogd AC, Groenewoud JH, Jansen FH, van Beek M, Louwman MW. Lower sensitivity of screening mammography after previous benign breast surgery. Int J Cancer 2012;130:122-8.

21. Setz-Pels W, Duijm LE, Groenewoud JH, Voogd AC, Jansen FH, Hooijen MJ, Louwman MW. Detection of bilateral breast cancer at biennial screening mammography in the Netherlands: a population based study. Radiology 2011;260:357-63.

22. Maes RM, Dronkers DJ, Hendriks JH, Thijssen MA, Nab HW. Do non-specific minimal signs in a biennial mammographic breast cancer screening programme need further diagnostic assessment? Br J Radiol 1997;70:34-8.

23. Duijm LEM, Groenewoud JH, Jansen FH, Fracheboud J, van Beek M, de Koning HJ. Mammography screening in the Netherlands: delay in the diagnosis of breast cancer after breast cancer screening. Br J Cancer 2004;91:1795-9.

24. Duijm LEM, Groenewoud JH, de Koning HJ, Coebergh JW, van Beek M, Hooijen MJHH, van de Poll-Franse LV. Delayed diagnosis of breast cancer in women recalled for suspicious screening mammography. Eur J Cancer 2009;45:774-81.

25. American College of Radiology: Breast Imaging Reporting and Data System (BI-RADS), 4th ed. Reston: ACR; 2003.

26. van der Steeg AF, Keyzer-Dekker CM, de Vries J, Roukema JA. Effect of abnormal screening mammogram on quality of life. Br J Surg 2011;98:537-42.

27. Hofvind S, Vacek PM, Skelly J, Weaver DL, Geller BM. Comparing screening mammography for early breast cancer detection in Vermont and Norway. J Natl Cancer Inst 2008;100:1082-91.

28. Goel A, Littenberg B, Burack RC. The association between the pre-diagnosis mammography screening interval and advanced breast cancer. Breast Cancer Res Treat 2007;102:339-45.

29. Mandelblatt JS, Cronin KA, Bailey S, Berry DA, de Koning HJ, Draisma G, Huang H, Lee SJ, Munsell M, Plevritis SK, Ravdin P, Schechter CB, Sigal B, Stoto MA, Stout NK, van Ravesteyn NT, Venier J, Zelen M, Feuer EJ; Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. Ann Intern Med 2009;151:738-47.

30. Crul BVM, Rijksen WP. "Toch kanker ondanks bevolkingsonderzoek". Medisch Contact 2002;4:149. (in Dutch)

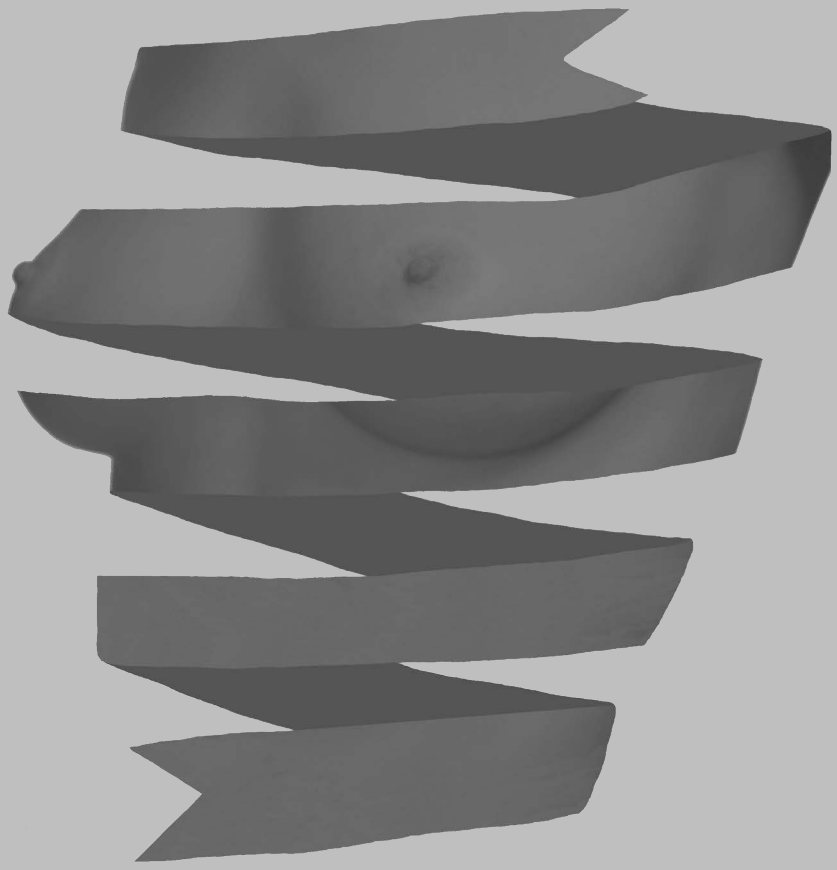
31. Berlin L. Malpractice and ethical issues in radiology: the duty to communicate. AJR 2011;197:W962.

32. Pisano ED, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, Conant EF, Fajardo LL, Bassett L, D'Orsi C, Jong R, Rebner M; Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group. Diagnostic performance of digital versus film mammography for breast-cancer screening. New Engl J Med 2005;353:1773-83.

33. Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population based screening program: follow-up and final results of Oslo II study. Radiology 2007;244:708–17.

Chapter 3

Replacing single-view by two-view mammography in subsequent screening rounds



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Two-view versus single-view mammography at subsequent screening in a region of the Dutch breast screening programme
van Breest Smallenburg V, Duijm LEM, den Heeten GJ, Groenewoud JH, Jansen FH, Fracheboud J, Plaisier ML, van Doorne-Nagtegaal HJ, Broeders MJ

Abstract

We retrospectively determined the effect of analogue two-view mammography versus single-view mammography at subsequent screens on breast cancer detection and determined financial consequences for a current digital mammography setting. Two screening radiologists reviewed the mammograms of 536 screen detected cancers (SDCs) and 171 interval cancers (ICs) with single-view mammography (medio-lateral-oblique view) at the last but one screen (SDCs) or latest screen (ICs). They determined whether two-view mammography at the last (but one) screen could have increased the cancer detection rate at that screening round. For subsequent screens, the radiologists also assessed the percentage of SDCs and ICs that had been missed at previous two-view screening (SDC) or the latest two-view screening (IC), respectively. Additional personnel and digital storage costs for standard two-view mammography at subsequent screening were calculated for digital screening. Two-view mammography could have facilitated earlier cancer detection in 40.9% (219/536) of SDCs and 39.8% (68/171) of ICs. For two-view screens, 24.4% of SDCs (213/871) were missed at previous two-view screening and 29.3% of ICs (110/375) were missed at the latest screen. Overall costs increased € 1.03 per screen after implementation of digital two-view mammography. Standard two-view mammography at subsequent screening may modestly increase cancer detection at an earlier stage, whereas additional screening costs are limited.

Introduction

Many countries have introduced breast cancer screening programmes over the past two decades in order to detect breast cancer at an early stage and to reduce its associated morbidity and mortality.[1] From 1989 the Netherlands started a nation-wide breast screening programme, nowadays offering biennial screening to women aged 50-75 years.

In the early eighties of the last century, several trials showed breast cancer mortality reduction using single-view (medio-lateral-oblique view, MLO) screening mammography.[2] One decade later, Walt et al.[3] found that, by adding the cranio-caudal view (CC), two-view mammography at initial screening increased breast cancer detection. Nowadays, two-view mammography is performed in most screening programs at initial screening.[4] Several studies have shown that standard two-view mammography at subsequent screens may also result in a significant increased cancer detection rate, if compared with single view mammography.[5,6] Many countries, including the United Kingdom (UK) and the United States (US), currently use two-view mammography in their screening programmes, both for initial and subsequent screens.

Nevertheless, although European guidelines recommend standard two-view mammography, The Netherlands, Denmark and some parts of Italy, still use single-view mammography at subsequent screening.[7,8] The Dutch screening programme offers two-view mammography at initial screening and single-view mammography (MLO) at subsequent screening.[9] An additional CC-view is obtained if indicated only. This policy for subsequent screens is used because of concerns about the effects of radiation exposure and economic issues. Standard two-view mammography is more time consuming and increases costs for data storage. Moreover, radiation exposure may induce breast cancer.[10] In addition, it can be argued whether additional CC-views will add information to the MLO-view in case of fatty breasts.

The recent conversion of the Dutch breast screening programme from analogue to digital screening, however, has raised the discussion in the Netherlands whether the selective use of two-view mammography at subsequent screening should be replaced by standard two-view mammography. The efficacy of selective two-view mammography at subsequent screening has not been studied before. Besides, concerns about the increased radiation exposure seem less important, as a recent study found a lower risk of inducing breast cancer from screening mammography than expected from earlier epidemiological studies.[11] Moreover, digital screening may lead to a significant reduction in radiation exposure.[12,13]

For these reasons, we performed a retrospective study to determine whether standard two-view mammography for subsequent screens, rather than selective two-view mammography, may increase breast cancer detection. In addition we determined the economic implications of standard two-view mammography for subsequent screens in a digital mammography setting.

Materials and methods

Study population

We included all 334,693 screens (44,341 initial screens and 290,352 subsequent screens in 83,460 women) which were performed at one of two specialized analogue screening units in a southern breast cancer screening region of the Netherlands between January 1, 1997 and July 1, 2008. All women had given written informed consent to use their screening and follow-up data for research purposes. Institutional review board approval was not required for this study.

Screening and referral procedure

Women aged 50-75 years were invited every two years for screening mammography in conformity with the Dutch guidelines for breast cancer screening. At the time of invitation, women were informed that they should seek medical attention, rather than attend screening mammography, in case of breast symptoms such as the presence of a palpable lesion, bloody nipple discharge or breast contour deformity. Women with prior benign breast surgery were routinely invited for screening and the Dutch guidelines on breast cancer screening advise that mammographic follow-up of women after breast conserving therapy should take place in an outpatient hospital setting for a period of 10 years before returning to routine screening.[14] More details of the Dutch nation-wide breast cancer screening programme have been described previously.[15] In summary, two-view mammography was performed in initial screens. Generally single-view mammography (MLO-view only) was carried out in subsequent screens. Over the study period, the proportion of women where an additional CC-view was obtained increased from 28.5% (1997) to 50.5% (2008) of subsequent screens. Indications for this two-view mammography included dense breast tissue, previous breast surgery, any changes in mammographic findings (such as new or increased densities or microcalcifications) and a more than two-year interval since the previous screen. The mammograms were obtained by specialized screening mammography radiographers and independently double read by a team consisting of 12 certified screening radiologists. Each radiologist had an annual reading volume of more than 5,000 screening mammograms. In case of normal or benign mammographic findings or non-specific minimal signs, women were not referred for further diagnostic workup. In case of a suspicious or malignant lesion, the woman was referred to a surgical oncologist for further analysis of the mammographic abnormality.

Screening follow-up

The follow-up period for screened women included the time period to the next screening round, with a screening interval of approximately 2 years. We collected data on diagnostic procedures, breast cancer diagnosis, histopathology and TNM (tumour-node-metastasis) classification of all referred women and of women with interval cancers (ICs). ICs are breast cancers diagnosed after a negative screening examination, but before the next screening examination. Procedures for the detection of ICs have been described previously;[16] most ICs were identified by linking the screening records to the regional cancer registry (Eindhoven Cancer Registry).

Review of single-view screening mammograms

Two screening radiologists (LD, FJ) reviewed the screening mammograms of all women with screen detected cancer (SDC) and single-view mammography (MLO) at the last but one screen and the mammograms of all women with IC and a single-view mammography (MLO) at their latest screen. For ICs, review also included the clinical mammogram obtained at the time of IC detection. At review, the breast density was assessed, according to the BI-RADS criteria for each MLO-view. Next, if the cancer was visible at the last but one MLO-view in case of SDC or at the last MLO-view in case of IC, the radiologists classified the mammographic abnormality into one of the following 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. asymmetry. Finally, the two radiologists determined whether or not the availability of an additional CC-view at the previous screen could have facilitated earlier breast cancer detection (e.g., a minimal sign density at the single-view screen showed a suspicious, indistinct border that was mainly visible at the CC-view of the latest screen (SDC) or clinical mammogram (IC)). The two radiologists were initially blinded to each other's review and discrepant readings were followed by consensus reading.

3

Review of two-view screening mammograms

Both radiologists also reviewed all two-view screening mammograms and determined the percentage of SDCs and ICs that had been missed, either at the last but one two-view screen (in case of SDC) or at the latest two-view screen (in case of IC). Again, discrepant readings were solved by consensus reading.

Replacement of selective two-view by standard two-view mammography at subsequent screens in a digital screening setting: determination of economic implications

We first determined the expected increase in CC-views in case of introduction of standard two-view mammography at subsequent screens. Throughout the years, the percentage of two-view mammography at subsequent screening gradually increased from approximately 30% to 50%. We used the proportion of two-view mammography at subsequent screening in 2008 as a baseline, because in 2009 there was a sharp increase of two-view mammography at subsequent screening. This was the consequence of the introduction of digital screening mammography, requiring that two-view mammography is performed in all women undergoing digital screening for the first time.

To determine the extra time needed for two-view mammography, mammography radiographers at one of the two screening units recorded the time needed to obtain single-view and two-view mammograms in a consecutive series of both analogue and digital screens. For analogue screening the time needed to obtain 69 single-view mammograms and 63 two-view mammograms was recorded. For digital screening in a series of 124 digital screens the time needed to make a single-view mammogram and the time for making an additional CC-view were recorded. The implications on personnel costs were calculated.

Finally the increase in costs for the obligatory storage of three digital screening rounds was estimated, as it is obligatory to store digital mammography data for at least three years.

Statistical analysis

All data were entered into a computerized spreadsheet (Excel; Microsoft, Redmond, WA, USA). We used Excel to calculate the standard deviations for the time needed to perform a single-view or two-view mammogram, both for film-screen and digital screening mammography.

Results

Screen detected cancers

A total of 334,693 screens were performed from January 1, 1997 to July 1, 2008 and 4,192 women (1.3%) were referred for further analysis (Figure) . Breast cancer was confirmed in 1,697 of referred women, resulting in a cancer detection rate of 5.1 per 1,000 screens and a positive predictive value of referral of 40.5%. Of these 1,697 women, 536 (31.6%) had undergone single-view mammography at the last but one screening round. The mammographic lesions at the MLO-view of the last but one screen consisted mainly of densities (53.4%) or lesions not visible on single view mammography (30.1%) (Table 1). At review, the radiologists concluded that in 40.9% of these women (219/536) an additional CC-view could have resulted in cancer detection at the last but one screen instead of detection at the latest screen (Table 1). An additional CC-view at the last but one screen could have resulted in earlier cancer detection in 37.0% (118/319) of women with category I dense breasts, 45.0% (84/187) of women with category II dense breasts and 58.6% (17/29) of women with category III dense breasts. Of the 219 SDCs, for which an additional CC-view at the last but one screen could have potentially led to breast cancer detection at this last but one screen, 21.5% (47/219) were T2+ tumours and 21.9% (48/219) of women had axillary lymph node metastasis.

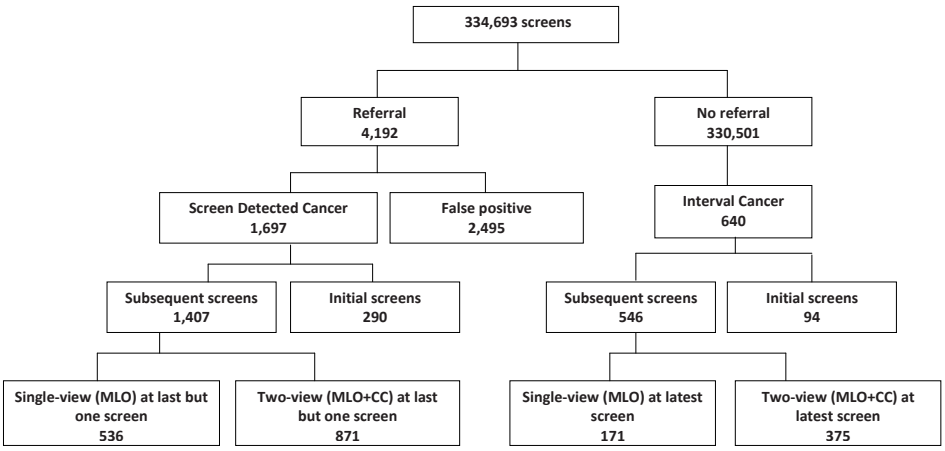


Figure. *Mammography screening outcome at 2-year follow-up.*

Table 1. *Screen detected cancers with single-view screening mammography at the last but one screen: mammographic and tumour characteristics according to probable benefit of additional cranio-caudal (CC) view.*

	Additional CC-view probably helpful for cancer detection at last but one screen, n=219 (40.9%)					**Additional CC-view not helpful for cancer detection at last but one screen, n=317 (59.1%)**				
Breast density (BI-RADS)	I 118 (53.9)	II 84 (38.4)	III 17 (7.8)	IV 0 (0.0)	**Total**	I 201 (63.4)	II 103 (32.5)	III 12 (3.8)	IV 1 (0.3)	**Total**
Mammographic lesion at last but one screen										
Density	70	39	8	0	117 (53.4)	26	7	2	1	36 (11.4)
Microcalcification	3	5	1	0	9 (4.1)	6	5	0	0	11 (3.5)
Density with microcalcifications	17	4	1	0	22 (10.0)	8	3	0	0	11 (3.5)
Asymmetry	0	0	0	0	0 (0.0)	0	0	0	0	0 (0.0)
Architectural distortion	1	3	1	0	5 (2.3)	1	0	0	0	1 (0.3)
No lesion visible	27	33	6	0	66 (30.1)	160	88	10	0	258 (81.4)
Tumour stage at time of diagnosis										
DCIS	7	6	2	0	15 (6.8)	37	19	5	0	61 (19.2)
T1a-c	96	51	8	0	155 (70.8)	138	71	7	1	217 (68.5)
T2+	15	25	7	0	47 (21.5)	26	13	0	0	39 (12.3)
Unknown	0	2	0	0	2 (0.9)	0	0	0	0	0 (0.0)
Lymph-node status of invasive cancers										
Positive	24	21	3	0	48 (23.5)	35	16	0	1	52 (20.3)
Negative	86	54	12	0	152 (74.5)	125	66	7	0	198 (77.3)
Unknown	1	3	0	0	4 (2.0)	4	2	0	0	6 (2.3)

Percentages are given in parentheses

Interval cancers

A total of 640 interval cancers were diagnosed among women who were screened with negative outcome, between January 1, 1997 and July 1, 2008 (Figure). Of these, 546 were diagnosed following a negative subsequent screen. Single-view mammography at the latest screen had been performed in 171 women (31%). The mammographic lesions at the last (single-view) screening consisted mostly of densities (60.3%) or lesions that were not visible on single view mammography (26.5%) (Table 2). At review, the radiologists concluded that, by adding the CC-view, 68 of these 171 ICs (39.8%) could have potentially been detected at the latest screen (Table 2). For category I, II and III breast density, two-view mammography at the latest screen might have resulted in SDCs rather than ICs in respectively 31.6% (30/95), 53.0% (35/66) and 30.0% (3/10) of cases. Of the 68 ICs that might have been detected at screening if two-view mammography had been performed, 41.2% (28/68) were T2+ tumours and 50.0% (34/68) of women had axillary lymph node metastasis.

Cancers missed at two-view screening mammography

The two radiologists considered 24.4% of SDCs (213/871) and 29.3% of ICs (110/375) as missed at the last but one two-view screen or latest two-view screen, respectively.

Additional personnel costs and storage costs for standard two-view mammography

Personnel costs

Mean acquisition time for analogue screening was 140±40 seconds for single-view mammography in 69 women and 225±43 seconds for two-view mammography in 63 women. In a series of 124 digital screens, addition of the CC-view increased the mean acquisition time by 143 seconds from 118±29 seconds at single-view mammography to 261±52 seconds at two-view mammography. In 2008 30,016 of all 33,611 screening examinations (89.3%) were subsequent screens. Two-view mammography had been performed in 50.5% of subsequent screens (15,170/30,016), which is in line with the nation-wide findings.[14] Under the assumptions of 35,000 attendees in 2011, 89.3% subsequent screens and an increase from 50.5% to 100% of two-view mammography at subsequent screening, additional CC-view will be obtained in an extra 15,471 (35,000x0.893x0.495) women. As two-view mammography generally takes 143 seconds extra time, 615 additional radiographer working hours are yearly needed to perform standard two-view mammography at subsequent screening. As a full time screening mammography radiographer works 1,631 hours per year for € 50,000, standard two-view screening at our two screening units will increase radiographer costs by € 19,000. At a nation-wide scale, standard two-view mammography of 900,000 initial and subsequent screens will approximately increase the number of additional CC-views with 795,663 (900,000x 0.893x0.495x2) and the personnel costs by € 488,570 (9.8 additional radiographers). The increased number of views at subsequent screening will not increase radiological assessment costs, as screening radiologists receive a fixed fee per screening examination which is independent of the number of views.

Table 2. *Interval cancers with single-view screening mammography at the last screen: mammographic and tumour characteristics according to probable benefit of additional cranio-caudal (CC) view.*

	Additional CC-view probably helpful for cancer detection at screening, n=68 (39.8%)					**Additional CC-view not helpful for cancer detection at screening, n=103 (60.2%)**				
Breast density (BI-RADS)	I 30 (44.1)	II 35 (51.5)	III 3 (4.4)	IV 0 (0.0)	**Total**	I 65 (63.10)	II 31 (30.1)	III 7 (6.8)	IV 0 (0.0)	**Total**
Mammographic lesion at latest screen										
Density	20	20	1	0	41 (60.3)	10	4	3	0	17 (16.5)
Microcalcification	2	1	0	0	3 (4.4)	4	2	2	0	8 (7.8)
Density with microcalcifications	2	0	0	0	2 (2.9)	1	1	1	0	3 (2.9)
Asymmetry	2	1	0	0	3 (4.4)	1	2	0	0	3 (2.9)
Architectural distortion	0	1	0	0	1 (1.5)	0	0	0	0	0 (0.0)
No lesion visible	4	12	2	0	18 (26.5)	49	22	1	0	72 (69.9)
Tumour stage at time of diagnosis										
DCIS	0	1	0	0	1 (1.5)	6	1	1	0	8 (7.8)
T1a-c	17	19	3	0	39 (57.4)	35	12	4	0	51 (49.5)
T2+	13	15	0	0	28 (41.2)	23	18	2	0	43 (41.7)
Unknown	0	0	0	0	0 (0.0)	1	0	0	0	1 (1.0)
Lymph-node status of invasive cancers										
Positive	17	15	2	0	34 (50.7)	28	12	1	0	41 (43.2)
Negative	12	18	1	0	31 (46.3)	29	18	5	0	52 (54.7)
Unknown	1	1	0	0	2 (3.0)	2	0	0	0	2 (2.1)

Percentages are given in parentheses

Digital storage costs

Yearly storage costs for digital images are € 29.35/1 Gigabyte (Gb). As a total of 160 mammographic images can be stored in 1 Gb, the 30,942 additionally obtained CC-views (for each of two breasts in 15,471 women) in our screening region yearly increase storage costs by € 5,676. The digital images have to be stored for a period of three years, so total storage costs will increase with € 17,028.

Total costs

Altogether, additional costs (personnel costs + storage costs) for standard two-view digital mammography are € 36,028 per year of screening (or € 1.03 per screen). As total acquisition costs per screen are € 53.3617, standard two-view subsequent screening will result in a 1.9% increase of total costs per screen.

Other costs and considerations

Costs of maintenance of screening equipment, as well as debit cost of the mammography units, are independent from the number of images obtained per screening examination. Currently, all women receive two-view mammography at their first digital screen. Therefore, the number of screening units does not need to be increased if a policy of standard two-view mammography will be continued in the future.

Discussion

We found that many women with single-view mammography at subsequent screening could have benefited from two-view mammography, as cancers would have probably been detected at an earlier screening round, in combination with a reduction of interval cancers. Although screening mammography aims to detect breast cancer at an early stage, more than 20% of the SDCs in women, who could have benefited from two-view mammography, were large invasive tumours (>20 mm) or tumours with axillary lymph node metastases. A substantial, albeit unknown, percentage of these cancers will have shown a less advanced tumour stage and thus a better prognosis of survival if they had been detected at a previous screening round. Tumour stage distribution of ICs in women who could have benefited from two-view mammography, was even worse. Standard two-view mammography at subsequent screening may not only result in the detection of smaller cancers, but may also decrease recall rates and the percentage of false positive referrals.[3,18] A reduction in the number of false positive referrals can reduce workup costs and the number of women experiencing referral related anxiety.

The percentage of additional CC-views in subsequent screening rounds in our overall screening population has increased from 28.5% to 50.5% over the 11.5 year study period. The cancer detection rate also increased from 4.6‰ (1997-1998) to 5.2‰ (2007-2008). Since the referral rate also increased over the study period, from 1.1% to 1.5%, both factors probably contributed to an increased number of screen detected cancers. Our results, however, that are based on the shortcomings of single-view mammography itself will not have been influenced by this increase of two-view mammograms. We calculated that in subsequent screens, in case of single-view mammography, a maximum of about 40% of SDCs and ICs could have been diagnosed at an earlier stage if two-view instead of single-view

mammography had been performed, however, we assume that the benefit will be much lower. Even at standard two-view mammography, a substantial percentage of SDCs (24.4% in our series) will be missed at a previous screening round, whereas ICs may be visible at the latest two-view screening mammogram (29.3% in our series). Moreover, breast cancers which are missed or misinterpreted at screening do not all result in a worse prognosis.[19]

For SDCs, we found a positive correlation between breast density and the percentage of women who could have benefited from two-view mammography. Duffy et al. recently demonstrated that additional views are helpful for a proper assessment of dense breasts.[20] Although the Dutch screening mammography protocol mentions that acquisition of a CC-view is mandatory in the presence of dense fibroglandular tissue, we found that single-view mammography had been performed at the last but one screen in 8% of women with a screen detected breast cancer and a BI-RADS III breast density (50%-75% residual fibroglandular tissue). This finding suggests that two-view mammography is not always obtained, when indicated, in daily screening practice. Moreover, the observation that in BI-RADS I density breasts (0%-25% residual fibroglandular tissue) a CC-view could have facilitated cancer detection in about one third of SDCs and ICs, implies that two-view mammography at subsequent screening also improves cancer detection in fatty breasts.

Implementation of standard two-view digital mammography at subsequent screening in the Dutch breast screening programme will result in a 1.9% (€ 1.03) increase in costs per screening examination. Digital storage costs account for almost 50% of these increased costs. Although the number of women who participate in the screening may rise in the future as the result of an aging population and inclusion of women aged under 50 years, digital storage costs are expected to decrease considerably in upcoming years. Mean acquisition time for two-view mammography was longer for digital screens (261 seconds) than for analogue screens (225 seconds). The acquisition time measurements for digital mammography were performed shortly after the introduction of digital screening mammography. An increasing experience in digital mammography among radiographers may shorten mammography acquisition time in the future.

The adverse effects of increased radiation exposure with routine two-view mammography at subsequent screening seem to be limited. Compared with other countries, including the US, the mean glandular dose at screening mammography in the Netherlands is low and in the range of 1.3 mGy[21] for analogue screening and 1.5 mGy for digital screening.[22] These two Dutch studies, however, calculated the mean glandular dose for the current screening protocol in the Netherlands with two-view mammography being obtained in approximately 50% of subsequent screens. The mean glandular dose at digital screening will be higher than 1.5 mGy after introduction of routine two-view subsequent screening, though acquisition of CC-views will less than double radiation dose.[5] Moreover there are developments that potentially decrease radiation exposure at digital mammography.[12,13] Annually, around 3,500 women die from breast cancer in the Netherlands. Deaths may be due to radiation exposure at breast cancer screening in a maximum of 3 breast cancer deaths a year.[21] This latter number will likely turn out to be lower, as a recent study found that the number of radiation induced fatal breast cancers may considerably be lower than expected from earlier studies.[11] Finally,

we know that as a result of early cancer detection at screening mammography 250-400 less women will die from breast cancer every year, resulting in a favourable balance of benefit over risk of breast cancer screening.[21]

Our study has several limitations. Data to determine the possible value of standard two-view mammography at subsequent screening were derived from an analogue screening setting, whereas we recently replaced analogue screening by digital screening. Although two-view digital screening seems to equal cancer detection rates found at analogue screening,[23] digital data on cancer detection at single-view subsequent screening mammography are lacking. Also, we currently cannot predict the effect of digital screening on the percentage of single-view mammography being obtained at subsequent screening if the policy of selective two-view mammography will be continued in the future. Another limitation is that the screening mammography performance may have been influenced by feedback on screening results. As part of our quality assurance programme, screening radiologists review the screening mammograms of interval cancers and advanced screen detected cancers at regular intervals.[24] Our retrospective analysis cannot take into account possible effects of this review on parameters such as referral rate and detection rate. Finally, at review of SDCs in our study, the radiologists were informed about the presence of breast cancer at the latest screen with the possible introduction of referral bias at the last but one screen.

We conclude that replacement of selective two-view mammography by routine two-view mammography at subsequent screening may modestly increase the detection rate of smaller cancers, at the expense of a limited increase in screening costs and limited increased radiation exposure risks.

References

1. Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: a summary of the evidence for the US preventive services task force. Ann Intern Med 2002;137:347-60.
2. Tábar L, Fagerburg CJ, Gad A, Holmberg LH, Ljungquist U, Fagerberg CJG, Baldetorp L, Gröntoft O, Lundström B, Manson JC, Eklund G, Day NE, Pettersson F. Reduction in mortality from breast cancer after mass screening with mammography: randomised trial from the Breast Cancer screening Working group of the Swedish national Board of Health and Welfare. Lancet 1985;1:829-32.
3. Wald NJ, Murphy P, Major P, Parkes C, Townsend J, Frost C. WUKCCCR multicentre randomised controlled trial of one and two view mammography in breast cancer screening. BMJ 1995;311:1189-93.
4. Ballard-Barbash R, Klabunde C, Paci E, Broders M, Coleman EA, Fracheboud J, Bouchard F, Rennert G, Shapiro S. Breast cancer screening in 21 countries: delivery of services, notification of results and outcomes ascertainment. Eur J Cancer Prev 1999;8:417-26.
5. Law J, Faulkner K. Two view screening and extending the age range: the balance of benefit and risk. Br J Radiol 2002;75:889-94.
6. Blanks, RG, Moss SM, Wallis MG. Use of two view mammography compared with one view in the detection of small invasive cancers: further results from the National Health Service breast screening programme. J Med Screen 1997;4:98-101.
7. ICSN data: Policies on Number of View and Double-Reading for Breast Cancer Screening Programs in 27 Countries, 2007-2008. http://appliedresearch.cancer.gov/icsn/breast/policies.reading.html (accessed July 10, 2011).
8. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann Oncol 2008;19:614-22.
9. Holland R, Rijken H, Hendriks J. The Dutch population based mammography screening: 30-year experience. Breast Care 2007;2:12-18.
10. Boice JD Jr, Land CE, Shore RE, Norman JE, Tokunaga M. Risk of breast cancer following low-dose radiation exposure. Radiology 1979;131:589-97.
11. Bijwaard H, Brenner A, Dekkers F, van Dillen T, Boice JD Jr, Land CE. Breast cancer risk from different mammography screening practices. Radiat Res 2010;174:367-76.
12. Svahn T, Hemdal B, Ruschin M, Chakraborty DP, Andersson I, Tingberg A, Mattsson S. Dose reduction and its influence on diagnostic accuracy and radiation risk in digital mammography: an observer performance study using an anthropomorphic breast phantom. Br J Radiol 2007;80:557-62.
13. Hendrick RE, Pisano ED, Averbukh A, Moran C, Berns EA, Yaffe MJ, Herman B, Acharyya S, Gatsonis C. Comparison of acquisition parameters and breast dose in digital mammography and screen-film mammography in the American College of Radiology Imaging Network digital mammographic imaging screening trial. AJR 2010;194:362-69.
14. Nationaal Borstkanker Overleg Nederland. CBO richtlijn mammacarcinoom. Amsterdam: NABON; 2008. (in Dutch)
15. Fracheboud J, de Koning HJ, Boer R, Groenewoud JH, Verbeek AL, Broeders MJ, van Ineveld BM, Hendriks JH, de Bruyn AE, Holland R, van der Maas PJ; National Evaluation Team for Breast cancer screening in The Netherlands. Nationwide breast cancer screening programme fully implemented in the Netherlands. Breast 2001;10:6-11.
16. Duijm LEM, Groenewoud JH, de Koning HJ, Coebergh JW, van Beek M, Hooijen MJ, van de Poll-Franse LV. Delayed diagnosis of breast cancer in women recalled for suspicious screening mammography. Eur J Cancer 2009;45:774-1.
17. National Evaluation Team for Breast Cancer Screening (NETB). National evaluation of breast cancer in the Netherlands 1990-2007, twelfth evaluation report. Rotterdam: Erasmus MC Rotterdam, Radboud University Nijmegen Medical Centre; 2009.
18. Blanks RG, Bennett RL, Patnick J, Cush S, Davison C, Moss SM. The effect of changing from one to two views at incident (subsequent) screens in the NHS breast screening programme in England: impact on cancer detection and recall rates. Clinical Radiol 2005;60:674-80.

19. Broeders MJM, Onland-Moret NC, Rijken HJTM, Hendriks JHCL, Verbeek ALM, Holland R. Use of previous screening mammograms to identify features indicating cases that would have a possible gain in prognosis following earlier detection. Eur J Cancer 2003;39:1770-5.

20. Duffy SW, Nagtegaal ID, Astley SM, Gillan MG, McGee MA, Boggis CR, Wilson M, Beetles UM, Griffiths MA, Jain AK, Johnson J, Roberts R, Deans H, Duncan KA, Iyengar G, Griffiths PM, Warwick J, Cuzick J, Gilbert FJ. Visually assessed breast density, breast cancer risk and the importance of the craniocaudal view. Breast Cancer Res 2008; 10: R64.

21. Zoetelief J, Thijssen MAO, de Koning HJ. Eindrapport CVZ project "Stralingsbelasting bij het bevolkingsonderzoek naar borstkanker in Nederland". Diemen: CVZ; 2005. (in Dutch)

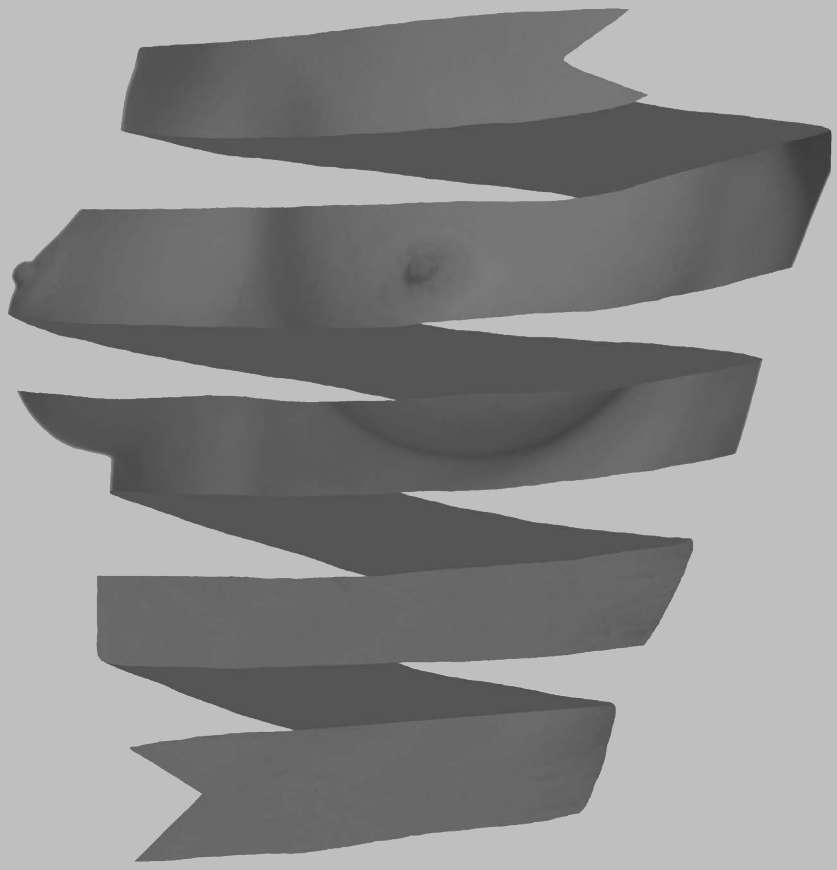
22. Broeders MJM, Schoor van G, Bluekens A, Visser R, Otten JDM, Paap E, Verbeek ALM, den Heeten GJ. Rapportage over eventuele leeftijdsverlaging van de onderste leeftijdsgrens van het bevolkingsonderzoek op borstkanker. Nijmegen: LRCB, UMC St Radboud; 2009.

23. Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population-based screening program: follow-up and final results of Oslo II study. Radiology 2007;244:708-17.

24. Duijm LEM, Louwman MWJ, Groenewoud JH, van de Poll-Franse LV, Fracheboud J, Coebergh JW. Inter-observer variability in mammography screening and effect of type and number of readers on screening outcome. Br J Cancer 2009 24;100:901-7.

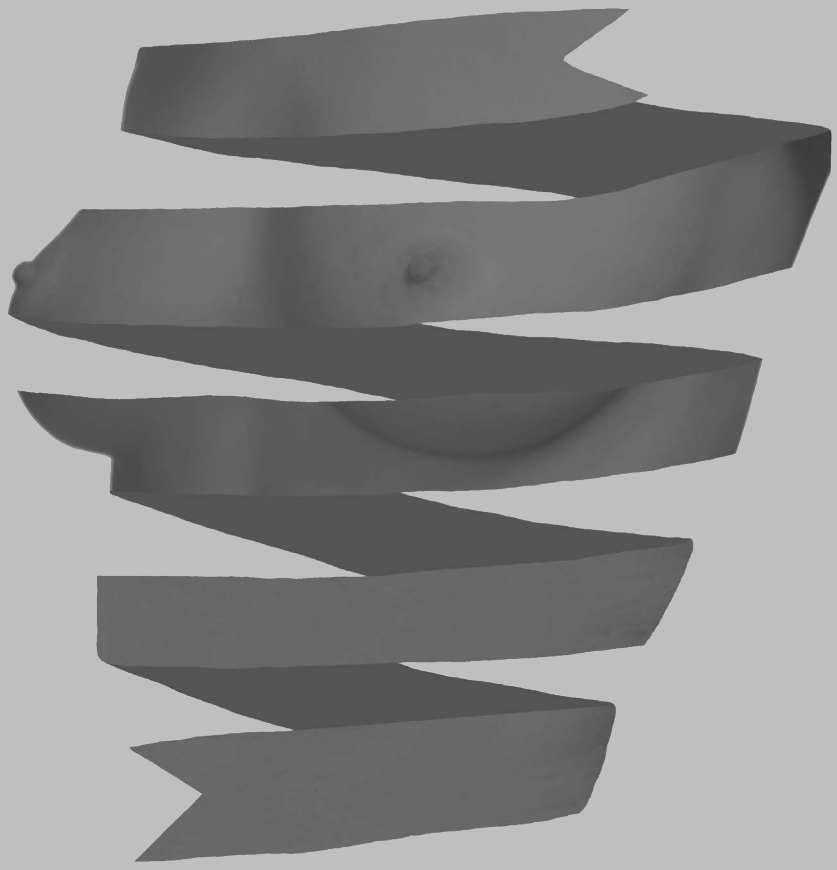
Chapter 4

Impact of benign breast surgery on screening mammography sensitivity



Chapter 4.1

Sensitivity of screening mammography after benign breast surgery



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Lower sensitivity of screening mammography after previous benign breast surgery
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Abstract

Few data are available on the effect of previous benign breast surgery on screening mammography accuracy. We determined whether sensitivity of screening mammography and tumour characteristics are different for women with and without previous benign breast surgery. We included a consecutive series of 317,398 screening mammograms of women screened between 1997 and 2008. During 2 year follow-up, clinical data, breast imaging-, biopsy- and surgery reports were collected of women with screen-detected or interval breast cancers. Screening sensitivity, tumour biology and tumour stages were compared between 168 women with breast cancer and prior ipsilateral benign breast surgery and 2,039 women with breast cancer, but without previous ipsilateral, benign breast surgery. The sensitivity of screening mammography was significantly lower for women with prior surgery (64.3% (108/168) versus 73.4% (1,496/2,039), p=0.01). The concomitant increased interval cancer risk remained significant after logistic regression adjustment for age and breast density (OR=1.5, 95%CI: 1.1-2.1). Comparing screen-detected cancers in women with and without prior breast surgery, no significant differences in estrogen-receptor status (p=0.56), mitotic activity (p=0.17), proportions of large (T2+) tumours (p=0.6) or lymph node positive tumours (p=0.4) were found. Also for interval cancers no differences were found in estrogen-receptor status (p=0.41), mitotic activity (p=0.39), proportions of large tumours (p=0.9) and lymph node positive tumours (p=0.5) between women with and without prior breast surgery. We conclude that sensitivity of screening mammography is significantly lower in women with previous benign breast surgery than without, but tumour characteristics are comparable both for screen detected cancers and interval cancers.

Introduction

Mammography screening aims to detect breast cancer at an early stage and several studies have shown that screening significantly reduces breast cancer mortality.[1-3] Many countries have introduced regional or nation-wide breast cancer screening programmes in the last two decades. The Netherlands has a long history of screening mammography and their nation-wide breast cancer screening programme offers biennial screening mammography for women aged 50-75 years.

Breast conserving treatment for breast cancer may cause rigorous mammographic changes, due to surgery and radiation therapy.[4-6] These changes frequently hamper the mammographic interpretation and may result in a lower sensitivity of mammography for breast cancer detection. On the other hand, post-treatment changes may simulate breast cancer at mammography and lead to an increase of false positive assessments, and thus a lower specificity. The Dutch guidelines on breast cancer screening advise that mammographic follow-up women after breast conserving therapy should take place in an outpatient hospital setting for a period of 5 to 10 years before returning to routine screening.[7]

Mammographic alterations occurring after breast surgery for benign disease and reduction surgery have also been described.[8-10] Studies report that 45%-50% of women with a history of excisional breast biopsy for benign disease develop mammographic findings that can be attributed to surgery.[8-11] This high incidence of mammographic changes after previous benign breast surgery may have a substantial influence on the interpretation of mammography in screening programmes. Slanetz et al. observed a significantly higher recall rate for women with a history of previous excisional biopsy for benign disease as compared to women without a history of biopsy.[12] United States (US) guidelines and European guidelines do not provide specific recommendations for screening of women with prior benign breast surgery. To our knowledge, only two studies have addressed the effect of previous benign breast surgery on screening mammography performance and no information is available whether tumour characteristics are different in women with previous breast surgery. Banks et al.[13] observed a borderline significant lower sensitivity after breast surgery for a condition other than breast cancer, whereas Taplin et al. only found a significantly lower specificity after previous benign breast surgery, but no difference in sensitivity[14].

The aim of the current study was to determine whether biennial screening mammography accuracy and tumour characteristics were different for women with and without previous benign breast surgery.

Materials and methods

Study population

We included all women who were screened at one of two specialized analogue screening units in the southern breast cancer screening region of the Netherlands between January 1, 1997 and January 1, 2008. Written informed consent regarding patient identification and exchange of data on screening and clinical follow-up was obtained from all women participating in the breast cancer screening programme. Institutional review board approval was not required for this study.

Screening and referral procedure

Details of the nation-wide breast cancer screening programme, offering biennial screening mammography for women aged 50-75 years, are described elsewhere.[15,16] In brief, two-view mammography (mediolateral-oblique and craniocaudal view) of each breast was performed in initial screens. In subsequent screens, generally single-view mammography (mediolateral-oblique view) was carried out. Additional cranio-caudal views of each breast were obtained in about 40% of subsequent screens and indications for this two-view mammography included any changes in mammographic findings, complicated judgment due to dense breast tissue, and a more than two year interval since the previous screen. Two-view mammography was also indicated after a previous lumpectomy for breast cancer, previous benign excisional biopsy or breast reduction surgery, unless the mediolateral-oblique view showed a predominantly fatty breast. In these cases, a second view was obtained at the discretion of the radiologic technician. All mammographic examinations were performed by specialized screening mammography technicians and independently double read by a group consisting of 12 certified screening radiologists. Since 2003, technologists have been actively participating in the assessment of screening mammograms and the examinations have always been read by two screening radiologists in addition.[17,18] Prior screening mammograms were always available for comparison at the time of subsequent screening and each of the screening radiologists evaluated at least 5,000 screening mammograms yearly. Women with normal or benign mammographic findings or with nonspecific minimal signs were not referred for further diagnostic workup. In case of a suspicious or malignant lesion, the woman was referred to a surgical oncologist or breast clinic for further analysis of the mammographic abnormality.

Follow-up procedure

The follow-up period for all screened women included the time through the next screening round (the screening interval was approximately 2 years). We collected data on diagnostic procedures, breast cancer diagnosis, histopathology and TNM (tumour-node-metastasis) classification of all referred women.[19] Procedures for the detection of interval cancers have been described previously.[20] An interval cancer is a breast cancer that is diagnosed after a negative screening mammography (that is, screening without a recommendation for referral), and before any subsequent screening examination.

Mammographic abnormalities attributed to prior benign breast surgery

Two screening radiologists (LD, FJ) reviewed the screening mammograms of all women with a screen-detected or interval breast cancer. For screen-detected cancers, each reader classified the breast density of the screening mammogram, for which the woman had been referred, according to the American College of Radiology BI-RADS.[21] In case of previous benign breast surgery, the two screening radiologists also determined whether the mammograms showed post surgical changes (focal architectural distortion, increased focal density, focal skin thickening or retraction, fat necrosis and focal calcifications). Previous benign breast surgery comprised benign excisional breast biopsy of palpable and nonpalpable breast lesions, breast reduction surgery and breast surgery for other benign conditions such as mastitis. For interval cancers, breast density and presence of post surgical changes were determined for the most recent screening examination, prior to the diagnosis of interval cancer. The two radiologists

were initially blinded to information from each other and discrepant assessments (4.9% (109/2,207) for breast density and 8.9% (15/168) for presence of post surgical changes) were followed by consensus reading.

Proportion of women with a history of benign breast disease

Before each screening examination, the woman completes a short questionnaire with questions about any previous breast surgery or breast malignancy, their family history of breast cancer and the use of hormone replacement therapy. Since May 2009, when digital screening mammography was introduced in the Netherlands, radiologic technicians enter these breast history data in the nation-wide digital screening database. For the current study, however, breast history data were not available electronically and had to be collected from the screening records for all women screened between January 1, 1997 and January 1, 2008 with an interval breast cancer or a positive screening result. To estimate the current proportion of screened women with prior benign breast surgery, we consulted the computer database of women who underwent digital screening mammography at our screening units between January 1, 2010 and April 1, 2010.

Statistical analysis

The primary outcome measures were sensitivity of screening mammography for breast cancer detection and tumour stages of screen-detected and interval breast cancers. These outcome measures were compared between women with a diagnosis of breast cancer in the ipsilateral breast after prior benign surgery and a control group of women with breast cancer but without a history of ipsilateral, benign breast surgery. Women with breast augmentation and women diagnosed with breast cancer who had undergone ipsilateral lumpectomy and radiation therapy were excluded from analysis. All data were entered into a computerized 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 double sided t-test was used to test differences between continuous variables, and the χ^2 test to test differences between categorical variables. Regression analysis was performed to calculate odds ratios (OR) and their confidence intervals (CI) for the effect of previous breast surgery on the detection of breast malignancy at screening, adjusting for age and breast density. The significance level was in all analyses set at 5%.

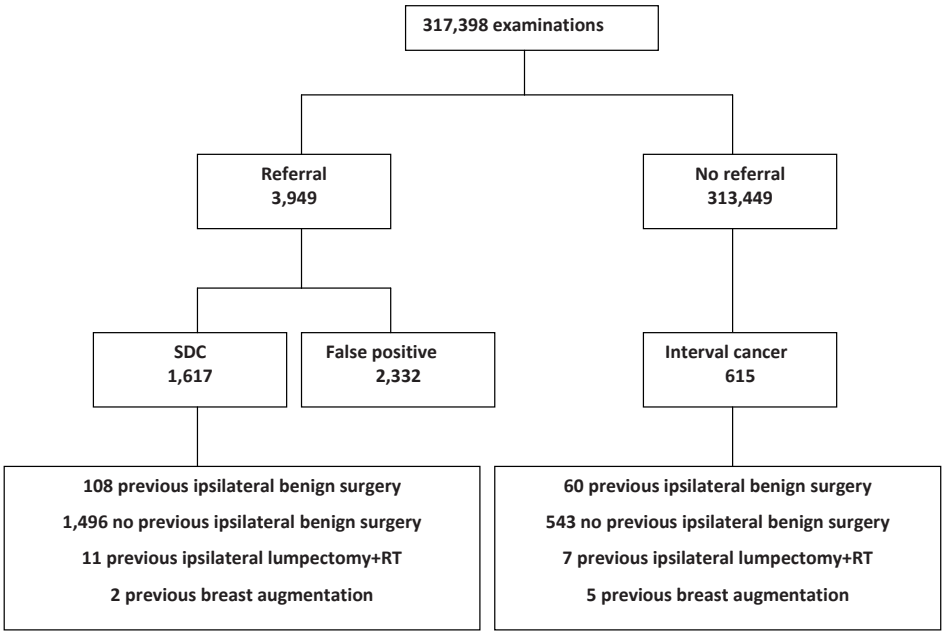
Results

A total of 317,398 screens in 81,679 women were obtained between January 1, 1997 and January 1, 2008; 42,560 were initial screens (13.4%) and 274,838 were subsequent screens (86.6%). For initial and subsequent screens combined, one-view mammography was performed in 159,932 examinations (50.4%) and two-view mammography in 159,466 (49.6%). Altogether, 3,949 (1.2%) women were referred for further diagnostic examination, of whom 1,617 had histologically proven breast cancer, yielding an overall cancer detection rate of 5.1 per 1,000 women screened and a true-positive referral rate of 40.9%.

One hundred eight of 1,617 breast cancers were detected in women with prior ipsilateral benign breast surgery and 1,496 breast cancers in women without prior ipsilateral benign breast surgery (Figure). Thirteen women had undergone ipsilateral treatment for breast

cancer (11 cases) or breast augmentation (2 cases) and were excluded. The most frequent reasons for benign surgery had been excision of a palpable lesion (e.g., fibroadenoma, cyst or mastopathy; 72 cases, 66.7%), mastitis (13 cases, 12.0%) and breast reduction (12 cases, 11.1%).

A total of 615 interval cancers were diagnosed, of which 60 in women with prior ipsilateral benign breast surgery and 543 without (Figure). Twelve other women with interval cancers were excluded from further analysis because of previous ipsilateral treatment for breast cancer (7 cases) or breast augmentation (5 cases). Again, excision of a palpable lesion (46 cases, 76.7%) and breast reduction (8 cases, 13.3%) had been the predominant reasons for prior benign breast surgery.



SDC = screen-detected cancer; RT = radiation therapy

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

Benign breast surgical procedures had been performed more than 3 years prior to the most recent screening examination in all 168 women with a diagnosis of breast cancer and previous benign surgery.

The characteristics of women with a diagnosis of breast cancer, according to their breast surgery status, are presented in Table 1. There were no significant differences regarding family history of breast cancer, use of hormone replacement therapy, percentage of initial screens, interval between latest screen and cancer diagnosis, number of views or breast density at the latest screening mammogram or tumour histology in women with a history of previous benign surgery compared with women without. However, the mean age of postoperative women was somewhat higher (63.5 years versus 61.8 years, p=0.004). Screening sensitivity

was significantly lower for women with prior surgery than without (64.3% (108/168) versus 73.4% (1496/2,039), p=0.01). The increased chance of a cancer being detected as an interval cancer in breasts that underwent prior benign breast surgery remained present after logistic regression adjustment for age and density (OR=1.5, 95%CI: 1.1-2.1).

Table 1. *Characteristics of women with a diagnosis of breast cancer according to ipsilateral breast surgery status.*

	Previous benign breast surgery N = 168	**No previous benign breast surgery N = 2,039**	***P*-value**
Mean age, years (95%CI)	63.5 (62.4-64.5)	61.8 (61.4-62.1)	0.004
Family history of breast cancer[±], No (%)	37 (22.0)	401 (19.7)	0.46
Use of hormone replacement therapy, No (%)	23 (13.7)	217 (10.6)	0.22
Initial screens, No (%)	22 (13.1)	343 (16.8)	0.21
Interval between latest screen and cancer diagnosis			0.07
<12 months	127 (75.6)	1660 (81.4)	
>12 months	41 (24.4)	379 (18.6)	
No (%) of views at latest screen[#]			0.74
1-view	16 (9.5)	211 (10.3)	
2-view	152 (90.5)	1828 (89.7)	
Breast density at screening mammogram[#], No (%)			0.60
0-25%	48 (28.6)	672 (33.0)	
25-50%	54 (32.1)	657 (32.2)	
50-75%	44 (26.2)	485 (23.8)	
75-100%	22 (13.1)	225 (11.0)	

[±]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
[#]Screening mammogram for which a woman had been referred or latest screening mammogram prior to a diagnosis of interval cancer

The distribution of cancer histology, estrogen-receptor status and mitotic activity did not differ statistically between women with or without previous surgery (Table 2). Also the proportions of DCIS (21.3% versus 16.0%, p=0.15), advanced (T2+) tumours (17.6% versus 22.1%, p=0.6) or lymph node positive tumours (21.2% versus 27.0%, p=0.4) of screen-detected breast cancers did not differ statistically between women with previous benign surgery and women without (Table 2); neither did the proportions of advanced tumours (51.7% versus 47.6%, p=0.9) or lymph node positive tumours (43.1% versus 46.1%, p=0.5) of the interval cancers.

The presence of mammographic changes as a result of benign breast surgery was similar for screen detected cancers and interval cancers (50.% (54/108) versus 53.3% (32/60), p=0.68). Of the 8,898 women who underwent digital screening mammography between January 1,

Table 2. *Characteristics of screen detected cancers and interval cancers according to ipsilateral breast surgery status.*

	Screen detected cancers		*P*-value	Interval cancers		*P*-value
	Previous benign breast surgery N = 108	No previous benign breast surgery N = 1,496		Previous benign breast surgery N = 60	No previous benign breast surgery N = 543	
Cancer histology, No (%)			0.41			0.25
DCIS	23 (21.3)	240 (16.0)		2 (3.3)	20 (3.7)	
Invasive ductal	63 (58.3)	954 (63.8)		41 (68.3)	380 (70.0)	
Invasive lobular	13 (12.0)	149 (10.0)		8 (13.3)	96 (17.7)	
Invasive ductal+lobular	2 (1.9)	68 (4.5)		2 (3.3)	23 (4.2)	
Other	7 (6.5)	78 (5.2)		6 (10.0)	19 (3.5)	
Unknown	0 (0.0)	7 (0.5)		1 (1.7)	5 (0.9)	
Estrogen-receptor status, No(%)[±]			0.56			0.41
Positive	61 (85.9)	1,001 (88.2)		46 (80.7)	386 (75.2)	
Negative	10 (14.1)	134 (11.8)		11 (19.3)	127 (24.8)	
Mitotic activity (No. (%) of mitoses per 2mm2)[±]						
<10	50 (75.8)	903 (84.5)	0.17	38 (76.0)	320 (67.6)	0.39
10-19	11 (16.7)	117 (10.9)		5 (10.0)	81 (17.1)	
20+	5 (7.6)	49 (4.6)		7 (14.0)	72 (15.2)	
Size of invasive cancers, No (%)			0.59			0.90
T1a-b	24 (28.2)	359 (28.6)		6 (10.3)	53 (10.1)	
T1c	46 (54.1)	609 (48.5)		21 (36.2)	206 (39.4)	
T2+	15 (17.6)	278 (22.1)		30 (51.7)	249 (47.6)	
Unknown	0 (0.0)	10 (0.8)		1 (1.7)	15 (2.9)	
Lymph-node status of invasive cancers, No(%)			0.35			0.48
Positive	18 (21.2)	339 (27.0)		25 (43.1)	241 (46.1)	
Negative	64 (75.3)	892 (71.0)		30 (51.7)	269 (51.4)	
Unknown	3 (3.5)	25 (2.0)		3 (5.2)	13 (2.5)	

[±] *Invasive cancers only (data not available for all invasive cancers)*

2010 and April 1, 2010, 593 (6.7%) reported previous benign breast surgery and another 65 women (0.7%) had undergone breast augmentation.

Discussion

Our results show that previous benign breast surgery had a negative impact on the sensitivity of screening mammography, with a concomitant increased risk of a cancer being detected as interval cancer.

In a United Kingdom (UK) screening programme, Banks et al. observed a borderline significant lower sensitivity after breast surgery for a condition other than breast cancer,[13] whereas a US study recently concluded that benign breast surgery significantly reduced mammographic specificity but not sensitivity.[14] Due to differences between the screening programmes and study designs, comparison of our biennial screening results with these two studies is limited. For example, the UK programme used a three year screening interval and the study does not provide information about the distribution of fibroglandular tissue density among women with and without previous surgery.[13] Moreover, the sensitivities in the UK study would have been considerably lower than those reported if a follow-up period of 3 years, rather than 1 year, had been used to allow for the detection of interval cancers after 1 year. The much higher incidence of ipsilateral breast cancer we observed following benign breast surgery, when compared to the US study (0.53 per 1,000 screens (168/317,398) versus 0.02 per 1,000 screens (40/1,747,238)), suggests the presence of significant differences in study population characteristics and workup strategies. All screening mammograms in our study were independently double read by two screening radiologists, whereas the US study did not provide detailed information about the reading protocol. Finally, the Dutch nation-wide breast screening programme is characterized by a much lower referral rate (currently 1.5-2%) if compared to the referral rates in UK and US screening programmes[22] and the effect of this low referral rate on the sensitivity in women with prior benign surgery is unknown.

Although tumour stages and tumour biology of screen-detected cancers and interval cancers were comparable for women with or without previous benign breast surgery, the lower sensitivity of screening for cancer in post surgical breasts may have implications for screening protocols. Similar to women with breast augmentation, women with a history of benign breast surgery may be informed at the time of invitation about the decreased sensitivity of screening mammography. This lower sensitivity may be due to a hampered mammographic interpretation of post surgical breasts or masking, because other important factors that influence the sensitivity of screening mammography, including breast density and the availability of previous screens for comparison,[23,24] were not significantly different between women with breast cancer who had or had not previous benign breast surgery. On the other hand, the lower sensitivity after excisional biopsy may be due to tissue characteristics (e.g. fibrocystic changes) rather than the biopsy itself as the presence of mammographic changes following benign breast surgery was similar for screen detected cancers and interval cancers in our study. Taplin et al. found that mammographic sensitivity was higher among women with excisional biopsy compared with women who had undergone less invasive fine needle aspiration biopsy.[14] Given the higher interval cancer rate, one may ultimately consider to offer women with previous benign breast surgery a biennial outpatient mammographic

examination as an alternative to routine screening mammography as part of a regional or nation-wide screening programme. In an outpatient setting, additional mammographic views and/or complementary breast ultrasound can easily be obtained if the radiologist encounters difficulties with mammographic interpretation. However, future research is needed to determine whether the latter strategy will be a valuable alternative to standard screening mammography in order to detect breast cancer at an earlier stage.

In our study, mammographic changes were observed on the most recent screening mammograms of about 50% of women who developed ipsilateral breast cancer after prior benign breast surgery. This finding is in line with the results of two retrospective studies that describe abnormalities attributed to prior excisional biopsies for benign breast disease in respectively 45% and 50% of patients.[8,11] Resolution of biopsy related mammographic abnormalities may be encountered with time and the mammographic changes following excisional biopsy will usually remain stable several years after surgery.[8,11] Previous benign breast surgery is not only correlated with a decreased sensitivity of screening mammography, but may also result in higher recall rates dependent on the type of surgical procedure. Slanetz et al. found a significantly higher recall rate for women with a prior biopsy for benign disease,[12] whereas Muir et al. did not observe an increase in recall rate for women post reduction mammoplasty.[25] Unfortunately, both studies did not provide information about the influence of breast surgery on the sensitivity of screening mammography. Miglioretti et al. found that breast augmentation decreased the sensitivity of screening mammography among asymptomatic women but did not increase the false-positive rate and that the tumour characteristics were not influenced by augmentation.[26] Therefore, the authors concluded that women with breast augmentation should still be invited for routine screening mammography at recommended intervals. In the Dutch situation, lower screening sensitivity following benign breast surgery is even more important than lower screening sensitivity following breast augmentation; almost 7 % of women that are currently screened report a history of benign breast surgery compared to less than 1% of women with breast augmentation. The nation-wide breast cancer screening programme in the Netherlands will be completely digitized in 2010 and computer assisted detection (CAD) may be introduced. Full-field digital mammography has been shown to have similar or higher sensitivity and higher specificity than conventional mammographic screening,[27,28] but the specific effect of digital screening mammography on cancer detection in post surgical breasts is yet unknown. In the Netherlands, all screening mammograms are double read by two screening radiologists. In the future, CAD may be used to assist radiologists at double reading or may replace one of the screening radiologists, although there are conflicting reports whether CAD-assisted single reading yields better detection performances than radiologist double reading.[29,30]

Our study has several limitations. First, we could neither determine the effect of previous benign breast surgery on the recall rate, nor determine the cancer rate among women with and without prior benign breast surgery in our series of analogue screens as we were not informed about the total number of women with previous breast surgery. Women with a history of benign breast surgery may be at higher risk for breast cancer; Taplin et al.[14] observed a higher breast cancer incidence at screening in women with prior excisional or surgical biopsies than in women without a biopsy history (5.2 versus 4.2 per 1,000 screens). Even

with lower sensitivity, women with previous benign breast surgery may therefore still have a considerable benefit from screening. Second, we relied on self-reported prior benign breast surgery and were not able to validate the accuracy of this information. Third, we are not certain whether the skills of the screening radiologists in our study reflect those of screening radiologists in other screening regions or screening programmes. However, our screening outcome parameters such as referral rate, cancer detection rate and positive predictive value of referral were consistent with the Dutch national screening results.[31] Fourth, some data about tumour characteristics, especially estrogen receptor status and mitotic activity, were incomplete because these characteristics have been routinely determined by pathology laboratories since the late 1990s only. Fifth, we could not adjust for all factors at an individual level that might affect the association between previous benign breast surgery and screening sensitivity, such as time since last mammogram, use of hormone replacement therapy, age at onset of menarche and age at birth of first child. Finally, we were unable to adjust for the radiologist who did the reading as the mammograms had been assessed independently by two readers and the high number of different radiologist couples resulted in too few cancers per couple to adjust at individual screeners level.[32]

In summary, we conclude that the sensitivity of screening mammography is significantly lower in women with previous benign breast surgery. For many years, studies have been reporting conflicting results about the benefits and harms of screening mammography and adding information about lower sensitivity after benign breast surgery may make women feel more insecure when participating in a mammography screening programme. Nevertheless, we suggest that women with previous benign breast surgery will be informed if further studies confirm that screening sensitivity is lower after benign breast surgery, especially if this lower sensitivity is due to postoperative mammographic changes rather than breast tissue characteristics. Women may then decide to choose between a clinical mammogram and screening examination.

References

1. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, Mandelblatt JS, Yakovlev AY, Habbema JD, Feuer EJ; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators. Effect of screening and adjuvant therapy on mortality from breast cancer. New Engl J Med 2005;353:1784-92.
2. Otto SJ, Fracheboud J, Looman CWN, Broeders MJM, Boer R, Hendriks JHCL, Verbeek ALM, de Koning HJ; the National Evaluation Team for Breast Cancer Screening. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003;361:1411-7.
3. Tabar L, Yen MF, Vitak B, Chen HH, Smith RA, Duffy SW. Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. Lancet 2003;361:1405-10.
4. Holli K, Saaristo R, Isola J, Hyoty M, Hakama M. Effect of radiotherapy on the interpretation of routine follow-up mammography after conservative breast surgery: a randomized study. Br J Cancer 1998;78:542-5.
5. Dershaw DD. Mammography in patients with breast cancer treated by breast conservation lumpectomy (with or without radiation). AJR 1995;164:309-16.
6. Mendelson EB. Evaluation of the postoperative breast. Radiol Clin North Am 1992; 30:107-38.
7. Nationaal Borstkanker Overleg Nederland. CBO richtlijn mammacarcinoom. Amsterdam: NABON; 2008. (in Dutch)
8. Sickles EA, Herzog KA. Mammography of the post surgical breast. AJR 1981;136:585-8.
9. Brown FE, Sargent SK, Cohen SR, Morain WD. Mammographic changes following reduction mammaplasty. Plast Reconstr Surg 1987;80:691-8.
10. Danikas D, Theodorou SJ, Kokkalis G, Vasiou K, Kyriakopoulou K. Mammographic findings following reduction mammoplasty. Aesthetic Plast Surg 2001;25:283-5.
11. Brenner RJ, Pfaff JM. Mammographic changes after excisional breast biopsy for benign disease. AJR 1996;167:1047-52.
12. Slanetz PJ, Giardino AA, McCarthy KA, Hall DA, Halpern EF, Moore RH, Kopans DB. Previous breast biopsy for benign disease rarely complicates or alters interpretation on screening mammography. AJR 1998;70:1539-41.
13. Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, Hilton E, Bailey S, Barrett N, Briers P, English R, Jackson A, Kutt E, Lavelle J, Rockall L, Wallis MG, Wilson M, Patnick J. Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study. BMJ 2004;329:477.
14. Taplin SH, Abraham L, Geller BM, Yankaskas BC, Buist DSM, Smith-Bindman R, Lehman C, Weaver D, Carney PA, Barlow WE. Effect of previous benign breast biopsy on the interpretive performance of subsequent screening mammography. J Natl Cancer Inst 2010;102:1040-51.
15. Fracheboud J, de Koning HJ, Boer R, Groenewoud JH, Verbeek ALM, Broeders MJM, van Ineveld M, Hendriks JHCL, de Bruyn AE, Holland R, van der Maas PJ; National Evaluation Team for breast Cancer screening in the Netherlands (NETB). Nationwide breast cancer screening programme fully implemented in the Netherlands. Breast 2001;10:6-11.
16. Duijm LEM, Groenewoud JH, Hendriks JHCL, de Koning HJ. Independent double reading of screening mammograms in the Netherlands: effect of arbitration following reader disagreements. Radiology 2004:231:564-70.
17. Duijm LEM, Groenewoud JH, Fracheboud J, de Koning HJ. Additional double reading of screening mammograms by radiologic technologists: Impact on screening performance parameters. J Natl Cancer Inst 2007;99:1162-70.
18. Duijm LEM, Groenewoud JH, Fracheboud J, van Ineveld BM, Roumen RMH, de Koning HJ. Introduction of additional double reading of mammograms by radiographers: effects on a biennial screening programme outcome. Eur J Cancer 2008;44:1123-8.

19. UICC (International Union against Cancer): TNM Classification of Malignant Tumours, 4th rev ed. Berlin: Springer Verlag, 1987.

20. Duijm LEM, Groenewoud JH, Jansen FH, Fracheboud J, van Beek M, de Koning HJ. Mammography screening in the Netherlands: delay in the diagnosis of breast cancer after breast cancer screening. Br J Cancer 2004;91:1795-99.

21. American College of Radiology: Breast Imaging Reporting and Data System (BI-RADS), 4th ed. Reston: American College of Radiology; 2003.

22. Smith-Bindman R, Chu PW, Miglioretti DL, Sickles EA, Blanks R, Ballard-Barbash R, Bobo JK, Lee NC, Wallis MG, Patnick J, Kerlikowske K. Comparison of screening mammography in the United States and the United Kingdom. JAMA 2003;290:2129-37.

23. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, Jong RA, Hislop G, Chiarelli A, Minkin S, Yaffe MJ. Mammographic density and the risk and detection of breast cancer. New Engl J Med 2007;356:227-36.

24. Roelofs AA, Karssemeijer N, Wedekind N, Beck C, van Woudenberg S, Snoeren PR, Hendriks JH, Rosselli del Turco M, Bjurstam N, Junkermann H, Beijerinck D, Séradour B, Evertsz EJ. Importance of comparison of current and prior mammograms in breast cancer screening. Radiology 2007;242:70-7.

25. Muir TM, Tresham J, Fritschi L, Wylie E. Screening for breast cancer post reduction mammoplasty. Clin Radiol 2010;65:198-205.

26. Miglioretti DL, Rutter CM, Geller BM, Cutter G, Barlow WE, Rosenberg R, Weaver DL, Taplin SH, Ballard-Barbash R, Carney PA, Yankaskas BC, Kerlikowske K. Effect of breast augmentation on the accuracy of mammography and cancer characteristics. JAMA 2004;291:442-50.

27. Pisano EA, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, Conant EF, Fajardo LL, Bassett L, D'Orsi C, Jong R, Rebner M. For the Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group. Diagnostic performance of digital versus film mammography for breast-cancer screening. New Engl J Med 2005;353:1773–83.

28. Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus fullfield digital mammography with soft-copy reading in population based screening program: follow-up and final results of Oslo II study. Radiology 2007;244:708–17.

29. Karssemeijer N, Otten JD, Verbeek AL, Groenewoud JH, de Koning HJ, Hendriks JH, Holland R. Computer-aided detection versus independent double reading of masses on mammograms. Radiology 2003;227:192–200.

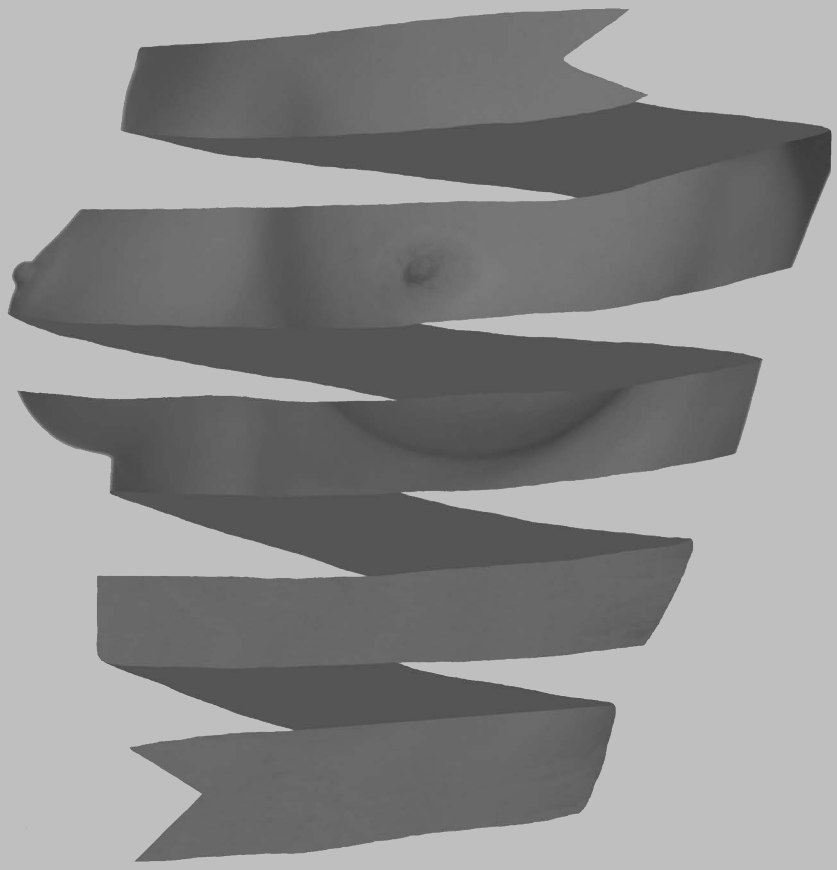
30. Fenton JJ, Taplin SH, Carney PA, Abraham L, Sickles EA, D'Orsi C, Berns EA, Cutter G, Hendrick E, Barlow WE, Elmore JG. Influence of computer-aided detection performance of screening mammography. N Engl J Med 2007;356:1399–09.

31. National Evaluation Team for Breast Cancer Screening (NETB). National evaluation of breast cancer in the Netherlands 1990-2007, twelfth evaluation report. Rotterdam: Erasmus MC Rotterdam, Radboud University Nijmegen Medical Centre; 2009.

32. Duijm LEM, Louwman MWJ, Groenewoud JH, van de Poll-Franse LV, Fracheboud J, Coebergh JW. Inter-observer variability in mammography screening and effect of type and number of readers on screening outcome. Br J Cancer 2009;100:901-7.

Chapter 4.2

Cause of lower sensitivity of screening mammography after benign breast surgery



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Mammographic changes resulting from benign breast surgery impair breast cancer detection at screening mammography
van Breest Smallenburg V, Duijm LEM, Voogd AC, Jansen FH, Louwman WJ

Abstract

Purpose

To study possible explanations for lower screening performance after previous benign breast surgery.

Patients and Methods

We included a consecutive series of 351,009 screening examinations in 85,274 women, obtained between January 1, 1997 and January 1, 2009. The examinations of women with screen detected cancers (SDCs) or interval cancers (ICs), diagnosed after previous benign breast surgery, were reviewed by two screening radiologists. They determined the presence and degree of post surgical changes, classified breast density and determined whether mammographic interpretation was hampered by tissue characteristics. They also assessed whether the cancer had already been visible at a previous screen.

Results

Screening sensitivity was lower in women with prior benign breast surgery than without (63.5% (115/181) versus 73.5% (1,643/2,236), p=0.004). A total of 115 SDCs and 66 ICs were diagnosed in breasts after previous benign breast surgery. Post surgical mammographic alterations in the breast segment where cancer was diagnosed were more distinct in ICs than in SDCs (p=0.001). Women with post surgical mammographic changes at the location of the breast cancer had an increased interval cancer risk (OR=2.12, 95%CI = 1.05-4.26). Limited mammographic interpretation due to tissue characteristics was mentioned, only in three SDCs and one IC. The proportions of SDCs and ICS that were already visible at a previous screen were comparable for women with and without prior surgery (SDC: 47.5% vs 43.8%, p=0.3, IC: 50.0% vs 48.4%, p=0.8).

Conclusion

Previous benign breast surgery decreases screening sensitivity and this is likely due to postoperative mammographic changes.

Introduction

Many countries have implemented screening mammography programs in order to detect breast cancer at an early stage and improve breast cancer survival.[1] Mammographic interpretation after conservative breast surgery and radiotherapy is frequently hampered by the presence of scar formation, contour deformity of the breast, thickened Cooper's ligaments, skin thickening and calcifications. Previous studies have shown that these changes compromise the sensitivity of mammography for breast cancer detection and lead to more additional diagnostic tests that will turn out to be negative at confirmation.[2,3]

Although European and United States (US) screening guidelines provide recommendations for screening after breast conserving surgery for malignant disease, recommendations for screening following benign breast surgery are lacking. Benign breast surgery, including excisional biopsy and breast reduction surgery, also leads to permanent postoperative mammographic changes in up to 50% of women.[4,5] A history of excisional biopsy for benign disease is associated with a higher recall rate and we recently reported a lower sensitivity of screening mammography after previous benign breast surgery.[6,7] However, it is not clear whether this impaired sensitivity is due to post surgical mammographic alterations or due to specific breast tissue characteristics such as breast density or fibrocystic changes.[7,8] The purpose of this study was to study possible explanations for lower screening performance after previous benign breast surgery.

Patients and Methods

Study population

We included 351,009 consecutive screening examinations of 85,274 women who underwent biennial screening mammography between January 1, 1997 and January 1, 2009. Screening was performed at one of two specialized analogue screening units in the southern breast cancer screening region of the Netherlands. Women with a history of ipsilateral breast conserving therapy or breast augmentation were excluded. Written informed consent regarding patient identification and exchange of data on screening and clinical follow-up was obtained from all women participating in the breast cancer screening programme. Institutional review board approval was waived by the Dutch Central Committee on Research Involving Human Subjects (CCMO).

Screening and referral procedure

Details about the screening procedure and referral procedure have been described previously.[7,9] In brief, before screening mammography was performed, women were asked to complete a short questionnaire about family history of breast cancer (defined as at least one first-degree relative with a diagnosis of breast cancer before the age of 50 years, or at least two second-degree relatives with breast cancer), the use of hormone replacement therapy, as well as issues related to previous breast malignancy or previous benign breast surgery. For all women with a screen detected cancer or interval cancer (an interval cancer is a breast cancer that is diagnosed after a negative screening mammography, that is screening without a recommendation for referral, and before any subsequent screening examination), we recorded the information of the basic questionnaire in our database. All mammographic examinations were performed by specialized screening mammography technicians and

independently double read by a group consisting of 12 certified screening radiologists. Prior screening mammograms were always available for comparison at the time of subsequent screenings and the screening radiologists had the completed questionnaire at their disposal at the time of reading. Discrepant readings between the two screening radiologist were either solved by consensus between the two radiologists or by radiologist panel arbitration. If consensus was not reached in a discrepant reading, or in case of a suspicious or malignant lesion, the woman was referred to a surgical oncologist or breast clinic for further analysis of the mammographic abnormality.

Follow-up procedure

The follow-up period for all screened women included the time through the next screening round (the screening interval was approximately 2 years). We collected data on diagnostic procedures, breast cancer diagnosis, histopathology and TNM (tumour-node-metastasis) classification of all referred women.[10] Breast malignancies other than primary breast cancers were excluded from the analysis and we considered lobular carcinoma in situ to be a benign lesion. Procedures for the detection of interval cancers have been described previously.[11,12] Most interval cancers were identified by linking the screening records to the regional cancer registry (Eindhoven Cancer Registry), regional radiotherapy institutes and regional pathology laboratories.

Review of screening mammograms

As part of our quality assurance programme, two screening radiologists (LD, FJ) routinely determine whether a cancer detected at a subsequent screen was already visible at the previous screening mammogram. For each interval cancer, they determine whether the cancer was already visible at the latest screening mammogram. At review, the radiologists have no information whether the cancer has been detected at screening or has emerged as an interval cancer. For the current study, they also divided each breast of women with a history of benign breast surgery in the following six segments: 1) cranio-medial quadrant, 2) cranio-lateral quadrant, 3) medio-caudal quadrant, 4) latero-caudal quadrant, 5) retromamillary region, and 6) axillary region. For each segment, the radiologist classified the degree of postoperative mammographic changes into one of the following four categories: 1) no changes, 2) minor changes, 3) moderate changes, or 4) substantial changes. For women who underwent screening mammography before (subsequent screens, n=156), each reviewer determined whether the last but one screening mammogram showed post surgical changes (i.e., focal architectural distortion, increased focal density, focal skin thickening or retraction, fat necrosis or focal calcifications). For those 25 women who had attended screening for the first time, presence of post surgical changes was determined on the initial screening examination. For each examination, the radiologist also determined whether mammographic interpretation was hampered by specific fibroglandular tissue characteristics such as diffuse macrocystic disease or a profound presence of segmental or diffuse areas of benign calcifications. Then, the latest screening mammogram was shown to the reviewer to correlate the breast segment containing the malignancy with the degree of post surgical changes scored by the reviewer. Finally, the reviewer classified the breast density of the latest screening mammogram according to the American College of Radiology BI-RADS.[13] The two radiologists were initially blinded to information from each other and discrepant assessments

for the presence and degree of post surgical changes and discrepancies in classification of breast density were followed by consensus reading.

Statistical analysis

Sensitivity of screening mammography for breast cancer detection and patient characteristics of screen-detected and interval breast cancers were compared between women with a breast cancer in the ipsilateral breast after prior benign surgery and women with breast cancer but without a history of ipsilateral, benign breast surgery. Furthermore, in women with prior benign surgery (n=181) the presence and degree of post surgical mammographic changes in the breast segment containing the cancer were compared between women with screen detected cancers and interval cancers. All data were entered into a computerized 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). A double sided t-test was used to test differences between continuous variables, and the χ^2 test to test differences between categorical variables. For those variables where cross-tabulations resulted in too few observations per cell, we performed Fisher's exact test. Regression analysis was performed to calculate odds ratios (OR) and their confidence intervals (CI) for the effect of previous breast surgery on the detection of breast malignancy at screening, adjusting for age and breast density. The significance level was in all analyses set at 5% and all tests were two-sided. To determine inter observer agreement between the two reviewers with regard to classification of post surgical mammographic changes in the breast segment containing the cancer and classification of breast density, the linear-weighted k statistic was calculated.

Results

4.2

Overall screening outcome

Between January 1, 1997 and January 1, 2009, a total of 351,009 screens were obtained in 85,274 women: 46,155 were initial screens (13.1%) and 304,854 were subsequent screens (86.9%). Altogether, 4450 (1.3%) screens were referred for further diagnostic examination, of whom 1,772 had histologically proven breast cancer, yielding an overall cancer detection rate of 5.0 per 1,000 women screened and a true-positive referral rate of 39.8%. A total of 671 interval cancers had been diagnosed at two year follow-up, resulting in a screening sensitivity of 72.5% (1,772/2,443, 95% CI = 70.8% to 74.3%) for breast cancer detection and an interval cancer rate of 1.9 (671/351,009) per 1,000 screens.

Screening sensitivity after benign breast surgery

A total of 14 screen detected cancers and 12 interval cancers were excluded from analysis because of prior, ipsilateral breast conserving therapy or breast augmentation. Of the remaining 1,758 women with screen detected breast cancer, 115 (6.5%) had a history of previous benign ipsilateral breast surgery. The remaining 659 interval cancer cases included 66 women with prior ipsilateral benign breast surgery. Postsurgical women were older than women without surgery (mean age 63 years versus 62 years, p=0.03), but other patient characteristics were comparable for both groups (Table 1). We found a significantly lower screening sensitivity for women with prior surgery than without (63.5% (115/181) versus 73.5%

(1,643/2,236), p=0.004). The increased interval cancer risk remained present after logistic regression adjustment for age and density (OR=1.66, 95%CI: 1.20-2.29).

Table 1. *Characteristics of women with a diagnosis of breast cancer according to ipsilateral breast surgery status.*

	Previous benign breast surgery N = 181	**No previous benign breast surgery N = 2,236**	***P*-value**
Mean age, years (95%CI)	63(61.8-63.9)	62(61.3-61.9)	0.03
Family history of breast cancer[±], No (%)	39 (21.5)	429 (19.2)	0.4
Use of hormone replacement therapy, No (%)	23 (12.7)	226 (10.1)	0.3
Initial screens, No (%)	22 (12.2)	362 (16.2)	0.2
No (%) of views at latest screen[#]			0.8
1-view	17 (9.4)	226 (10.1)	
2-view	164 (90.6)	2,010 (89.9)	
Breast density at screening mammogram[#], No (%)			0.5
0-25%	50 (27.6)	729 (32.6)	
25-50%	60 (33.1)	732 (32.7)	
50-75%	47 (26.0)	535 (23.9)	
75-100%	24 (13.3)	240 (10.7)	

[±]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
[#]Screening mammogram for which a woman had been referred or latest screening mammogram prior to a diagnosis of interval cancer

Patient characteristics of women with screen detected cancers and interval cancers after ipsilateral benign breast surgery

One hundred fifteen of 1,772 screen detected breast cancers (6.5%) were diagnosed in women with prior ipsilateral benign breast surgery. The most frequent reasons for benign surgery had been excision of a palpable lesion (e.g., fibroadenoma, cyst or mastopathy; 79 cases, 68.7%), mastitis treatment by surgical incision and drainage, (13 cases, 11.3%) and breast reduction (12 cases, 10.4%) (Table 2).

Prior ipsilateral benign breast surgery had been performed in 66 out of 663 interval cancers (10.0%). Excision of a palpable breast lesion (71.2%) or breast reduction surgery (15.2%) were the most commonly performed surgical procedures among these 66 women. The type of previous ipsilateral benign surgery showed no statistically significant difference between the screen detected and interval cancer group (p=0.55).

Benign breast surgical procedures had been performed more than 5 years prior to the most recent screening examination in all but one of 181 women with a diagnosis of breast cancer and

previous benign surgery. Mean age was higher in women with screen detected cancer and a history of ipsilateral benign breast surgery (p=0.002). There were no significant differences in family history of breast cancer, use of hormone replacement therapy, proportion of initial screens or breast density at the latest screening mammogram between the two groups. Apart from breast density, a limitation in mammographic interpretation as a result of breast tissue characteristics was considered to be present, only in three screen detected cancers (fibrocystic changes, two cases; multiple coarse calcifications, one case) and one interval cancer (fibrocystic changes). The linear-weighted k value regarding the classification of breast density was 0.94 (95% CI = 0.91 to 0.97), indicating very good agreement between the two reviewers.

Post surgical mammographic changes

Mammographic changes as a result of benign breast surgery were reported in 49.6% (57/115) of screen detected cancers and in 53.0% (35/66) of interval cancers. These changes were not significantly more frequently located in breast segments harbouring interval cancers (p=0.10) (Table 3). However, post surgical mammographic alterations in the breast segment where the cancer was diagnosed were significantly more distinct in interval cancers than in screen detected cancers (p=0.001), with less minor and more moderate and substantial changes being present among patients with interval cancers. The linear-weighted k value regarding the classification of post surgical mammographic changes in the breast segment including the cancer was 0.87 (95% CI = 0.82 to 0.92), indicating very good agreement between the two radiologists. In a logistic regression analysis, adjusting for age and breast density, women with post surgical mammographic changes at the location of the breast cancer had a significantly increased chance of a cancer being diagnosed as interval cancer rather than screen detected cancer (OR = 2.12, 95% CI = 1.05 to 4.26, Table 3).

Visibility of screen detected cancers and interval cancers at previous screening mammogram

Respectively 66 (10.0% (66/659)) and 593 (90.0% (593/659)) interval cancers had been diagnosed in women with or without previous benign surgery. The proportion of cancers visible at the latest screen was comparable for both groups (50.0% (33/66) versus 48.4% (287/593, p=0.8). Of the 1,465 women with cancer detected at subsequent screening, 99 (6.3%) had undergone previous benign breast surgery. The proportion of cancers visible at the previous screening round neither differed significantly between women with or without previous surgery (47.5% (47/99) versus 43.8% (578/1,366, p=0.3).

Table 2. *Screen detected cancers and interval cancers in women with a history of ipsilateral benign breast surgery.*

	Screen detected cancers N = 115	**Interval cancers N = 66**	***P*-value**
Mean age, years (95%CI)	64.1 (62.8-65.4)	60.7 (59.1-62.3)	0.002
Family history of breast cancer, No (%)[±]	27 (23.5)	12 (18.2)	0.40
Use of hormone replacement therapy, No (%)	12 (10.4)	11 (16.7)	0.22
Type of previous ipsilateral benign surgery, No(%)			0.55
Excision of palpable lesion	79 (68.7)	47 (71.2)	
Excision of nonpalpable lesion	4 (3.5)	2 (3.0)	
Mastitis	13 (11.3)	3 (4.5)	
Breast reduction	12 (10.4)	10 (15.2)	
Other	7 (6.1)	4 (6.1)	
Initial screens, No (%)	16 (13.9)	6 (9.1)	0.34
Breast density at latest screening mammography, No (%)			0.25
0-25%	34 (29.6)	16 (24.2)	
25-50%	38 (33.0)	22 (33.3)	
50-75%	32 (27.8)	15 (22.7)	
75-100%	11 (9.6)	13 (19.7)	
Post-surgical mammographic changes, No (%)[#]			0.10
No	58 (50.4)	31 (47.0)	
Yes, located in breast tumour segment	30 (26.1)	26 (39.4)	
Yes, not located in breast tumour segment	27 (23.5)	9 (13.6)	
Degree of post-surgical mammographic changes in breast tumour segment, No (%)[#]			0.001
Minor	14 (46.7)	3 (11.5)	
Moderate	12 (40.0)	19 (73.1)	
Substantial	4 (13.3)	4 (15.4)	

[±]*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*
[#]*Post-surgical mammographic changes were determined on the last but one screening examination for subsequent screens and on the initial screening examination for women attending screening for the first time*

Table 3. *Odds of having post surgical mammographic changes located in the breast tumour segment, each variable adjusted for all others.*

	OR	95% CI	*P*-value
Post-surgical mammographic changes in breast tumour segment[±]			
No	1		
Yes	2.12	1.05-4.26	0.04
Age	0.94	0.89-0.98	0.01
Breast density at latest screening mammography			
0-25%	0.59	0.20-1.75	0.9
25-50%	0.55	0.19-1.60	0.7
50-75%	0.45	0.16-1.30	0.3
75-100%	1		

[±]*Post surgical mammographic changes were determined on the last but one screening examination for subsequent screens and on the initial screening examination for women attending screening for the first time*

Discussion

To our knowledge, this is the first analysis investigating the causes of lower sensitivity of screening mammography for cancer detection in a breast following ipsilateral benign breast surgery. The current study shows a lower sensitivity of screening mammography after previous benign breast surgery and we found that this lower sensitivity is most likely to be the result of postoperative mammographic changes rather than differences in breast density or the presence of specific tissue characteristics. Post surgical mammographic alterations in the breast segment where the cancer was diagnosed were significantly more distinct in interval cancers than in screen detected cancers and women with post surgical mammographic changes at the location of the breast cancer had an increased chance of a cancer being diagnosed as interval cancer rather than screen detected cancer. Breast density at the latest screening examination was similar for screen detected cancers and interval cancers that had been detected in postoperative breasts and the reviewers rarely reported that specific tissue characteristics such as fibrocystic disease or extensive calcifications hampered mammographic interpretation. The proportion of interval cancers and screen detected cancers that were retrospectively visible, respectively at the latest screen (for interval cancers) or previous screen (for screen detected cancers), did not differ significantly between women with or without previous benign breast surgery.

We recently reported that previous benign breast surgery negatively influences screening sensitivity, although tumour stages and tumour biology of screen-detected cancers and interval cancers are comparable for women with or without previous benign breast surgery.[7] Banks et al. found a borderline significant lower sensitivity after breast surgery for a condition other than breast cancer, but the authors did not correct for breast density.[14] Taplin et al. observed that previous benign breast biopsy significantly reduced screening specificity but not sensitivity and specificity was lower among women with percutaneous biopsy than among women with a history of surgical biopsy.[15] This latter finding made the authors hypothesize that differences in screening mammography performance after previous benign breast biopsy

were likely because of tissue characteristics rather than the biopsy itself. Unfortunately, the study did not report on the frequency of specific breast tissue characteristics among their study population. The divergent observations may also be explained by significant differences in study population characteristics and workup strategies as the incidence of ipsilateral breast cancer after benign breast surgery in their study was much lower than in ours (0.02 per 1,000 screens (40/174,723) versus 0.52 per 1,000 screens (181/351,009)).

The finding of a lower screening sensitivity following benign breast surgery may have implications for future screening guidelines. Although diagnostic surgical biopsy has largely been replaced by percutaneous biopsy techniques,[15,16] 6.7% of women in our screening programme currently mention a history of benign breast surgery, whereas 11.7% of women in the UK study of Banks et al. reported previous breast surgery for conditions other than cancer.[7,14]

Our study has several strengths and limitations. It is the largest series of screened women who developed breast cancer after previous benign breast surgery. All screening examinations were read by two screening radiologists, and from 2003 by two mammography technicians in addition, and we applied extensive follow-up to detect a maximum of interval cancers. On the other hand, our study comprised analogue screens only, whereas many screening units are now digital. The nation-wide breast cancer screening programme in the Netherlands has completely been digitized in 2010 and full-field digital screening mammography yields a similar or higher sensitivity than analogue screening.[17,18] The recent implementation of full-field digital mammography in the Netherlands has resulted in higher referral rates and increased cancer detection rates, at the expense of a decreased positive predictive value of referral.[19,20] However, the effect of the transition from screen-film mammography to digital mammography on interval cancer rates and on cancer detection in post surgical breasts is yet unknown.

Generalization of our study results may be limited by the presence of differences between our screening practice and those of other countries. The Dutch nation-wide screening programme offers biennial screening, which is in contrast to the annual screening mammography recommendation in the US and triennial screening in the UK[21,22] Our referral rate of 1.3% at analogue screening is in line with the average 1.3% nationwide referral rate in the Netherlands and is much lower than the 5-10% referral rates usually found in US and UK screening programmes.[23,24] We do not know the impact of this low referral rate on cancer detection in post surgical breasts. In subsequent screens, scoring of mammographic changes that could be attributed to previous surgery was done on the last but one examination in order to blind the reviewer for the location of the cancer. However, we cannot rule out the presence of bias at review of screen detected cancers in women who had attended for the first time and where the reviewers could thus not be blinded for tumour location. It is unlikely that the degree of postoperative changes substantially differed between the last but one and latest screening examination. Benign breast surgery had been performed more than 5 years prior to the most recent screening examination in all but one of 181 women in our series and several studies have shown that postoperative changes usually stabilize within 1-2 years

after surgery.[2,4] Finally, we were not able to calculate screening specificity as we were not informed about the total number of screened women with a history of benign breast surgery.

In summary, we conclude that previous benign breast surgery lowers screening sensitivity and this is likely due to postoperative mammographic changes. At screening, utmost attention should be paid to mammographic breast segments showing postoperative changes in order to reduce the risk of interval cancer. In order to prevent an adverse effect on screening sensitivity, excision of breast lesions with conclusive, benign pathology at percutaneous biopsy should only be considered if a woman persists on removal of the lesion.

References

1. Dowling EC, Klabunde C, Patnick J, Ballard-Barbash R; International Cancer Screening Network (ICSN). Breast and cervical cancer screening programme implementation in 16 countries. J Med Screen 2010;17:139-146.
2. Holli K, Saaristo R, Isola J, Hyöty M, Hakama M. Effect of radiotherapy on the interpretation of routine follow-up mammography after conservative breast surgery: a randomized study. Br J Cancer 1998;78:542-5.
3. Houssami N, Abraham LA, Miglioretti DL, Sickles EA, Kerlikowske K, Buist DS, Geller BM, Muss HB, Irwig L. Accuracy and outcomes of screening mammography in women with a personal history of early-stage breast cancer. JAMA 2011;305:790-9.
4. Brenner RJ, Pfaff JM. Mammographic changes after excisional breast biopsy for benign disease. AJR 1996;167:1047-52.
5. Muir TM, Tresham J, Fritschi L, Wylie E. Screening for breast cancer post reduction mammoplasty. Clin Radiol 2010; 65:198-205.
6. Slanetz PJ, Giardino AA, McCarthy KA, Hall DA, Halpern EF, Moore RH, Kopans DB. Previous breast biopsy for benign disease rarely complicates or alters interpretation on screening mammography. AJR 1998;170:1539-41.
7. van Breest Smallenburg V, Duijm LEM, Voogd AC, Groenewoud JH, Jansen FH, van Beek M, Louwman MWJ. Lower sensitivity of screening mammography after previous benign breast surgery. Int J Cancer 2012;130:122-8.
8. Taplin SH, Abraham L, Geller BM, Yankaskas BC, Buist DS, Smith-Bindman R, Lehman C, Weaver D, Carney PA, Barlow WE. Effect of previous benign breast biopsy on the interpretive performance of subsequent screening mammography. J Natl Cancer Inst 2010;102:1040-51.
9. Setz-Pels W, Duijm LEM, Groenewoud JH, Voogd AC, Jansen FH, Hooijen MJ, Louwman MW. Detection of bilateral breast cancer at biennial screening mammography in the Netherlands: a population based study. Radiology 2011;260:357-63.
10. UICC (International Union against Cancer): TNM Classification of Malignant Tumours, 4th rev ed. Berlin: Springer Verlag; 1987.
11. Duijm LEM, Groenewoud JH, Jansen FH, Fracheboud J, van Beek M, de Koning HJ. Mammography screening in the Netherlands: delay in the diagnosis of breast cancer after breast cancer screening. Br J Cancer 2004;91:1795-99.
12. Duijm LEM, Groenewoud JH, de Koning HJ, Coebergh JW, van Beek M, Hooijen MJ, van de Poll-Franse LV. Delayed diagnosis of breast cancer in women recalled for suspicious screening mammography. Eur J Cancer 2009;45:774-81.
13. American College of Radiology: Breast Imaging Reporting and Data System (BI-RADS), 4th ed. Reston: American College of Radiology; 2003.
14. Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, Hilton E, Bailey S, Barrett N, Briers P, English R, Jackson A, Kutt E, Lavelle J, Rockall L, Wallis MG, Wilson M, Patnick J. Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study. BMJ 2004;329:477.
15. Duijm LEM, Groenewoud JH, Roumen RMH, de Koning HJ, Plaisier ML, Fracheboud J. A decade of breast cancer screening in the Netherlands: trends in the preoperative diagnosis of breast cancer. Breast Cancer Res Treat 2007;106:113-9.
16. Duijm LEM, Groenewoud JH, Fracheboud J, Plaisier ML, Roumen RM, van Ineveld BM, van Beek M, de Koning HJ. Utilization and cost of diagnostic imaging and biopsies following positive screening mammography in the southern breast cancer screening region of the Netherlands, 2000-2005. Eur Radiol 2008;18:2390-97.
17. Pisano EA, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, Conant EF, Fajardo LL, Bassett L, D'Orsi C, Jong R, Rebner M; Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group. Diagnostic performance of digital versus film mammography for breast-cancer screening. New Engl J Med 2005;353:1773-83.

18. Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus fullfield digital mammography with soft-copy reading in population based screening program: follow-up and final results of Oslo II study. Radiology 2007; 244:708-17.

19. Bluekens AM, Karssemeijer N, Beijerinck D, Deurenberg JJ, van Engen RE, Broeders MJ, den Heeten GJ. Consequences of digital mammography in population-based breast cancer screening: initial changes and long-term impact on referral rates. Eur Radiol 2010;20:2067-73.

20. Timmers JM, den Heeten GJ, Adang EM, Otten JD, Verbeek AL, Broeders MJ. Dutch digital breast cancer screening: implications for breast cancer care. Eur J Public Health 2012;22:925-9.

21. National Comprehensive Cancer network: practice guidelines in oncology; v.2.2009. Fort Washington: Fort Washington; 2009.

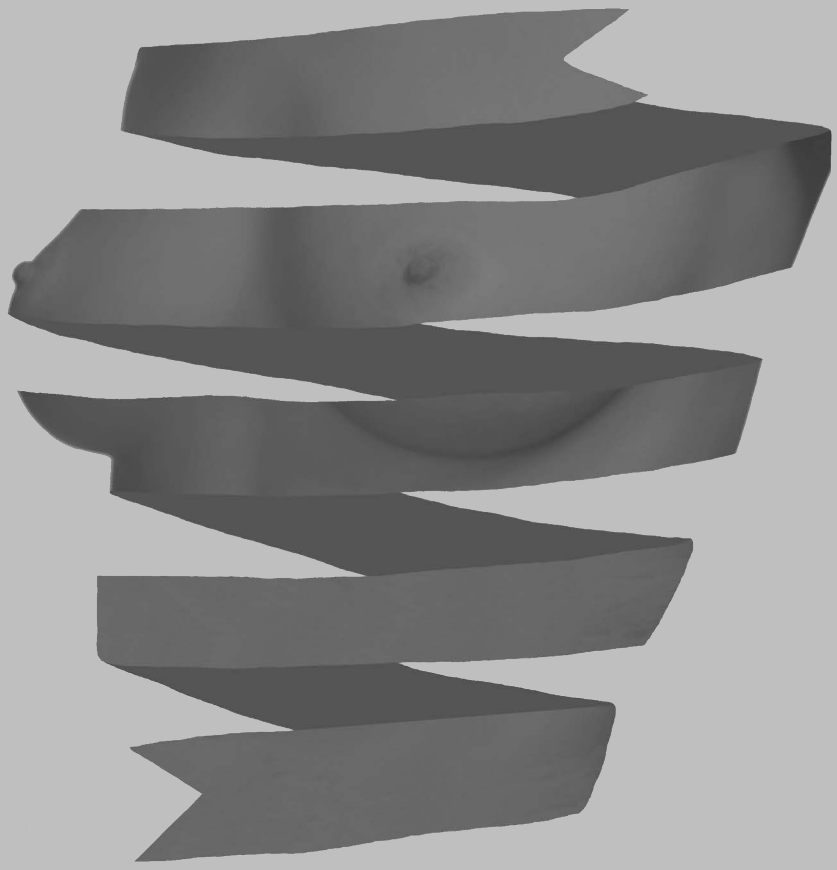
22. NHS breast screening programme: Breast screening, a pocket guide 2008. London: NHS cancer screening programmes; 2008.

23. National Evaluation Team for Breast Cancer Screening (NETB). National evaluation of breast cancer in the Netherlands 1990-2007, twelfth evaluation report. Rotterdam: Erasmus MC Rotterdam, Radboud University Nijmegen Medical Centre; 2009.

24. Smith-Bindman R, Chu PW, Miglioretti DL, Sickles EA, Blanks R, Ballard-Barbash R, Bobo JK, Lee NC, Wallis MG, Patnick J, Kerlikowske K. Comparison of screening mammography in the United States and the United Kingdom. JAMA 2003;290:2129-37.

Chapter 4.3

Trends in biopsies for (benign) breast lesions detected at screening



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Trends in breast biopsies for abnormalities detected at screening mammography; a population based study in the Netherlands

van Breest Smallenburg V, Nederend J, Voogd A, Coebergh JWW, van Beek M, Jansen FH, Louwman WJ, Duijm LEM

Abstract

Background

Breast surgery decreases the sensitivity of screening mammography. The use of diagnostic surgical breast biopsies should therefore be as low as possible. We determined trends in breast biopsies for abnormalities detected at screening mammography.

Methods

We included 417,013 screens obtained between January 1, 1997 and January 1, 2011. During two year follow-up clinical data, breast imaging-, biopsy-, surgery- and pathology-reports were collected of all 6,230 referred women. Furthermore, in breast cancers diagnosed more than 3 months after referral (delays), mammograms and pathology specimens were reviewed.

Results

Benign diagnoses after referral that were made by fine-needle aspiration cytology (FNAC) remained stable, from 8.0% (1997-1998) to 6.0% (2009-2010) ($p=0.2$), percutaneous core-needle biopsies (CB) increased from 1.9% to 33.6% ($p<0.0001$) and surgical biopsies decreased from 22.5% to 1.5% ($p<0.0001$). In women diagnosed with breast cancer after referral, FNAC decreased from 19.2% to 0.7% ($p<0.0001$), CBs increased from 16.5% to 96.8% ($p<0.0001$) and surgical biopsies decreased from 58.9% to 0.9% ($p<0.0001$). Delays in breast cancer diagnosis decreased from 6.7% to 1.8% ($p=0.003$).

Conclusion

The use of diagnostic surgical biopsies for screening mammography abnormalities has decreased substantially. They have mostly been replaced by CBs and this replacement did not result in more 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. The incidence of breast cancer in the Netherlands is among the highest in the world with the age-standardised rate being 128/100,000 person years (European Standardised Rate, ESR) and the incidence is still increasing. Breast cancer survival has, however, improved over the last decades[2,3,4] and this is probably due to the introduction of mammography screening and improvements in treatment.[2,5] Breast cancer screening enables early detection of breast cancer, resulting in a more favourable tumour stage distribution and a better prognosis.[6,7]

In the Netherlands, women aged 50-75 years are invited every two years to undergo mammography screening. In case of a mammographic abnormality at screening, women are referred to a hospital for further diagnostic workup. This workup may consist of additional imaging (additional mammographic views, breast ultrasonography, magnetic resonance mammography (MRI)), 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 open surgical biopsy (excisional biopsy). A majority of breast biopsies are, however, negative for cancer and it is important to realize that surgical biopsies in women with benign outcome have adverse effects.[8,9] A false-positive screening mammogram causes unnecessary psychological distress and the degree of distress is related to the invasiveness of the assessment after referral.[10,11] Furthermore, benign breast surgery, including surgical biopsy, may complicate interpretation of subsequent mammograms due to postoperative changes.[12-16] Because of these adverse effects, surgical biopsies should generally be prevented in the workup of screening mammography abnormalities.

In the current population based study we determined the trends in breast biopsies for abnormalities detected at screening mammography. We also determined the proportion of referred women who experienced a delay in breast cancer diagnosis due to false negative biopsy results.

Materials and methods

Study population

We included all women who underwent biennial screening mammography at one of two specialized screening units (one fixed unit and one mobile unit) in the southern breast cancer screening region of the Netherlands between January 1, 1997 and January 1, 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. Institutional review board approval was not required for this type of study.

Screening procedure and diagnostic workup

Details of the nation-wide breast cancer screening programme have been described previously.[17,18] The Dutch nation-wide breast cancer screening programme offers biennial

screening mammography to women aged 50-75 years. Digitization 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. All mammograms in this study were obtained by specialized screening mammography radiographers and the examinations were independently double read by a group consisting of 12 certified screening radiologists. Each of the screening radiologists evaluates at least 5,000 screening mammograms yearly. From 2003, in addition to radiologist double reading, the radiographers also actively participated in the assessment of the screening mammograms.[19] 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. After a physical examination, a complete mammographic workup was performed of all suspect mammographic areas. The radiologist classified the radiologic findings according to the American College of Radiology BI-RADS and then decided whether additional procedures such as breast ultrasonography, MRI and/or biopsy were indicated.[20] The choice of additional procedures also depended on the diagnostic workup protocols and the facilities available at the hospitals 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.[21] In 2008 a new guideline increased the target for preoperative diagnoses to 90%.[22] Biopsy of nonpalpable lesions in our study population was always performed by radiologists, 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. A total of 16 hospitals were involved in the diagnostic workup of the referred women. Between 1999 and 2007, out-patient breast clinics became available at these hospitals 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 approximately 2 years).

Delay in breast cancer diagnosis

A definite diagnosis of breast cancer more than three months after referral was considered as a diagnostic delay.[23] 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 negative 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 percentage of referred women who underwent a percutaneous or surgical biopsy at workup and the percentage of women who experienced a delay in breast cancer diagnosis. All data were entered into a computerized spreadsheet (Excel; Microsoft, Redmond, WA, USA). Statistics were performed using the SPSS program version 17.0 (Statistical Package for the Social Sciences; SPSS inc., Chicago, IL, USA). A χ^2 test was used to test differences between categorical variables. The significance level was set at 5%.

Results

Overall screening results

From January 1, 1997 to January 1, 2011 a total of 417,013 screening examinations had been performed. Altogether, 6,230 women were referred for further diagnostic workup of a mammographic abnormality (referral rate, 1.5%). Breast cancer was diagnosed in 2,214 referred women, yielding a cancer detection rate of 5.3 per 1,000 screening examinations and a true positive referral rate of 35.6%. Nine women had either not been referred by their general practitioner or their follow-up was unknown and 4,007 (64.4 %) women had a benign outcome (ie, false positive referrals).

Biopsies in women with benign outcome

In 2,426 of the 4,007 referred women with a benign outcome (60.5%), evaluation of the abnormality detected at screening consisted of imaging only (additional mammographic views, breast ultrasonography and/or MRI). In the other 1,581 women with benign outcome imaging was not sufficient for making the diagnosis. In many women a combined diagnostic approach was used because of inconclusive results from FNAC and/or percutaneous CB (Table 1). The final diagnosis was made by FNAC in 422 (10.5%) referred women, by a CB in 900 women (22.5%) and by a surgical biopsy in 255 (6.4%) women (Table 1). Diagnoses made by FNAC fluctuated, however in the final years FNAC returned more or less to the initial level; 8.0% (25/311) of the diagnoses was made by FNAC in 1997-1998 and 6.0% (81/1,344) in 2009-2010 (p=0.2) (Figure 1). Diagnoses made by CB increased from 1.9% (6/311) in 1997-1998 to 33.6% (451/1,344) in 2009-2010 (p<0.0001). Simultaneously, diagnoses made by surgical biopsies significantly decreased from 22.5% (70/311) in 1997-1998 to 1.5% (20/1,344) in 2009-2010 (p<0.0001) (Figure 1).

Table 2 shows the reasons for diagnostic surgical biopsies in women with benign outcome. In 1997-1998, the majority of surgical biopsies had been performed specifically for diagnostic purposes (81.4%, 57/70). In 2009-2010, however, the majority of surgical biopsies (95.0%,

Table 1. *Diagnostic procedures in women with benign outcome after referral for a screening mammography abnormality.*

	97-98	99-00	01-02	03-04	05-06	07-08	09-10	Total
Total screens, No	48,721	53,718	53,489	61,251	66,300	67,530	66,004	417,013
Total referred, No (%)	537 (1.1)	499 (0.9)	553 (1.0)	985 (1.6)	874 (1.3)	1003 (1.5)	1,779 (2.7)	6,230 (1.5)
Total false positive referrals*, No (%)	311 (58.1)	223 (44.7)	299 (54.1)	632 (64.4)	550 (63.0)	648 (64.7)	1,344 (75.6)	4,007 (64.4)
Diagnostic work-up, No(%)								
Breast imaging only	208 (66.9)	137 (61.4)	188 (62.9)	370 (58.5)	317 (57.6)	415 (64.0)	791 (58.9)	2,426 (60.5)
+ FNAC	25 (8.0)	27 (12.1)	44 (14.7)	76 (12.0)	89 (16.2)	80 (12.3)	81 (6.0)	422 (10.5)
+ FNAC and core-needle biopsy (CB)	4 (1.3)	10 (4.5)	25 (8.4)	122 (19.3)	102 (18.5)	125 (19.3)	423 (31.5)	811 (20.2)
+ CB	2 (0.6)	3 (1.3)	7 (2.3)	15 (2.4)	23 (4.2)	11 (1.7)	28 (2.1)	89 (2.2)
+ FNAC/CB and surgical biopsy	54 (17.4)	31 (13.9)	23 (7.7)	16 (2.5)	5 (0.9)	4 (0.6)	1 (0.1)	134 (3.3)
+ surgical biopsy	16 (5.1)	15 (6.7)	11 (3.7)	33 (5.2)	14 (2.5)	13 (2.5)	19 (1.4)	121 (3.0)
Unknown	2 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	4 (0.1)
Total diagnosis by FNAC	25 (8.0)	27 (12.1)	44 (14.7)	76 (12.0)	89 (16.2)	80 (12.3)	81 (6.0)	422 (10.5)
Total diagnosis by core-needle biopsy	6 (1.9)	13 (5.8)	32 (10.7)	137 (21.7)	125 (22.7)	136 (21.0)	451 (33.6)	900 (22.5)
Total diagnosis by surgical biopsy	70 (22.5)	46 (20.6)	34 (11.4)	49 (7.8)	19 (3.5)	17 (2.6)	20 (1.5)	255 (6.4)
Surgical biopsy per 1,000 screens	1.4	0.9	0.6	0.8	0.3	0.3	0.3	0.6

**women not diagnosed with breast cancer after referral*

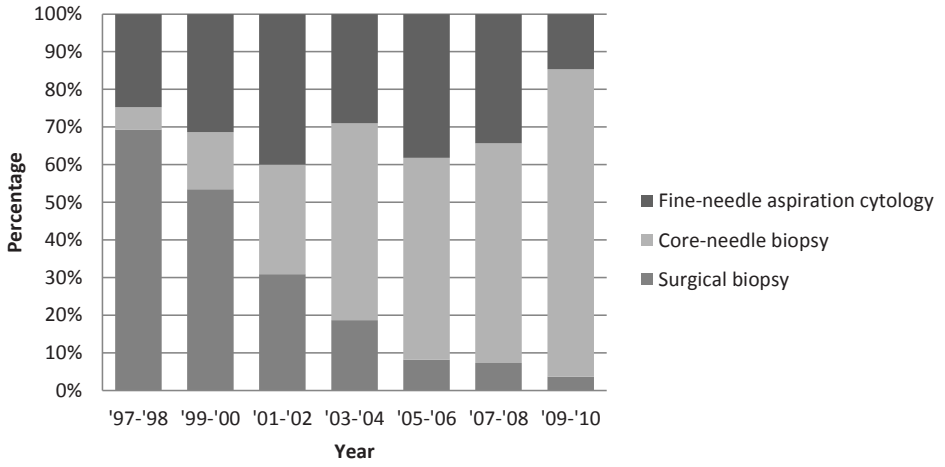


Figure 1. *Trends in biopsy procedures in women with benign outcome after referral, 1997-2011.*

Table 2. *Reasons for surgical biopsies in women with benign outcome after referral for screening years 1997-1998 and 2009-2010.*

1997-1998 N=70		2009-2010 N=20	
High risk/premalignant lesion at CB	1	High risk/premalignant lesion at CB	11
Inconclusive result at FNAC and CB	2	Inconclusive histology at CB	6
Women's desire to excise a lesion with benign cytology at FNAC	2	Women's desire to excise a lesion with benign histology at CB	2
Atypical cytology at FNAC	3	Sebaceous cyst	1
Primary excisional biopsy for making the diagnosis	57		
Unknown	5		

CB = core biopsy
FNAC = fine-needle aspiration cytology

19/20) had been preceded by a percutaneous biopsy and main reasons for surgical biopsies were possible (pre)cancerous lesions and inconclusive results at FNAC or CB.

Biopsies in women with malignant outcome

Breast cancer was diagnosed in 2,214 referred women. In 62 (2.8%) of these women, evaluation of the abnormality detected at screening consisted of imaging only. In these cases the breast cancer was initially not detected and the majority of these women (88.7%, 55/62) returned later with a delay in breast cancer diagnosis. In many of the 2,214 women with malignant outcome a combined diagnostic approach was used because of inconclusive results from FNAC and/or CB (Table 3). The final diagnosis was made by FNAC in a total of 282

Table 3. *Diagnostic procedures in women with malignant outcome after referral for a screening mammography abnormality.*

	97-98	99-00	01-02	03-04	05-06	07-08	09-10	Total
Total screens, No	48,721	53,718	53,489	61,251	66,300	67,530	66,004	417,013
Total referred, No (%)	537 (1.1)	499 (0.9)	553 (1.0)	985 (1.6)	874 (1.3)	1,003 (1.5)	1,779 (2.7)	6,230 (1.5)
Total true positive referrals*, No (%)	224 (41.9)	276 (55.3)	254 (45.9)	350 (35.6)	323 (37.0)	354 (35.3)	433 (24.4)	2,214 (35.6)
Diagnostic work-up No(%)								
Breast imaging only	12 (5.4)	12 (4.3)	10 (3.9)	13 (3.7)	6 (1.9)	2 (0.6)	7 (1.6)	62 (2.8)
+ FNAC	43 (19.2)	49 (17.8)	41 (16.1)	59 (16.9)	49 (15.2)	38 (10.7)	3 (0.7)	282 (12.7)
+ FNAC and core-needle biopsy (CB)	5 (2.2)	19 (6.9)	22 (8.7)	22 (6.3)	25 (7.7)	17 (4.8)	0 (0.0)	110 (5.0)
+ CB	32 (14.3)	76 (27.5)	121 (47.6)	226 (64.6)	228 (70.6)	285 (80.5)	419 (96.8)	1,387 (62.6)
+ FNAC/CB and surgical biopsy	27 (12.1)	28 (10.1)	32 (12.6)	20 (5.7)	10 (3.1)	11 (3.1)	3 (0.7)	131 (5.9)
+ surgical biopsy	105 (46.9)	92 (33.3)	28 (11.0)	10 (2.9)	5 (1.5)	1 (0.3)	1 (0.2)	242 (10.9)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total diagnosis by FNAC	43 (19.2)	49 (17.8)	41 (16.1)	59 (16.9)	49 (15.2)	38 (10.7)	3 (0.7)	282 (12.7)
Total diagnosis by core-needle biopsy	37 (16.5)	95 (34.4)	143 (56.3)	248 (70.9)	253 (78.3)	302 (85.3)	419 (96.8)	1,497 (67.6)
Total diagnosis by surgical biopsy	132 (58.9)	120 (43.5)	60 (23.6)	30 (8.6)	15 (4.6)	12 (3.4)	4 (0.9)	373 (16.8)
Surgical biopsy per 1,000 screens	2.9	2.3	1.1	0.5	0.2	0.2	0.1	0.9

**women diagnosed with breast cancer after referral*
FNAC = fine-needle aspiration cytology

(12.7%) referred women with breast cancer, CB in 1,497 women (67.6%) and by a diagnostic surgical biopsy in 373 (16.8%) women. Preoperative confirmations of breast cancer by FNAC decreased from 19.2% (43/224) in 1997-1998 to 0.7% (3/433) in 2009-2010 (p<0.0001). Diagnoses made by CB increased from 16.5% (37/224) in 1997-1998 to 97.8% (419/433) in 2009-2010 (p<0.0001). Simultaneously, the proportion of women who underwent a surgical biopsy (or lumpectomy) for diagnostic purposes, decreased from 58.9% (132/224) in 1997-1998 to 0.9% (4/433) in 2009-2010 (p<0.0001) (Figure 2).

Diagnostic delays

In 96 of the 2,214 women with breast cancer (4.3%) the diagnosis was made more than three 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 more than 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 4. A total of 27 women with a delay (28.1%) had an advanced tumour stage at time of diagnosis (advanced cancers were defined as invasive cancers with a tumour size > 20 mm (T2) and/or presence of metastasis in axillary lymph nodes). The total amount of women with a diagnostic delay decreased, from 6.7% (15/224) in 1997-1998 to 1.8% (8/344) in 2009-2010 (p=0.003). The majority of the diagnostic delays resulted from an erroneous BI-RADS assessment (57.3%, 55/96) or false negative biopsy result (32.3%, 31/96). 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 4. The pathologist reported that all false negative biopsy results were due to sampling errors and not the result of erroneous pathologic assessments.

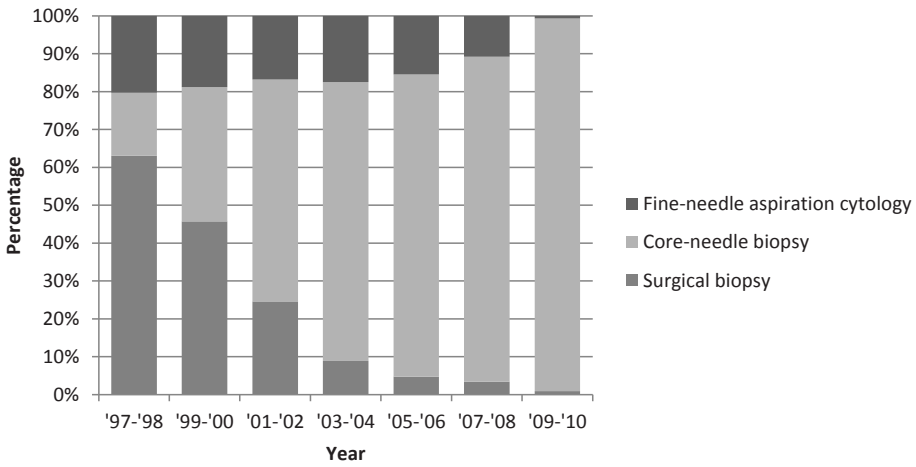


Figure 2. *Trends in biopsy procedures in women with malignant outcome after referral, 1997-2011.*

Table 4. *Details of delays in breast cancer diagnosis after referral.*

	97-98	99-00	01-02	03-04	05-06	07-08	09-10	Total
Total true positive referrals*, No (%)	224	276	254	350	323	354	433	2,214
Delay in cancer diagnosis, No (%)	15 (6.7)	17 (6.2)	17 (6.7)	17 (4.9)	13 (4.0)	9 (2.5)	8 (1.8)	96 (4.3)
Length of diagnostic delay								
4-6 months	5 (33.3)	5 (29.4)	4 (23.5)	4 (23.5)	5 (38.5)	2 (22.2)	1 (12.5)	26 (27.1)
7-12 months	7 (46.7)	6 (35.3)	8 (47.1)	6 (35.3)	3 (23.1)	3 (33.3)	3 (37.5)	36 (37.5)
13-24 months	3 (20.0)	3 (17.6)	0 (0.0)	7 (41.2)	4 (30.8)	2 (22.2)	2 (25.0)	21 (21.9)
>24 months	0 (0.0)	3 (17.6)	5 (29.4)	0 (0.0)	1 (7.7)	2 (22.2)	2 (25.0)	13 (13.5)
Causes of diagnostic delay								
Incorrect BI-RADS	12 (80.0)	11 (64.7)	10 (58.8)	10 (58.8)	5 (38.5)	2 (22.2)	5 (62.5)	55 (57.3)
False negative biopsy	3 (20.0)	4 (23.5)	5 (29.4)	5 (29.4)	6 (46.2)	6 (66.7)	2 (25.0)	31 (32.3)
Other reason	0 (0.0)	2 (11.8)	2 (11.8)	2 (11.8)	2 (15.4)	1 (11.1)	1 (12.5)	10 (10.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
False negative biopsy according to type of biopsy procedure								
FNAC	2 (66.7)	1 (20.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (12.5)
CB	1 (33.3)	0 (0.0)	1 (20.0)	3 (60.0)	6 (10.,0)	3 (50.0)	1 (50.0)	15 (46.9)
FNAC and CB	0 (0.0)	2 (40.0)	0 (0.0)	1 (20.0)	0 (0.0)	3 (50.0)	1 (50.0)	7 (21.9)
Surgical biopsy	0 (0.0)	2 (40.0)	4 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (18.8)
Tumour size of cancers with diagnostic delay								
DCIS	4 (26.7)	5 (29.4)	2 (11.8)	6 (35.3)	1 (7.7)	1 (11.1)	2 (25.0)	21 (21.9)
T1a-b	4 (26.7)	5 (29.4)	7 (41.2)	2 (11.8)	5 (38.5)	2 (22.2)	2 (25.0)	27 (28.1)
T1c	6 (40.0)	4 (23.5)	6 (35.3)	9 (52.9)	4 (30.8)	3 (33.3)	1 (12.5)	33 (34.4)
T2+	1 (6.7)	3 (17.6)	2 (11.8)	0 (0.0)	3 (23.1)	2 (22.2)	3 (37.5)	14 (14.6)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (1.0)
Axillary lymph node status								
N+	3 (20.0)	1 (5.9)	4 (23.5)	6 (35.3)	2 (15.4)	3 (33.3)	0 (0.0)	19 (19.8)
N-	12 (80.0)	14 (82.4)	13 (76.5)	9 (52.9)	10 (76.9)	6 (66.7)	8 (100.0)	72 (75.0)
Nx	0 (0.0)	2 (11.8)	0 (0.0)	2 (11.8)	1 (7.7)	0 (0.0)	0 (0.0)	5 (5.2)

**women diagnosed with breast cancer after referral*

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

Discussion

In earlier studies we reported that benign breast surgery, including surgical biopsy, can result in a lower sensitivity for breast cancer detection at subsequent screening mammography.[15,16] Currently, almost 7% of women who undergo breast cancer screening in the southern screening region of the Netherlands have a history of benign breast surgery, mainly due to a prior excision of a palpable breast lesion.[15] This relatively high prevalence of women with prior benign breast surgery can be explained by the fact that in the 1990s, when breast cancer screening was implemented in the southern screening region of the Netherlands, diagnostic workup frequently included surgical biopsy. Over the years, however, surgical biopsies have mostly been replaced by percutaneous biopsies in the diagnostic workup of suspicious breast lesions. This 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[21] and the 2008 guideline increased this target to 90%.[22]

The use of FNAC in women with benign outcome fluctuated and slightly decreased in the final years of our study and in women with malignant outcome the use of FNAC decreased substantially. FNAC is still important for the assessment of cystic lesions and is therefore still used in the workup of benign (cystic) breast abnormalities.[22] For solid lesions FNAC has a higher insufficient sample rate and a lower diagnostic accuracy than other biopsy methods and because FNAC is often inconclusive, additional CB is frequently required.[24-26] This means that women experience a longer period of anxiety and uncertainty before knowing the diagnosis. Therefore, in case of a solid lesion, FNAC should not be considered the diagnostic procedure of first choice.

During the 14-year period of our study the use of CBs increased substantially, both in women with benign and malignant outcome after referral. Percutaneous CBs are equally accurate to surgical biopsies and have advantages like lower costs, a more rapid way of providing a diagnosis and lower complication rates.[27-30] Furthermore, in malignant cases, percutaneous CB makes it possible to have a preoperative confirmation of breast cancer. A preoperative confirmation of the malignant nature of a breast lesion gives the patient and surgeon the possibility to discuss treatment options and it allows a better preoperative planning.[31,32] Furthermore, a preoperative diagnosis is associated with a lower likelihood of multiple breast surgeries.[33,34] Because of these benefits, 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.[35-37] 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.[22,38,39] Furthermore, a surgical biopsy can be the biopsy-method of choice when patient characteristics (for example extreme obesity or dementia) impede percutaneous biopsy.

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.[22,40,41] 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.[42-44] Also false negative biopsy results are known as probable causes of diagnostic delays.[45] The majority of false negative biopsy results in our study consisted of CBs (68.8%), all were due to sampling errors. Researchers describe that approximately 4% of CB results, both ultrasound- and stereotactic guided, are false negative.[22] Therefore, attention for radiologic-histologic correlation is very important.[45-47] If biopsy results do not provide a sufficient explanation for the mammographic abnormality, the lesion may not have been sampled adequately and a repeated biopsy is needed. When using CB, in approximately 10% a repeat biopsy is required.[45] False-negative results and delays in diagnosis from both erroneous BI-RADS assessments and false negative biopsies can be reduced with optimization of multidisciplinary approach and clear post-biopsy protocols.

There are certain 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 differ 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.[48,49] Furthermore, the incidence of open surgical biopsies is much higher in the US than in the UK and the Netherlands. Recent data suggest that in the US, 30-40% of diagnostic breast biopsies still consist of surgical biopsies.[50,51] Our findings show that there may be room for decreasing the number of open breast biopsy procedures in US screening programmes.

We conclude that women with a benign diagnosis after referral for a screening mammography abnormality are nowadays rarely confronted with a diagnostic surgical biopsy. Surgical biopsies have mostly been replaced by core-needle biopsies. Also in women diagnosed with breast cancer, the use of surgical biopsies for diagnostic purposes has decreased substantially and these women nowadays rarely undergo surgery without a preoperative diagnosis. The replacement of surgical biopsies by percutaneous biopsies did not increase the amount of delays in breast cancer diagnosis.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Autier P, Boniol M, La Vecchia C, Vatten L, Gavin A, Hery C, Heanue M. Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database. BMJ 2010;34:c3620.
3. Louwman WJ, Voogd AC, van Dijck JA, Nieuwenhuijzen GA, Ribot J, Pruijt JF, Coebergh JW. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: a long-term population-based study in southeastern Netherlands. Cancer Causes Control 2008;19:97-106.
4. Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive epidemiology of female breast cancer: an international comparison of screening, incidence, survival and mortality. Cancer Epid 2012;36:237-48.
5. Louwman WJ, van de Poll-Franse LV, Fracheboud J, Roukema JA, Coebergh JW. Impact of a programme of mass mammography screening for breast cancer on socio-economic variation in survival: a population-based study. Breast Cancer Res Treat 2007;105:369-75.
6. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, Mandelblatt JS, Yakovlev AY, Habbema JD, Feuer EJ. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784-92.
7. Soerjomataram I, Louwman MW, Ribot JG, Roukema JA, Coebergh JW. An overview of prognostic factors for long-term survivors of breast cancer. Breast Cancer Res Treat 2008;107:309-30.
8. Kerlikowske K, Smith-Bindman R, Ljung BM, Grady D. Evaluation of abnormal mammography results and palpable breast abnormalities. Ann intern med 2003;139:274-84.
9. Sickles EA, Ominsky SH, Sollitto RA, Galvin HB, Monticciolo DL. Medical audit of a rapid-throughput mammography screening practice: methodology and results of 27,114 examinations. Radiology 1990;175:323-7.
10. Bond M, Pavey T, Welch K, Cooper C, Garside R, Dean S, Hyde CJ (2012) Psychological consequences of false-positive screening mammograms in the UK. Evid Based Med 2012. (in press), doi: 10.1136/eb-***2012***-10060
11. Brett J, Austoker J. Women who are recalled for further investigation for breast screening: psychological consequences 3 years after recall and factors affecting re-attendance. J Public Health Med 2001;23:292-300.
12. Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, Hilton E, Bailey S, Barrett N, Briers P, English R, Jackson A, Kutt E, Lavelle J, Rockall L, Wallis MG, Wilson M, Patnick J. Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study. BMJ 2004;329: 477.
13. Brenner RJ, Pfaff JM. Mammographic changes after excisional breast biopsy for benign disease. AJR 1996;167:1047-52.
14. Taplin SH, Abraham L, Geller BM, Yankaskas BC, Buist DS, Smith-Bindman R, Lehman C, Weaver D, Carney PA, Barlow WE. Effect of previous benign breast biopsy on the interpretive performance of subsequent screening mammography. J Natl Cancer Inst 2010;102:1040-51.
15. van Breest Smallenburg V, Duijm LE, Voogd AC, Groenewoud JH, Jansen FH, van Beek M, Louwman MW. Lower sensitivity of screening mammography after previous benign breast surgery. Int J Cancer 2012;130:122-8.
16. van Breest Smallenburg V, Duijm LE, Voogd AC, Jansen FH, Louwman MW. Mammographic changes resulting from benign breast surgery impair breast cancer detection at screening mammography. Eur J Cancer 2012;48:2097-103.
17. Duijm LE, Groenewoud JH, Hendriks JH, de Koning HJ. Independent double reading of screening mammograms in The Netherlands: effect of arbitration following reader disagreements. Radiology 2004;231:564-70.
18. Fracheboud J, de Koning HJ, Beemsterboer PM, Boer R, Hendriks JH, Verbeek AL, van Ineveld BM, de Bruyn AE, van der Maas PJ. Nation-wide breast cancer screening in The Netherlands: results of initial

and subsequent screening 1990-1995. National Evaluation Team for Breast Cancer Screening. Int J Cancer 1998;75:694-8.

19. Duijm LE, Groenewoud JH, Fracheboud J, de Koning HJ. Additional double reading of screening mammograms by radiologic technologists: impact on screening performance parameters. J Natl Cancer Inst 2007;99:1162-70.

20. American College of Radiology: Breast Imaging Reporting and Data System (BI-RADS), 4th ed. Reston: American College of Radiology; 2003.

21. Rutgers EJ, Tuut MK. CBO guideline 'Breast cancer: screening and diagnosis'. Ned Tijdschr Geneeskd 2001;145:115-9. (In Dutch)

22. Nationaal Borstkanker Overleg Nederland. CBO richtlijn mammacarcinoom. NABON: Amsterdam; 2008. (in Dutch)

23. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet 1999;353:1119-26.

24. Duijm LE, Groenewoud JH, Roumen RM, de Koning HJ, Plaisier ML, Fracheboud J. A decade of breast cancer screening in The Netherlands: trends in the preoperative diagnosis of breast cancer. Breast Cancer Res Treat 2007;106:113-9.

25. Pisano ED, Fajardo LL, Caudry DJ, Sneige N, Frable WJ, Berg WA, Tocino I, Schnitt SJ, Connolly JL, Gatsonis CA, McNeil BJ. Fine-needle aspiration biopsy of nonpalpable breast lesions in a multicenter clinical trial: results from the radiologic diagnostic oncology group V. Radiology 2001;219:785-92.

26. Willems SM, van Deurzen CH, van Diest PJ. Diagnosis of breast lesions: fine-needle aspiration cytology or core needle biopsy? A review. J Clin Path 2012; 65:287-92.

27. Bruening W, Fontanarosa J, Tipton K, Treadwell JR, Launders J, Schoelles K. Systematic review: comparative effectiveness of core-needle and open surgical biopsy to diagnose breast lesions. Ann Int Med 2010;152:238-46.

28. Fajardo LL, Pisano ED, Caudry DJ, Gatsonis CA, Berg WA, Connolly J, Schnitt S, Page DL, McNeil BJ. Stereotactic and sonographic large-core biopsy of nonpalpable breast lesions: results of the Radiologic Diagnostic Oncology Group V study. Acad Radiol 2004;11:293-308.

29. Golub RM, Bennett CL, Stinson T, Venta L, Morrow M. Cost minimization study of image-guided core biopsy versus surgical excisional biopsy for women with abnormal mammograms. J Clin Oncol 2004;22:2430-7.

30. Verkooijen HM. Diagnostic accuracy of stereotactic large-core needle biopsy for nonpalpable breast disease: results of a multicenter prospective study with 95% surgical confirmation. Int J Cancer 2002;99:853-9.

31. James TA, Mace JL, Virnig BA, Geller BM. Preoperative needle biopsy improves the quality of breast cancer surgery. J Am Coll Surg 2012;215:562-8.

32. White RR, Halperin TJ, Olson JA, Jr., Soo MS, Bentley RC, Seigler HF. Impact of core-needle breast biopsy on the surgical management of mammographic abnormalities. Ann Surg 2001;233:769-77.

33. Duijm LE, Groenewoud JH, de Koning HJ, Coebergh JW, van Beek M, Hooijen MJ, van de Poll-Franse LV. Delayed diagnosis of breast cancer in women recalled for suspicious screening mammography. Eur J Cancer 2009;45:774-81.

34. Friese CR, Neville BA, Edge SB, Hassett MJ, Earle CC. Breast biopsy patterns and outcomes in Surveillance, Epidemiology, and End Results-Medicare data. Cancer 2009;115:716-24.

35. Brenner RJ, Bassett LW, Fajardo LL, Dershaw DD, Evans WP, 3rd, Hunt R, Lee C, Tocino I, Fisher P, McCombs M, Jackson VP, Feig SA, Mendelson EB, Margolin FR, Bird R, Sayre J. Stereotactic core-needle breast biopsy: a multi-institutional prospective trial. Radiology 2001;218:866-72.

36. Crowe JP, Jr., Rim A, Patrick R, Rybicki L, Grundfest S, Kim J, Lee K, Levy L. A prospective review of the decline of excisional breast biopsy. Am J Surg 2002;184:353-5.

37. Meyer JE, Smith DN, Lester SC, Kaelin C, DiPiro PJ, Denison CM, Christian RL, Harvey SC, Selland DL, Durfee SM. Large-core needle biopsy of nonpalpable breast lesions. JAMA 1999;281:1638-41.

38. Shin SJ, Rosen PP. Excisional biopsy should be performed if lobular carcinoma in situ is seen on needle core biopsy. Arch Pathol Lab Med 2002;126:697-701.

39. Sydnor MK, Wilson JD, Hijaz TA, Massey HD, Shaw de Paredes ES. Underestimation of the presence of breast carcinoma in papillary lesions initially diagnosed at core-needle biopsy. Radiology 2007;242:58-62.

40. Pruthi S, Brandt KR, Degnim AC, Goetz MP, Perez EA, Reynolds CA, Schomberg PJ, Dy GK, Ingle JN. A multidisciplinary approach to the management of breast cancer, part 1: prevention and diagnosis. Mayo Clin Pros 2007;82:999-1012.

41. Rabinowitz B. Interdisciplinary breast cancer care: declaring and improving the standard. Oncology (Williston Park) 2004;18:1263-8; discussion1268-70,1275.

42. Ciatto S, Houssami N, Ambrogetti D, Bonardi R, Collini G, Del Turco MR. Minority report - false negative breast assessment in women recalled for suspicious screening mammography: imaging and pathological features, and associated delay in diagnosis. Breast Cancer Res Treat 2007;105:37-43.

43. Ganry O, Peng J, Dubreuil A. Influence of abnormal screens on delays and prognostic indicators of screen-detected breast carcinoma. J Med Screen 2004;11:28-31.

44. Giess CS, Frost EP, Birdwell RL. Difficulties and errors in diagnosis of breast neoplasms. Semin Ultrasound CT MR 2012;33:288-99.

45. Youk JH, Kim EK, Kim MJ, Lee JY, Oh KK. Missed breast cancers at US-guided core needle biopsy: how to reduce them. Radiographics 2007;27:79-94.

46. Berg WA, Hruban RH, Kumar D, Singh HR, Brem RF, Gatewood OM. Lessons from mammographic-histopathologic correlation of large-core needle breast biopsy. Radiographics 1996;16:1111-30.

47. Parikh J, Tickman R. Image-guided tissue sampling: where radiology meets pathology. Breast J 2005;11:403-9.

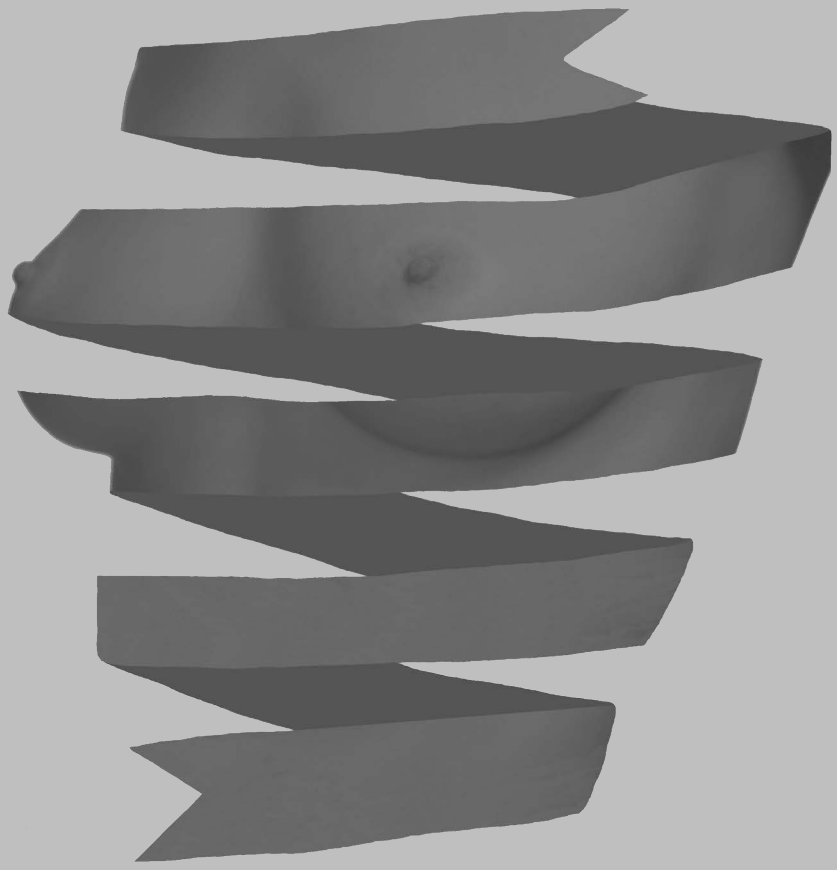
48. Dowling EC, Klabunde C, Patnick J, Ballard-Barbash R. Breast and cervical cancer screening programme implementation in 16 countries. J Med Screen 2010;17:139-46.

49. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann Oncol 2008;19:614-22.

50. Clarke-Pearson EM, Jacobson AF, Boolbol SK, Leitman IM, Friedmann P, Lavarias V, Feldman SM. Quality assurance initiative at one institution for minimally invasive breast biopsy as the initial diagnostic technique. J Am Coll Surg 2009;208:75-8.

51. Gutwein LG, Ang DN, Liu H, Marshall JK, Hochwald SN, Copeland EM, Grobmyer SR. Utilization of minimally invasive breast biopsy for the evaluation of suspicious breast lesions. Am J Surg 2011;202:127-32.

Chapter 5
General Discussion



Despite the favourable evidence of many trials and population based studies, there is an continuing debate on the effectiveness and potential disadvantages of breast cancer screening. With the intention to end the debate, an independent review article on the benefits and harms of breast cancer screening has recently been published in the Lancet.[1] The British authors used data from 10 breast cancer screening trials, including data from the 8 trials that are discussed in the Cochrane review.[2] They concluded that screening reduces breast cancer mortality with 20% and that the overall overdiagnosis rate is an acceptable 11%. The authors therefore recommended a continuation of breast cancer screening in the United Kingdom (UK).

Also in the Netherlands the benefits of breast cancer screening seem to outweigh the harms. However, despite of the encouraging screening results, there is still room for improvements. Interval cancer (IC) rates are a major determinant of the success of a screening programme and both Dutch national data and data of the southern screening region of the Netherlands show that the incidence of ICs remained more or less stable since the introduction of screening. This is somewhat disappointing, because due to many improvements in the quality of screening in the past years, one would expect a reduction in IC rates. IC rates are closely related to screening sensitivity and as screening mammography sensitivity is only about 70-80%, there is a potential for a further improvement of screening results. In this thesis several factors are explored that influence screening mammography sensitivity. The studies have been performed at 2 screening centres in the southern breast cancer screening region of the Netherlands.

In this thesis I studied:

1. The current sensitivity of screening mammography, missed cancers at screening and related malpractice claims
2. The effect of replacing single-view by two-view mammography in subsequent screening rounds
3. The impact of prior benign breast surgery on the sensitivity of screening mammography and trends in the use of breast biopsies for (benign) screen detected breast lesions

Current screening sensitivity, missed cancers and malpractice claims

Current sensitivity

In the first study of this thesis (Chapter 2) we found that the sensitivity of screening mammography in the southern screening region of the Netherlands was 73%. This percentage corresponds with the 70-80% sensitivity reported in international studies.[3,4] The moderate sensitivity makes mammography not a perfect screening test, however, as mentioned in the General Introduction of this thesis, at present only mammography seems to be an appropriate modality for breast cancer screening in the general population.

Missed cancers

Between January 1, 1997 and January 1, 2009 a total of 351,009 screens were performed at two screening centres in the southern breast cancer screening region of the Netherlands. Two experienced screening radiologists reviewed the screening mammograms of all screen

detected cancers and interval cancers diagnosed in this period. This included mammograms of 1,475 women with a screen detected cancer (SDC) at a subsequent screening round and 670 women with an IC (Figure). The review demonstrated that 21% of the SDCs had been missed at the previous screening mammogram and that 22% of SDCs had been visible as a minimal sign. Review of screening mammograms from the women with an IC showed that 24% of the breast cancers had been missed at the latest screening mammogram, whereas another 25% had been visible as a minimal sign.

The missed cancer rates in our study are substantial, but in line with those observed in other mass mammography screening programmes.[5-7] Furthermore, it is important to realise what the principle goal of breast cancer screening is. Screening is initiated by the government with the assumption that early cancer detection improves curative chances. At screening mammograms will be categorized as normal or abnormal/needs further investigation. In women with a normal screening mammogram, however, the absence of breast cancer cannot be excluded with certitude. Screening for disease in asymptomatic women is far different from investigating a mammogram of a symptomatic woman with breast complaints. Women who present themselves with breast complaints in a hospital will undergo a physical examination, a mammogram and, if necessary, additional imaging. Furthermore, to confirm the diagnosis, a needle aspiration (fine-needle aspiration cytology (FNAC)) or biopsy can be done. This almost watertight combination is not available at screening, at screening there is only a mammogram.

As mentioned before, the sensitivity of screening mammography is only 70-80% and this depends on several factors, including the radiologists' interpretation. The radiologists' interpretation is a complex interplay of elements that influence visual perception and it is known that cancers can be misinterpreted or overlooked. Research has shown that rare abnormalities are easily missed, and the low prevalence of breast cancer at screening mammograms could therefore negatively influence the detection rate.[8] Furthermore, some cancers are just not visible at mammography[9] as eye-tracking experiments show that also at blinded review radiologists do not spot these cancers, meaning that some cancers seem intrinsically undetectable.[10] To improve the detection of breast cancers at screening we could try to improve screening sensitivity, as described in Chapter 3 and 4 of this thesis. Furthermore, we could try to improve the radiologists' interpretation. The radiologists' performance can be improved by regular review of (missed) interval cancers, because learning about the characteristics of these cancers can help to detect them in future mammograms.[11] Review of interval cancers is therefore recommended by European screening guidelines and is part of the quality assurance programme of screening mammography in the Netherlands.[12] Missed cancers should thus not only be regarded as diagnostic errors, they should also be seen as learning oppurtunities.[13] Therefore close monitoring and registration of interval cancers is important.

Besides missed cancers, a substantial proportion of the cancers in our study were at retrospect visible as a minimal sign on the previous mammogram. Small vague densities, indefinable micro-calcifications and subtle architectural distortions are non-specific appearances of breast cancer and are considered as minimal signs.[14] In the Netherlands women with a

nonspecific minimal sign at mammography are not referred because minimal signs have a less than 1% chance of malignancy and are present at about 10% of screening mammograms.[14] Referral of all minimal signs would therefore result in a substantial increase of false positive referrals. We do not know the impact of minimal signs at digital mammography on screening outcome parameters yet. Further research is needed to decide whether it would be useful to refer certain subsets of minimal signs in the current digital screening setting.

Malpractice claims

The Physicians Insurers Association of America (PIAA) reported, first in 1995 and once more in 2002, that a delay in breast cancer diagnosis had become the most common reason for medical malpractice lawsuits in the United States (US).[15] Through the high amount of breast cancer-related lawsuits the radiologist has become the most litigated physician in the US and as a consequence the number of radiologists willing to read mammograms in the US is decreasing. This trend may impede access to breast cancer screening in the US in the future.

Lawsuits concerning delays in breast cancer diagnosis are based on the fact that a delay may reduce breast-conserving treatment options and prognosis. Researchers describe that women with a delay of 3 months or more have a 12% lower 5-year survival compared to women with a delay of less than 3 months.[16] Moreover, the risk of advanced or metastatic disease seems to increase with 22% for women with a delay of 3 months or more, compared to delays of less than 3 months.[17] It is, however, important to realize that not all women with cancer that is detectable at retrospect would have had an improved prognosis with earlier detection. For example, women with Ductal Carcinoma In Situ (DCIS) or a slow growing invasive tumour will not necessarily suffer from a delayed diagnosis.

Breast cancer incidence in the US is 122/100,000 person years (2009, US standardised rate)[18] and thus comparable with the incidence in the Netherlands (128/100,000 ESR). The US breast cancer screening programme, however, differs from the Dutch programme in several aspects. For example, women are offered annual rather than biennial screening mammography in US programmes and US referral rates of 10% are much higher than the 1-2% referral rates observed in the Netherlands. The high amount of malpractice claims regarding screening mammography in the US can possibly be explained by the public's high expectations of mammography performance. The limitations of screening are often poorly understood and this is probably the result of screening campaigns, which tend to emphasize only the benefits of screening. Also the media give a distorted image of the benefits of screening, the screen detected breast cancer of former US president's wife Nancy Reagan, has for example, been widely discussed in the media. It is therefore important to inform women about the probability that a cancer can be 'missed' at screening. In the Netherlands women receive detailed information about breast cancer and screening at the time of screening invitation. This results in a realistic knowledge on screening and probably avoids false-reassurance.[19] Also the possibility of a 'no-win-no-fee' policy for US lawyers and high awards paid to patients following a jury verdict could influence the amount of claims. A majority of claims is related to mammographic misinterpretation and failure to communicate openly with patients about these errors.[20,21] Discussing errors with patients could enhance their satisfaction and an open and clear communication with screened women may thus reduce the number of malpractice

claims.[22] However, fear of lawsuits makes disclosure of medical errors to patients difficult and recent studies suggest that communicating openly about errors is the exception rather than the rule.[23,24]

Few data have been published with respect to screening mammography claims in Europe and no data have been published on the risk of claims in the Netherlands. We therefore decided to determine the type and frequency of malpractice claims in our breast cancer screening region. Despite of 21% missed SDCs and 24% missed ICs, only 19 women (0.8% of women with a SDC or IC) contacted the screening organisation between 1997 and 2011. Of these women, 8 had a SDC (one of these had been missed at the last-but-one screening mammogram) and 11 women were diagnosed with an IC (two of them were missed at the latest screening mammogram). Subsequently, all 19 women had a conversation with the coordinating screening radiologist of our screening region, either by telephone or by face to face contact. None of these 19 women started a malpractice lawsuit or insurance claim for financial compensation. A total of 3 women with an IC initiated an insurance claim for financial compensation without previously having contacted the screening organization. One of these claims has been rejected (latest screen showed a minimal sign lesion), whereas the verdicts of the other 2 claims (two ICs that had been missed at the latest screen) still have to be finalized. Although false positive (FP) referrals result in unnecessary diagnostics and anxiety, only 1 woman (out of 2,671 FP referrals) complained about her false positive referral and she demanded the screening organization for compensation of the costs of her clinical mammogram and breast ultrasonography. The Dutch breast cancer screening programme does, however, not cover any costs related to diagnostic procedures after referral. Finally, we also determined whether any of the true positive referred women filed a claim, because of a delay in breast cancer diagnosis after referral. A total of 89 women (5% of referred women) experienced a more than 3 months delay in cancer diagnosis after referral. These delays were most frequently due to erroneous interpretation or classification of breast lesions at clinical breast imaging. None of these women filed a malpractice claim (Figure).

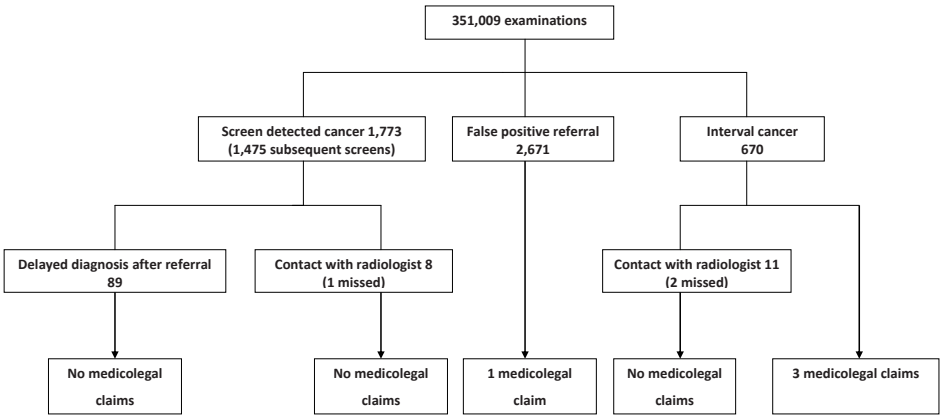


Figure. *Malpractice claims at screening mammography.*

We attributed the low rate of malpractice claims to the following factors:
- The open communication between the screening radiologist and screened women
- Sufficient information about breast cancer screening before participation
- The organisation of the Dutch justice system (relatively low payouts when one wins a claim and absence of a 'no-win-no-fee' policy for lawyers)
- A good communication between women and physicians at the hospitals

The finding that the risk of a lawsuit is low may be of value for screening radiologists, as the risk of lawsuits may cause uncertainty of the interpreting radiologist and can result in higher recall rates and a lower positive predictive value of referral.[25,26] Low numbers of false positive referrals are important because they limit the number of women experiencing referral related anxiety as well as workup costs.

Attention for missed cancers and women that contact the screening organisation for questions related to their SDC or IC remains, however, important. The number of women that contacted the screening organisation increased during the years of our study, as a majority of the 19 women (11/19; 58%) that contacted the screening organisation had been screened between 2005-2009. This finding suggests that the proportion of women who contact the screening organization after a diagnosis of breast cancer will probably increase in the future and finally also the number of malpractice claims may increase. It is therefore important that the Radiological Society of the Netherlands (NVvR) develops a protocol for the communication with women who contact screening organisations with questions related to missed cancers and for medicolegal cases. In court the judge will have to decide whether the conduct of the radiologist, who owes the patient a duty of care, was a breach of that duty because it fell below the standard of care. Courts commonly require input from an expert to determine whether the assessment of the defending radiologist met the standard. These expert witnesses are asked to review mammograms with the 'missed' cancers. However, studies have shown that with outcome knowledge, radiologists report many more abnormalities when re-examining a mammogram than at blinded review.[6,27] Therefore a blinded review protocol for assessment of missed cancers in medico-legal cases is essential.[27,28] A protocol for blinded review of slides in clinical pathology has recently be designed[29] and the NVvR should endeavour to develop such a protocol for radiology, as this will improve the status of the radiologist in litigation procedures and it will accelerate the completion of medico-legal trials.

The effect of replacing single-view by two-view mammography in subsequent screening rounds

Two-view mammography at initial and subsequent screening increases the detection of breast cancer with 24-45%, if compared to single-view mammography.[30,31] Moreover, two-view mammography can especially increase the detection of invasive lobular carcinoma, a type of cancer that is usually difficult to identify at mammography. This type of cancer occurs in 5-15% of breast cancer patients and is better visible on cranio-caudal (CC) views.[32] Finally, two-view mammography may decrease referral rates.[30,33,34] Because of these advantages, many countries use standard two-view mammography in their screening programmes, both at initial and subsequent screening rounds. European guidelines recommend standard two-

view mammography as well.[12] In the Netherlands however, until recently, we used two-view mammography at initial screening and single-view mammography (mediolateral oblique, MLO) at subsequent screening. At subsequent screening an additional CC-view was obtained only if indicated. This second view was obtained at the discretion of the radiologic technician and indications for two-view mammography included dense breast tissue, previous breast surgery, any changes in mammographic findings (such as new or increased densities or microcalcifications) and a more than two-year interval since the previous screen. This policy for subsequent screens was used because of concerns about the effects of radiation exposure and because of financial considerations. Standard two-view mammography increases costs as it is more time consuming and results in more film copies or, in the digital screening setting, an increase of data storage.

In our study (Chapter 3), based on analogue mammograms obtained between January 1997 and July 2008, we found that two-view mammography in subsequent screens could have facilitated earlier detection of breast cancer in 40% of women with a SDC or IC. This high percentage is of course influenced by hindsight-bias; the radiologists knew that they were reviewing mammograms with cancers. Furthermore, even at two-view mammography 24% of SDCs and 29% of ICs appeared to be missed at a previous screening examination. When making a cautious estimation, I think that approximately 10-15% of women with a SDC or IC will benefit from standard two-view mammography in subsequent screening rounds. Especially women diagnosed with an IC could benefit from standard two-view mammography, as 41% of the missed ICs in our study were T2+ tumours and 50% of the women with a missed IC had axillary lymph node metastasis. Besides the effect on breast cancer detection, we also determined the financial consequences of standard two-view mammography in subsequent screening rounds. This calculation was based on a digital screening setting as the Dutch breast cancer screening programme has been completely digitized in 2010. Implementation of standard digital two-view mammography will increase costs with €1.03/screen. Standard two-view mammography will therefore marginally increase the overall screening costs by less than 2%.

Concerns on radiation exposure may not be too relevant in the Dutch screening setting. Two recent Dutch studies on radiation exposure reported a lower risk of inducing breast cancer by screening mammography than previously assessed.[35,36] Furthermore, the conversion of the Dutch breast screening programme from analogue to digital screening is expected to result in a further decrease of radiation exposure.[37]

The Netherlands has recently implemented a full digital breast screening programme. The first digital screening round included a two-view mammogram for each participating woman. Therefore, conversion to standard two-view mammography was not that radical and when the first digital screening round was completed, the National Expert and Training Centre For Breast Cancer Screening (LRCB) recommended a continuation of standard two-view mammography at subsequent screening rounds. Our study played an important role in this recommendation and the National Institute for Public Health and the Environment (RIVM) has recently decided to temporarily comply with routine two-view screening. A request for

a permit for routine two-view screening mammography has been submitted with the Health Council and we expect a positive advice to the secretary of Health in due time.

Impact of prior benign breast surgery on the sensitivity of screening mammography

Sensitivity of screening mammography after benign breast surgery

Studies report that in up to 50% of mammograms of women with prior benign breast surgery (including surgical biopsies), postoperative mammographic alterations can be visible.[38,39] This high incidence of mammographic changes after previous benign breast surgery may have a substantial influence on the interpretation of mammography at screening programmes. We decided to determine the proportion of screened women with prior benign breast surgery and to examine the impact of benign breast surgery on the sensitivity of subsequent screening mammography (Chapter 4.1). Our study showed that approximately 7% of women screened in the south of the Netherlands had a history of benign breast surgery. The sensitivity of screening mammography for the detection of cancer in non-operated breasts was 73%, whereas the sensitivity for breasts with a history of benign breast surgery was significantly lower, namely 64%.

Only two other studies have reported on the sensitivity of screening mammography after previous benign breast surgery.[40,41] Both studies have been performed in the US and in these studies the proportion of women with prior benign surgery was 11.6% and 14.6%, respectively. These high rates are probably explained by higher referral rates in the US and higher rates of diagnostic surgical biopsies. Taplin et al. found a borderline significant decreased sensitivity after benign breast surgery and a 2.4% significant decrease in specificity.[40] Banks et al. reported a 5.9% decrease in mammography sensitivity after benign breast surgery.[41] Taplin et al. suggested that the lower sensitivity in women with prior benign breast surgery was probably the result of breast tissue characteristics rather than due to alterations resulting from the prior surgery. They assumed that the intrinsic characteristics of the breast tissue, such as fibrocystic changes (FCC) or fibroglandular breast structure, were responsible for the interpretive differences and that the biopsy history was an associated phenomenon. On the other hand, as mentioned before, postsurgical changes are visible in up to 50% of mammograms after benign breast surgery. Therefore, postsurgical changes may also be responsible for the lower sensitivity of mammography following benign breast surgery.

Cause of lower sensitivity of screening mammography after benign breast surgery

As the cause of the lower sensitivity after benign breast surgery remained unclear, we decided to examine possible explanations for this lower sensitivity in another study (Chapter 4.2). In this study we concluded that the lower sensitivity of screening mammography after previous benign breast surgery is likely due to postoperative mammographic changes and not the result of specific breast tissue characteristics. Postoperative alterations in the breast segment of the cancer were significantly more distinct in ICs than in SDCs. Furthermore, breast cancers that emerged in the same breast segment as the postsurgical changes were significantly more frequently diagnosed as IC rather than SDC. Breast density at the latest screening examination was similar for SDCs and ICs that had been detected in postoperative breasts

and the reviewers rarely reported that specific tissue characteristics, such as fibrocystic disease or extensive calcifications, hampered mammographic interpretation.

The current screening guidelines pay no attention to women with prior benign breast surgery. Approximately 1,000,000 women yearly undergo screening in the Netherlands. When assuming that about 7% of these women have a history of benign breast surgery, then around 70,000 screened women may be exposed to a decreased sensitivity at screening at a yearly base. A screening mammography sensitivity of about 64% after prior benign breast surgery implies that approximately 1 out of 3 breast cancers will be missed at screening. Furthermore, a sensitivity of 64% corresponds with the overall 57-70% sensitivity of screening mammography after breast-conserving therapy for breast cancer.[42,43] Dutch screening guidelines recommend annual clinical mammography after breast-conserving therapy because of the lower sensitivity of screening.[44] If future research confirms our results, women with prior benign breast surgery should at least be informed about the effects on mammographic sensitivity. When properly informed, women could decide by themselves to choose between a clinical mammogram or screening examination. If research demonstrates that screening mammography sensitivity after benign breast surgery actually equals mammography sensitivity after breast-conserving surgery for breast cancer, it should even be considered to offer women with previous benign breast surgery a biennial outpatient mammographic examination as an alternative to routine screening mammography. In an outpatient setting, additional mammographic views and/or complementary breast ultrasound can easily be obtained if the radiologist encounters difficulties with mammographic interpretation. This policy will obviously increase screening costs. However, these increased costs will only be temporary as the prevalence of women with benign breast surgery will decrease in the future due to a decreased use of surgical biopsies in the workup of breast abnormalities. The trends in biopsies for (benign) breast lesions are examined in our final study (Chapter 4.3).

Trends in biopsies for (benign) screen detected breast lesions

There are various breast biopsy procedures available, including percutaneous fine-needle aspiration cytology (FNAC), percutaneous core-needle biopsy (CB) (ultrasound- or stereotactic guided) and open surgical biopsy (excisional biopsy). We determined trends in biopsies for abnormalities detected at screening mammography (Chapter 4.3) and paid extra attention to trends in surgical biopsies for benign breast lesions. Between January 1, 1997 and January 1, 2011 the use of diagnostic surgical biopsies for workup of screening mammography abnormalities decreased substantially. The use of diagnostic surgical biopsies for benign lesions decreased from 23% (1997-1998) to 2% (2009-2010) and simultaneously the use of CB increased from 2% to 34%. The use of diagnostic surgical biopsies for malignant lesions decreased from 59% to 1%, whereas the amount of CB increased from 17% to 97%. Thus, nowadays mainly CBs are employed for obtaining a histological diagnosis in lesions detected at screening mammography. Currently, surgical biopsy is only performed in one of the following situations:

- In case of a non-representative percutaneous biopsy
- In case of a high risk lesion or premalignant finding at percutaneous biopsy
- If patient characteristics impede percutaneous biopsy (e.g. severe obesity, inability to perform percutaneous biopsy in unwilling patients)

We believe that the replacement of surgical biopsies by percutaneous biopsies was probably due to the introduction and revision of Dutch breast cancer guidelines.[44,45] The first guideline, published in 2000, required a target for a preoperative diagnosis in women with suspected breast cancer of at least 70%, using either FNAC or CB. The revised 2008 guideline increased this target to 90%. The decrease of surgical biopsies is beneficial for both women with benign and malignant outcome. Women with a benign diagnosis will no longer present with postoperative alterations that might hamper the interpretation of subsequent mammography. Women with a malignancy nowadays rarely undergo surgery without a preoperative diagnosis. This provides the patient and surgeon the possibility to discuss treatment options and it allows a better preoperative planning. Also, a preoperative diagnosis is associated with a lower likelihood of multiple breast surgeries.[46,47]

The replacement of surgical biopsies by percutaneous biopsies may hypothetically have resulted in more delays (defined as a breast cancer diagnosis more than 3 months after referral)[15] in breast cancer diagnosis due to more false negative biopsies. Therefore, we also determined the frequency and causes of diagnostic delays in our study population. Delays in the diagnosis of breast cancer decreased from 7% (1997-1998) to 2% (2009-2010). The replacement of surgical biopsies by CBs did thus not result in more diagnostic delays and CBs thus seem to be a reliable alternative for surgical biopsies.

Interpretation of our results

The relevance of the studies for the current digital screening setting

The transition from analogue to digital screening in the Netherlands was completed in 2010. All the studies in this thesis are based on analogue screening mammograms, however, our outcomes will also be relevant for the current digital screening setting. With our studies we aimed to improve screening sensitivity and to decrease the IC rates. Several studies on the implementation of digital screening in the Netherlands report that referral rates have increased when compared to analogue screening, and that this includes high numbers of false-positive referrals.[48,49] However, cancer detection has also improved, especially for cancers showing micro-calcifications (DCIS as well as certain invasive cancers). These conclusions are comparable with the latest report of the NETB, that shows several changes in screening outcome parameters over the past years.[50] These changes are probably mainly the result of the digitization of the screening programme. Referrals increased, including many false-positive referrals (from 8.1/1,000 screened women in 1998-2005 to 14.3/1,000 in 2010) and the positive predictive value of referral showed a dramatically decrease (from 38% in 1998-2005 to 29% in 2010). There are no Dutch studies available yet that examine the effect of digitisation on screening mammography sensitivity and IC rates. Skaane et al. reported a 15% increased sensitivity for digital mammography in Norway.[51] However, the screening sensitivity of the analogue mammograms in their study was somewhat low (61.5%). Hoff et al. recently reported that digital screening mammography in Norway does not decrease IC rates when compared to analogue screening.[52] Therefore, also in the digital screening setting improvements leading to an increased mammographic sensitivity are welcome.

After our publication on the benefits of routine two-view screening mammography, the RIVM decided to temporarily continue with two-view mammography at subsequent screening

rounds in the current digital screening setting and a request for a permit for routine two-view mammography has been submitted with the Health Council. Our study was very important for the recommendation to change the policy, and therefore one of the studies in this thesis has already proven to be of additional value for digital breast cancer screening.

The specific effect of digital screening mammography on cancer detection in postsurgical breasts is yet unknown. I expect that the interpretational problems will not be solved by digital mammography. The increased local contrast at digital mammography increases the detection of breast cancers, however it also increases the suspiciousness of normal breast tissue.[53] Therefore digital mammography may accentuate scar tissue and could therefore potentially increase false positive referrals or hamper the detection of underlying cancers. Further research is needed to determine the exact consequences of prior benign and malignant breast surgery on the interpretability of digital mammograms. If breast cancer detection is hampered in both groups, also women with prior benign breast surgery will need special attention.

Meaning of the study results for the southern breast cancer screening region

The current sensitivity of breast cancer screening at Breast Cancer Screening South (BOZ) is approximately 73%, meaning that a considerable proportion of cancers is still missed at screening and this probably has a negative impact on prognosis. When we are able to improve the sensitivity and decrease the proportion of ICs, breast cancer death rates may further decrease.

Our study on the consequences of replacing single-view by two-view mammography has contributed to the (temporarily) adaptation of performing standard two-view mammography at subsequent screening. I estimate that approximately 10-15% of women with a SDC or IC will benefit from standard two-view mammography by means of earlier cancer detection. Currently, more than 1,200 breast cancers are annually detected at screening in the southern breast cancer screening region of the Netherlands. Therefore, at least 120-180 women will yearly benefit from two-view mammography. Unfortunately, recent IC rates of the entire southern screening region are not available yet, so I am unable to estimate the amount of women that will benefit from two-view mammography in this particular group.

We found a 9% lower sensitivity of screening mammography in women with a history of benign breast surgery. In the southern screening region of the Netherlands approximately 7% of women report a history of benign breast surgery. This means that around 14,000 out of the 200,000 women screened each year at BOZ are exposed to a decreased mammography sensitivity due to prior benign breast surgery. About 1 out of 3 breast cancers will be missed in these women at routine screening mammography, resulting in a delay and possible worsening of prognosis. As mentioned before, further research of (digital) screening mammography sensitivity in women with prior benign breast surgery is needed. If future studies confirm our findings of a significantly lower screening sensitivity following benign breast surgery, these women should at least be informed about this potential shortcoming. It should also be considered to offer these women regular clinical mammography instead of routine screening.

Conclusion

The incidence of breast cancer in the Netherlands is among the highest in the world and the incidence is still increasing. It is also one of the most important causes of cancer death in Dutch women and therefore decreasing breast cancer mortality is important. The implementation of screening and improvements of treatment have increased breast cancer survival in the past decades. Screening results are, however, not optimal yet as a substantial proportion of cancers is still missed at screening mammography. Cancer detection can be improved by optimizing the sensitivity of screening. Standard two-view mammography increases breast cancer detection and currently all women participating in the Dutch breast cancer screening programme undergo standard two-view mammography. The exact effect of prior benign breast surgery on screening mammography sensitivity, especially in the current digital screening setting, has to be examined by further studies. If other studies confirm that the sensitivity of screening mammography after benign breast surgery actually equals the mammographic sensitivity after treatment for breast cancer, it should be considered to also offer women with prior benign breast surgery a regular clinical mammography as an alternative to routine screening. Finally, it remains important to continue the careful monitoring of the Dutch screening results. Monitoring gives us the opportunity to examine screening outcomes and to continue improving breast cancer screening results. Regional cancer registries, as the Eindhoven Cancer Registry (IKZ), should play a key role in this monitoring, by collection of data, stimulation of local research and stimulation in improvement of local treatment. Furthermore, interval cancer rates are a major determinant of the success of screening and therefore, as part of the monitoring, the registration of interval cancers should be improved by systematic linking of regional screening organisation data and data of local cancer registries.

In the near future mammography will likely remain the only appropriate screening modality for breast cancer, as other possible screening methods, like, for example, measurement of breast cancer related biomarkers in the blood,[54] are still under development. Only with optimal results women will remain attending for screening and therefore we should focus on improvements of breast cancer screening. Furthermore, optimisation of screening results will probably result in a further decrease of breast cancer related mortality.

References

1. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet 2012;380:1778-86.
2. Gøtsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? Lancet 2000;355:129-34.
3. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of the factors that influence them: an analysis of 27,825 patient evaluations. Radiology 2002;225:165-75.
4. Yankaskas BC, Cleveland RJ, Schell MJ, Kozar R. Association of recall rates with sensitivity and positive predictive values of screening mammography. AJR 2001;177:543-9.
5. Hoff SR, Abrahamsen AL, Samset JH, Vigeland E, Klepp O, Hofvind S. Breast cancer: missed interval and screening-detected cancer at full-field digital mammography and screen-film mammography-- results from a retrospective review. Radiology 2012;264:378-86.
6. Hofvind S, Skaane P, Vitak B, Wang H, Thoresen S, Eriksen L, Bjørndal H, Braaten A, Bjurstam N. Influence of review design on percentages of missed interval breast cancers: retrospective study of interval cancers in a population-based screening program. Radiology 2005;237:437-43.
7. Hoff SR, Samset JH, Abrahamsen AL, Vigeland E, Klepp O, Hofvind S. Missed and true interval and screen-detected breast cancers in a population based screening program. Acad Radiol 2001;18:454-60.
8. Wolfe JM, Horowitz TS, Van Wert MJ, Kenner NM, Place SS, Kibbi N. Low target prevalence is a stubborn source of errors in visual search tasks. J Exp Psychol Gen 2007;136:623-38.
9. Yankaskas BC, Schell MJ, Bird RE, Desrochers DA. Reassessment of breast cancers missed during routine screening mammography: a community-based study. AJR 2001;177:535-41.
10. Nodine CF, Mello-Thoms C, Weinstein SP, Kundel HL, Conant EF, Heller-Savoy RE, Rowlings SE, Birnbaum JA. Blinded review of retrospectively visible unreported breast cancers: an eye-position analysis. Radiology 2001;221:122-9.
11. de Rijke JM, Schouten LJ, Schreutelkamp JL, Jochem I, Verbeek AL. A blind review and an informed review of interval breast cancer cases in the Limburg screening programme, the Netherlands. J Med Screen 2000;7:19-23.
12. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann Oncol 2008;19:614-22.
13. Pinto A, Acampora C, Pinto F, Kourdioukova E, Romano L, Verstraete K. Learning from diagnostic errors: a good way to improve education in radiology. Eur J Radiol 2011;78:372-6.
14. Maes RM, Dronkers DJ, Hendriks JH, Thijssen MA, Nab HW. Do non-specific minimal signs in a biennial mammographic breast cancer screening programme need further diagnostic assessment? Br J Radiol 1997;70:34-38.
15. Physician Insurers Association of America. PIAA 2002 breast cancer study. Rockville: Physician Insurers Association of America; 2002.
16. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet 1999; 353:1119-26.
17. Richards MA, Smith P, Ramirez AJ, Fentiman IS, Rubens RD. The influence on survival of delay in the presentation and treatment of symptomatic breast cancer. Br J Cancer 1999;79:858-64.
18. Website of the Department of Health and Human Services Centres for Disease Control and Prevention. http://apps.nccd.cdc.gov/uscs/toptencancers.aspx (accessed October 31, 2012)
19. de Gelder R, van As E, Tilanus-Linthorst MM, Bartels CC, Boer R, Draisma G, de Koning HJ. Breast cancer screening: evidence for false reassurance? Int J Cancer 2008;123:680-6.
20. Berlin L. Breast cancer, mammography, and malpractice litigation: the controversies continue. AJR 2003;180:1229-37.

21. Kopans DB. Mammography screening is saving thousands of lives, but will it survive medical malpractice? Radiology 2004;230:20-4.

22. Berlin L. Malpractice and ethical issues in radiology: the duty to communicate. AJR 2011;197:W962.

23. Gallagher TH, Cook AJ, Brenner RJ, Carney PA, Miglioretti DL, Geller BM, Kerlikowske K, Onega TL, Rosenberg RD, Yankaskas BC, Lehman CD, Elmore JG. Disclosing harmful mammography errors to patients. Radiology 2009;253:443-52.

24. Robinson AR, Hohmann KB, Rifkin JI, Topp D, Gilroy CM, Pickard JA, Anderson RG. Physician and public opinions on quality of health care and the problem of medical errors. Arch Intern Med 2002;162:2186-90.

25. Smith-Bindman R, Chu PW, Miglioretti DL, Sickles EA, Blanks R, Ballard-Barbash R, Bobo JK, Lee NC, Wallis MG, Patnick J, Kerlikowske K. Comparison of screening mammography in the United States and the United Kingdom. JAMA 2003;290:2129-37.

26. Carney PA, Yi JP, Abraham LA, Miglioretti DL, Aiello EJ, Gerrity MS, Reisch L, Berns EA, Sickles EA, Elmore JG. Reactions to uncertainty and the accuracy of diagnostic mammography. J Gen Intern Med 2007;22:234-241.

27. Semelka RC, Ryan AF, Yonkers S, Braga L. Objective determination of standard of care: use of blind readings by external radiologists. AJR 2010 Aug;195:429-31.

28. Giard RWM, Broekman JM. Objective re-evaluation procedures in cases of possible diagnostic error. Ned Tijdschr Geneeskd 2000;144:566-71. (in Dutch)

29. Giard RWM. 'When is the practice of pathology malpractice?'. J Clin Pathol 2010;63:957-961.

30. Wald NJ, Murphy P, Major P, Parkes C, Townsend J, Frost C. WUKCCCR multicentre randomised controlled trial of one and two view mammography in breast cancer screening. BMJ 1995;311:1189-93.

31. Blanks, RG, Moss SM, Wallis MG. Use of two view mammography compared with one view in the detection of small invasive cancers: further results from the National Health Service breast screening programme. J Med Screen1997;4:98-101.

32. Garnett S, Wallis M, Morgan G. Do screen-detected lobular and ductal carcinoma present with different mammographic features? Br J Radiol 2009;82:20-7.

33. Warren RM, Duffy SW, Bashir S. The value of the second view in screening mammography. Br J Radiol 1996;69:105-8.

34. Bryan S, Brown J, Warren R. Mammography screening: an incremental cost effectiveness analysis of two view versus one view procedures in London. J Epidemiol Community Health1995;49:70-8.

35. de Gelder R, Draisma G, Heijnsdijk EA, de Koning HJ. Population-based mammography screening below age 50: balancing radiation-induced vs prevented breast cancer deaths. Br J Cancer 2011;104:1214-20.

36. Bijwaard H, Brenner A, Dekkers F, van Dillen T, Land CE, Boice JD Jr. Breast cancer risk from different mammography screening practices. Radiat Res 2010;174:367-76.

37. Hendrick RE, Pisano ED, Averbukh A, Moran C, Berns EA, Yaffe MJ, Herman B, Acharyya S, Gatsonis C. Comparison of acquisition parameters and breast dose in digital mammography and screen-film mammography in the American College of Radiology Imaging Network digital mammographic imaging screening trial. AJR 2010;194:362-9.

38. Brenner RJ, Pfaff JM. Mammographic changes after excisional breast biopsy for benign disease. AJR 1996;167:1047-52.

39. Sickles EA, Herzog KA. Mammography of the post surgical breast. AJR 1981;136:585-8.

40. Taplin SH, Abraham L, Geller BM, Yankaskas BC, Buist DSM, Smith-Bindman R, Lehman C, Weaver D, Carney PA, Barlow WE. Effect of previous benign breast biopsy on the interpretive performance of subsequent screening mammography. J Natl Cancer Inst 2010;102:1040-51.

41. Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, Hilton E, Bailey S, Barrett N, Briers P, English R, Jackson A, Kutt E, Lavelle J, Rockall L, Wallis MG,Wilson M, Patnick J. Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study. BMJ 2004;329:477.

42. Houssami N, Abraham LA, Miglioretti DL, Sickles EA, Kerlikowske K, Buist DS, Geller BM, Muss HB, Irwig L. Accuracy and outcomes of screening mammography in women with a personal history of early-stage breast cancer. JAMA 2011;305:790-9.

43. Orel SG, Troupin RH, Patterson EA, Fowble BL. Breast cancer recurrence after lumpectomy and irradiation: role of mammography in detection. Radiology 1992;183:201-6.

44. Nationaal Borstkanker Overleg Nederland. CBO richtlijn mammacarcinoom. Amsterdam:NABON;2008. (in Dutch)

45. Rutgers EJT, Tuut MK. CBO-richtlijn 'Mammacarcinoom: screening en diagnostiek'. Ned Tijdschr Geneeskd 2001;145:115-9. (in Dutch)

46. James TA, Mace JL, Virnig BA, Geller BM. Preoperative needle biopsy improves the quality of breast cancer surgery. J Am Coll Surg 2012;215:562-8.

47. Friese CR, Neville BA, Edge SB, Hassett MJ, Earle CC. Breast biopsy patterns and outcomes in surveillance, epidemiology, and end results-medicare data. Cancer 2009;115:716-24.

48. Bluekens AM, Holland R, Karssemeijer N, Broeders MJ, den Heeten GJ. Comparison of digital screening mammography and screen-film mammography in the early detection of clinically relevant cancers: a multicenter study. Radiology 2012;265:707-14.

49. 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;23:3098-103.

50. National Evaluation Team for Breast Cancer Screening (NETB). NETB report 2012, main results 2010 breast cancer screening programme in the Netherlands. Rotterdam: Erasmus MC Rotterdam, Radboud University Nijmegen Medical Centre; 2012.

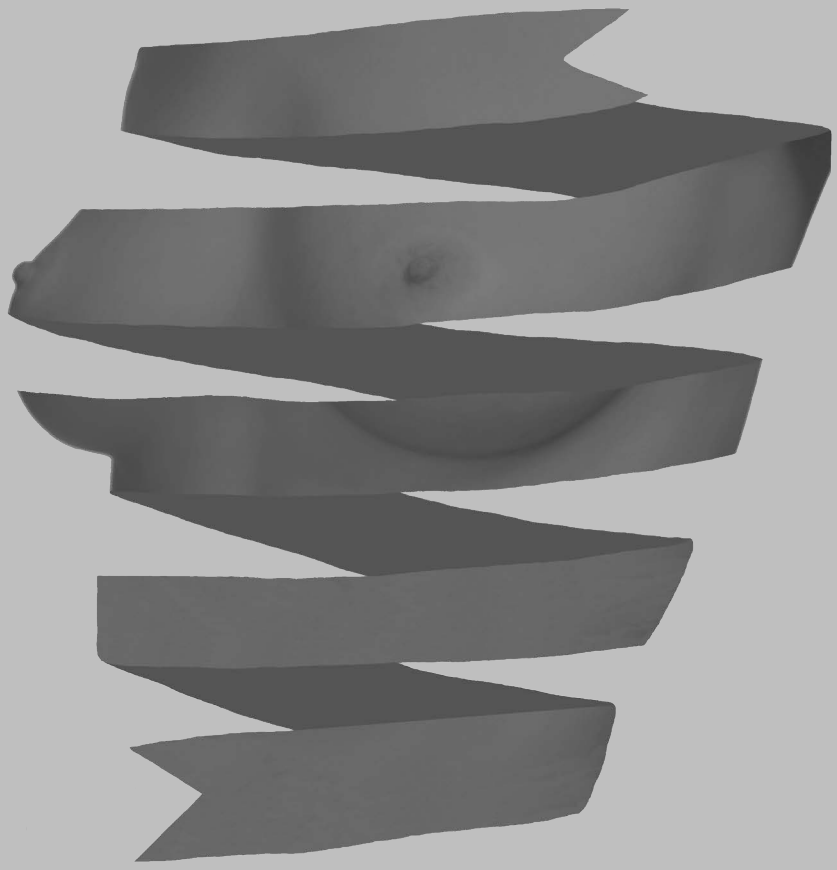
51. Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population-based screening program: follow-up and final results of Oslo II study. Radiology 2007;244:708-17.

52. Hoff SR, Abrahamsen AL, Samset JH, Vigeland E, Klepp O, Hofvind S. Breast cancer: missed interval and screening detected cancer at full field digital mammography and screen film mammography—results from a retrospective review. Radiology 2012;264:378-86.

53. Visser R, Veldkamp WJ, Beijerinck D, Bun PA, Deurenberg JJ, Imhof-Tas MW, Schuur KH, Snoeren MM, den Heeten GJ, Karssemeijer N, Broeders MJ. Increase in perceived case suspiciousness due to local contrast optimisation in digital screening mammography. Eur Radiol 2012;22:908-14.

54. Kloten V, Becker B, Winner K, Schrauder MG, Fasching PA, Anzeneder T, Veeck J, Hartmann A, Knuchel R, Dahl E. Promoter hypermethylation of the tumor suppressor genes ITIH5, DKK3, and RASSF1A as novel biomarkers for blood-based breast cancer screening. Breast Cancer Res 2013;15:R4.

Summary



Breast cancer is the most frequently diagnosed cancer around the world and the leading cause of cancer death among females. Also in the Netherlands breast cancer is an important threat for public health as the incidence of breast cancer in the Netherlands is among the highest in the world and the incidence is still increasing.

Many countries have introduced screening mammography programmes with the aim to reduce breast cancer mortality and in the Netherlands, a nation-wide breast cancer screening programme was implemented between 1989-1997. Since the start of breast cancer screening in the Netherlands, continuous improvements have been made in the awareness of breast cancer, the detection of breast cancer and treatment of breast cancer and this has resulted in a decrease of breast cancer mortality. The exact contribution of each improvement on breast cancer mortality is, however, difficult to determine.

About 10 years ago, the first critical appraisals were published on the effectiveness of breast cancer screening, and since then there has been an ongoing debate on the benefits and harms of screening. Several Dutch studies have concluded that breast cancer screening indeed reduces the risk of breast cancer death and the benefits of screening in the Netherlands seem to outweigh the harms. However, in spite of the good Dutch screening results, there is still room for improvement as interval cancer (IC) rates have more or less remained stable since the introduction of breast cancer screening. A reduction in IC rates will improve screening results and potentially further decreases breast cancer mortality. ICs have a close relationship with screening sensitivity and because the current sensitivity of screening mammography is only 70-80% there is room for improvements.

In this thesis several of the factors that influence screening mammography sensitivity are explored. In the second chapter of this thesis I describe the current sensitivity of screening, the rate of missed cancers at screening and related malpractice claims. In the third chapter the effect of replacing single-view by two-view mammography in subsequent screening rounds on screening outcome is examined and also its financial consequences. In the fourth chapter the impact of prior benign breast surgery on screening mammography sensitivity is examined, as well as trends in the use of biopsies for (benign) screen detected breast lesions. The studies have been performed in a southern screening region of the Netherlands in collaboration with Breast Cancer Screening South (BOZ) and the Comprehensive Cancer Centre South (IKZ).

Current sensitivity, missed cancers and malpractice claims

The sensitivity of screening mammography in the southern screening region of the Netherlands is currently 73% (Chapter 2). This corresponds with the sensitivity reported by international studies. Review of mammograms of women with a screen detected breast cancer (SDC) showed that 21% of these cancers had been missed at the previous screening examination. Review of screening mammograms of women with ICs showed that 24% of these cancers had been missed at the latest screening examination. During 1997-2011 only 19 women with breast cancer contacted the screening organisation for additional information. None of these women filed a claim. A total of 3 women with an interval cancer, who had not contacted the screening organisation, filed a malpractice claim. One claim has been rejected,

the others have still to be finalised. We can thus conclude that despite of the considerable proportion of missed cancers, women rarely asked for additional information and rarely filed a malpractice claim. An open communication between the screening organization and women who contacted the screening organisation was probably an important reason for the low number of claims. The number of women that contacted the screening organisation for additional information increased over the years and also the number of malpractice claims may increase in the future. It is therefore important that the Radiological Society of the Netherlands (NVvR) develops a protocol for the communication with women who contact screening organisations with questions related to missed cancers and a protocol should be developed for medicolegal trials.

Replacing single-view by two-view mammography in subsequent screening rounds

Many countries use standard two-view mammography in their screening programmes, as two-view mammography at initial and subsequent screening increases the detection of breast cancer when compared to single-view mammography. In the Netherlands, however, until recently, screening mammography consisted of two-view mammography at initial screening and single-view mammography (MLO) at subsequent screening. At subsequent screening an additional craniocaudal-view (CC-view) was obtained if indicated only. This policy of selectively performing a second view at subsequent screening was used because of concerns about the effects of radiation exposure and because of financial considerations. Review of a consecutive series of SDCs and ICs showed that two-view mammography at subsequent screens could have facilitated earlier detection of breast cancer in 40% of women with a SDC or IC (Chapter 3). However, the benefit of standard two-view mammography at subsequent screening rounds will probably be lower, as 24% of SDCs and 29% of ICs consisting of two-view mammography were missed at a previous screening examination. Implementation of standard digital two-view mammography will increase screening costs with €1.03/screen. So the replacement of selective two-view mammography by routine two-view mammography at subsequent screening will probably increase the detection rate of breast cancers, at the expense of a limited increase in screening costs.

Impact of benign breast surgery on screening mammography sensitivity

Sensitivity of screening mammography after benign breast surgery

Several studies report postoperative mammographic changes in women with a history of benign breast surgery. These mammographic changes may have a substantial influence on the interpretation of mammography in screening programs. Approximately 7% of women screened in the south of the Netherlands reported a history of benign breast surgery (Chapter 4.1). The sensitivity of screening mammography for the detection of cancer in non-operated breasts was 73%, whereas the sensitivity in breasts with a history of benign breast surgery was significantly lower, namely 64%. This finding implies that approximately 1 out of 3 breast cancers will be missed at screening in women with prior benign breast surgery. If further studies indeed confirm our observation that screening sensitivity is lower after benign breast surgery, women should be informed about this decreased sensitivity. The decreased sensitivity of screening mammography after benign breast surgery seems to

equal the decreased sensitivity after breast surgery for cancer. When studies confirm that the sensitivity after prior benign breast surgery is similar to the sensitivity after surgery for breast cancer, we should even consider to offer women with a history benign breast surgery a biennial outpatient mammographic examination as an alternative to routine screening mammography.

Cause of lower screening mammography sensitivity after benign breast surgery

It was unclear whether the lower screening sensitivity of breasts after benign surgery is due to postoperative mammographic changes or due to certain characteristics of the breast tissue. We found that the lower sensitivity of screening mammography after previous benign breast surgery is likely due to postoperative mammographic changes as postoperative alterations in the breast segment of the cancer were significantly more distinct in interval cancers than in screen detected cancers (Chapter 4.2). Furthermore, breast cancers that emerged in the same segment as the postsurgical changes, were more often diagnosed as ICs rather than SDCs. Finally, breast density at the latest screening examination was similar for SDCs and ICs that had been detected in postoperative breasts and the reviewers rarely reported that specific tissue characteristics hampered mammographic interpretation. Therefore, utmost attention should be paid at screening to mammographic breast segments showing postoperative changes in order to reduce the risk of interval cancer. Also, excision of breast lesions with conclusive, benign pathology at percutaneous biopsy should only be considered if a woman persists on removal of the lesion.

Trends in biopsies for (benign) breast lesions detected at screening

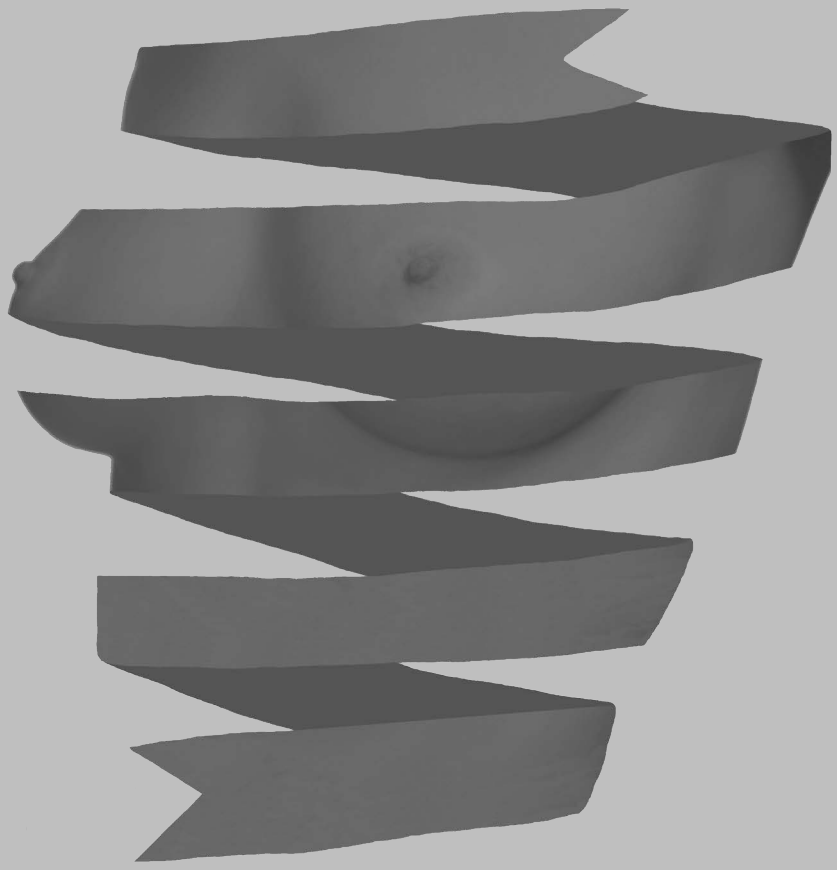
The aim of this study was to determine trends in breast biopsies used for the workup of abnormalities detected at screening mammography. We included all screens obtained at our breast cancer screening region between1997-2011. In women with a benign diagnosis after referral the use of fine-needle aspiration cytology (FNAC) remained more or less stable, from 8% to 6%. Benign diagnoses made by percutaneous core-needle biopsies (CB) increased from 2% to 34% and simultaneously diagnoses made by surgical biopsies decreased from 23% to 2%. In women diagnosed with breast cancer after referral, diagnoses made by FNAC decreased from 19% to 1%. Diagnoses made by CB increased from 17% to 97%, whereas diagnoses made by surgical biopsies decreased from 59% to 1%. Delays in the diagnosis of breast cancer decreased from 7% to 2%. Our study shows that the use of surgical biopsies for diagnostic workup of screening mammography abnormalities has decreased substantially, in both women with benign and with malignant outcome after referral. Surgical biopsies have mostly been replaced by CBs and this replacement did not result in more diagnostic delays.

Conclusion

The sensitivity of screening mammography in the southern screening region is currently 73%. Despite of missed cancer rates of over 20% women seldom file a malpractice claim. With an improvement of the sensitivity we can probably reduce the number of missed cancers. The sensitivity increases with the implementation of standard two-view mammography in both initial and subsequent screening rounds. Our study findings have resulted in a (temporarily) change of screening policy in the Netherlands; currently all women undergo standard two-

view mammography at both initial and subsequent screening rounds and a continuation of routine two-view screening in future screening rounds is expected. Furthermore, we found that women with a history of benign breast surgery have a significantly lower screening sensitivity because of postoperative mammographic changes. Currently approximately 7% of women in the southern screening region have a history of benign breast surgery. In the last years surgical biopsies have mostly been replaced by percutaneous core-needle biopsies for the workup of suspicious breast lesions and therefore I expect the number of women with a history of benign breast surgery to decrease in the future. The lower sensitivity in women with prior benign breast surgery possibly equals the sensitivity of mammography after surgery for breast cancer. If further studies confirm our findings, women with a history of benign surgery should be informed and we should consider to offer these women a biennial outpatient mammographic examination as an alternative to screening mammography. This will increase healthcare costs, however, this will also improve screening results and will probably improve the cancer detection in women with prior benign breast surgery. Furthermore, this increase of costs will only be temporarily because of the probable decrease in prevalence of women with prior benign breast surgery in the future.

Samenvatting



Borstkanker is wereldwijd de meest gediagnosticeerde kanker en de belangrijkste oorzaak van kankersterfte bij vrouwen. Ook in Nederland is borstkanker een belangrijke bedreiging voor de volksgezondheid, de incidentie van borstkanker in Nederland behoort namelijk tot de hoogste in de wereld en de incidentie neemt nog steeds toe.

Veel landen hebben borstkanker screening programma's ingevoerd om de borstkankersterfte te verminderen. In Nederland is gedurende 1989-1997 een landelijk bevolkingsonderzoek naar borstkanker ingevoerd. Verbeteringen in het bewustzijn van borstkanker, de invoering van de screening en de behandeling van borstkanker hebben geresulteerd in een daling van de borstkankersterfte. De precieze bijdrage van elke verbetering op de borstkankersterfte is echter moeilijk te bepalen.

Ongeveer 10 jaar geleden werden de eerste artikelen gepubliceerd die twijfelden aan de effectiviteit van borstkankerscreening en dit was het begin van een alsmaar voortdurende discussie over de voor-en nadelen van screening. Een aantal Nederlandse studies heeft geconcludeerd dat screening op borstkanker wel degelijk de aan borstkanker gerelateerde sterfte verminderd en tevens lijken de voordelen van de screening in Nederland op te wegen tegen de nadelen. Ondanks de goede Nederlandse screeningsresultaten, is er echter nog ruimte voor verbetering van de screening. Het percentage interval kankers (IK) is min of meer stabiel gebleven sinds de invoering van de borstkankerscreening. IK's worden ontdekt tussen 2 screeningsronden in en deze borstkankers hebben vaak een slechter tumorstadium en een slechtere prognose dan kankers die bij de screening worden ontdekt. Een verlaging van het aantal IK's zal de screenings resultaten verbeteren en mogelijk ook resulteren in een verdere daling van de borstkankersterfte. IK's hebben een nauwe relatie met de screenings sensitiviteit en omdat de huidige sensitiviteit van screenings mammografie slechts 70-80% is, is er ruimte voor verbeteringen.

In dit proefschrift worden een aantal factoren onderzocht die van invloed zijn op de sensitiviteit van screenings mammografie. In het tweede hoofdstuk van dit proefschrift beschrijf ik de huidige sensitiviteit van de screening, het aantal gemiste kankers de daarmee samenhangende medische schadeclaims. In het derde hoofdstuk wordt het effect van het vervangen van mammografie in 1 richting door mammografie in 2 richtingen in vervolgrondes van de screening onderzocht. Tevens wordt berekend wat de financiële gevolgen zouden zijn van de invoering van standaard screeningsmammografie in 2 richtingen. In het vierde hoofdstuk wordt de invloed van een benigne borstoperatie op de sensitiviteit van screenings mammografie onderzocht en worden de trends in het gebruik van biopten voor (goedaardige) borstlaesies weergegeven. De studies zijn uitgevoerd in een zuidelijke screenings regio van Nederland in nauwe samenwerking met Bevolkingsonderzoek Zuid en het Integraal Kankercentrum Zuid.

Huidige sensitiviteit, gemiste kankers en medische schadeclaims

De sensitiviteit van screenings mammografie in de zuidelijke screeningsregio van Nederland is 73%. Deze sensitiviteit wordt ook beschreven in internationale studies. Herbeoordeling van oude screeningsmammogrammen toonde dat 21% van de screenings gedetecteerde borstkankers (SGK) op het voorgaande mammogram was gemist. Uit herbeoordeling van

mammogrammen van vrouwen met een IK bleek dat 24% op het laatste screeningsonderzoek was gemist. Tijdens 1997-2011 namen slechts 19 vrouwen met borstkanker contact op met de screeningsorganisatie voor meer informatie. Geen van deze vrouwen heeft een claim ingediend. Drie vrouwen met een IK dienden een schadeclaim in, geen van deze vrouwen had van te voren contact opgenomen met de screenings organisatie. Eén schadeclaim is inmiddels afgewezen, de anderen moeten nog worden afgerond. Ondanks dat dus vrij veel kankers eerder hadden kunnen worden ontdekt, waren er nauwelijks vrouwen die om nadere informatie vroegen of een schadeclaim indienden. Waarschijnlijk is de open communicatie tussen de screeningsorganisatie en de vrouwen met borstkanker die contact opnamen voor aanvullende informatie een belangrijke reden voor het lage aantal claims. Het aantal vrouwen dat contact opnam met de screeningsorganisatie voor aanvullende informatie nam over de jaren toe. Mogelijk zal het aantal schadeclaims in de toekomst ook toenemen. Daarom moet de Nederlandse Vereniging voor Radiologie (NVvR) een protocol maken waarin staat beschreven hoe men het beste om kan gaan met vrouwen die nadere informatie willen over een gemist mammacarcinoom en een protocol over de gang van zaken in het geval van een medische schadeclaim.

Gevolg van een vervanging van mammografie in 1 richting door mammografie in 2 richtingen in vervolgronden van de screening

In vele landen wordt de borst bij de screening standaard in 2 richtingen afgebeeld omdat is aangetoond dat de detectie van borstkanker op een mammogram in 2 richtingen hoger is dan op een mammogram in 1 richting. In Nederland werd tot voor kort echter alleen in de eerste screeningsronde een mammogram in 2 richtingen gemaakt, in vervolgronden werd de borst in 1 richting afgebeeld. Alleen op indicatie werd in vervolgronden een tweede richting bijgemaakt. Dit werd gedaan omdat dit de stralenbelasting en de kosten zou beperken. Uit herbeoordeling van mammogrammen in 1 richting van vrouwen die meededen aan een vervolgronde bleek dat 40% van de borstkankers mogelijk eerder zou zijn ontdekt als de borst in 2 richtingen was afgebeeld. Echter, ook bij borsten die in 2 richtingen waren afgebeeld was 24-29% van de kankers gemist op een eerder screenings mammogram. De opbrengst van standaard screenen in 2 richtingen zal dus waarschijnlijk wel wat lager liggen dan 40%, maar het lijkt toch zinvol om in te voeren. De kosten van de screening zullen met €1.03/per onderzoek toenemen, dit is slechts een bescheiden bedrag.

Impact van een eerdere benigne borstoperatie op de sensitiviteit van screenings mammografie

Sensitiviteit van screeningsmammografie na een benigne borstoperatie

Meerdere studies beschrijven postoperatieve veranderingen in borsten van vrouwen die in het verleden een benigne borstoperatie hebben ondergaan. Deze mammografische veranderingen kunnen de beoordeelbaarheid van screenings mammografie negatief beïnvloeden. Ongeveer 7% van de vrouwen in de zuidelijke screeningsregio gaf aan dat ze en eerdere benigne operatie had ondergaan. De sensitiviteit van screenings mammografie voor borstkankerdetectie was bij vrouwen zonder eerdere operatie 73%. Bij vrouwen met een eerdere benigne operatie was de sensitiviteit echter 9% lager, namelijk 64%. Dit betekent dat bij deze categorie vrouwen tijdens het screenen 1 op de 3 kankers wordt

gemist. Indien toekomstige studies onze onderzoeksresultaten bevestigen, dan moeten vrouwen met een eerdere benigne borstoperatie worden geïnformeerd over de lagere sensitiviteit. De sensitiviteit van screenings mammografie na een benigne borstoperatie lijkt vergelijkbaar met de sensitiviteit na een operatie voor borstkanker. Als studies bevestigen dat de sensitiviteit van mammografie na een benigne borstoperatie inderdaad overeenkomt met de sensitiviteit van mammografie na een borstoperatie voor kanker, zou moeten worden overwogen om vrouwen na een benigne borstoperatie buiten de screening om een tweejaarlijks mammogram aan te bieden.

Oorzaak van de lagere sensitiviteit van screeningsmammografie na een benigne borstoperatie

Het was vooralsnog onbekend wat de oorzaak was van de lagere sensitiviteit van screeningsmammografie na een benigne borstoperatie. Het zou het gevolg van de operatie kunnen zijn, maar in een eerdere studie werd geopperd dat het mogelijk kwam door karakteristieken van het borstklierweefsel zelf. De lagere sensitiviteit na benigne borstoperatie is waarschijnlijk toch het gevolg van de postoperatieve veranderingen in de borst. Tumoren in een gebied met postoperatieve veranderingen presenteerden zich vaker als een IK dan als een SGK. Tevens waren de postoperatieve veranderingen veel uitgesprokener aanwezig in borsten van vrouwen met een IK. Tot slot was de densiteit van de mammogrammen van SGKs en IKs gelijk en werden er bij review nauwelijks mammogrammen waargenomen waar het borstklierweefsel zelf voor een bemoeilijkte interpretatie zorgde. Het lijkt dus van belang dat radiologen extra aandacht besteden aan een screeningsmammogram als er postoperatieve veranderingen zichtbaar zijn. De kans op een IK wordt daarmee mogelijk verkleind. Ook zou het vrouwen moeten worden ontraden om histologisch bewezen benigne borstlaesies te laten verwijderen.

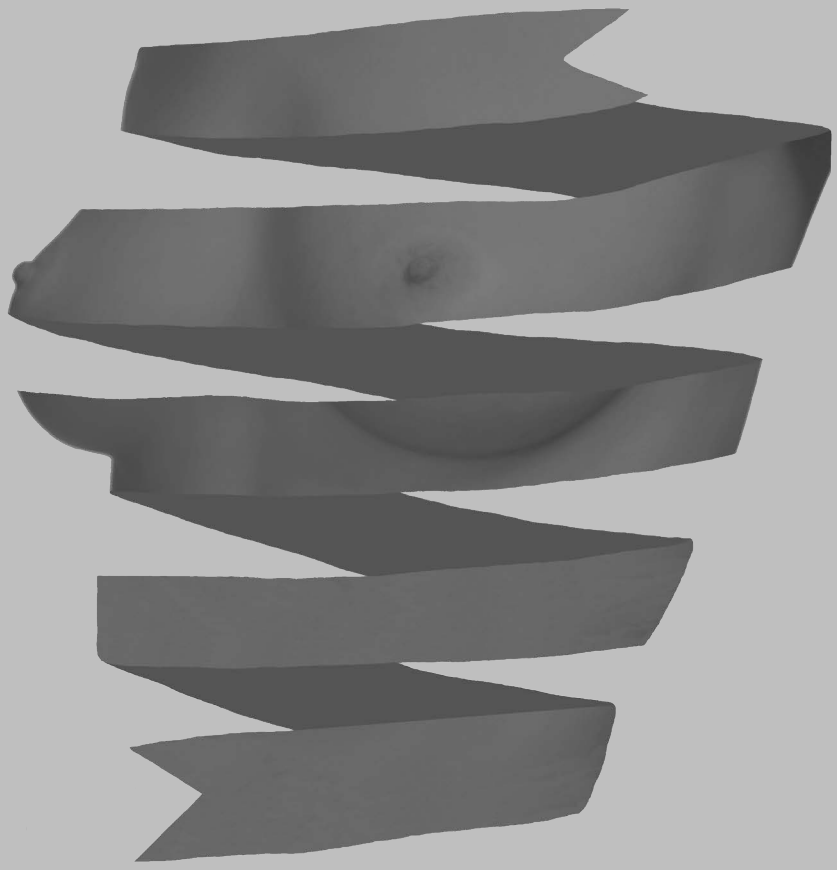
Trends in biopsieën voor (benigne) mammografische afwijkingen gevonden bij de borstkankerscreening

Het doel van deze laatste studie was om trends in borstbiopsieën voor afwijkingen gevonden bij screenings mammografie te bepalen. We includeerden alle screenings onderzoeken die tussen 1997-2011 hadden plaatsgevonden in onze screeningsregio. Bij vrouwen met een goedaardige diagnose na verwijzing bleef het gebruik van cytologie (FNAC) min of meer stabiel, van 8% naar 6%. Goedaardige diagnoses gemaakt door percutane naald biopten (PNB) stegen van 2% naar 34% en tegelijkertijd nam het aantal diagnoses middels chirurgische biopten af; van 23% naar 2%. Bij vrouwen die een mammacarcinoom bleken te hebben na verwijzing, daalden de diagnoses gemaakt met behulp van FNAC; van 19% naar 1%. Diagnoses gesteld door PNB stegen van 17% naar 97%, terwijl diagnoses gemaakt door chirurgische biopten afnamen van 59% naar 1%. Het aantal vertragingen in de diagnose van borstkanker, gedefinieerd als een diagnose die pas na meer dan 3 maanden na verwijzing werd gesteld, daalde van 7% naar 2%. Onze studie toont aan dat het gebruik van chirurgische biopsieën voor diagnostisch onderzoek van mammografische afwijkingen die worden gevonden bij de screening aanzienlijk is gedaald, bij zowel vrouwen met een goedaardige als met een maligne uitkomst. Chirurgische biopsieën zijn grotendeels vervangen door PNBs en deze vervanging resulteerde niet in meer diagnostische vertragingen.

Conclusie

De gevoeligheid van screeningsmammografie in de zuidelijke screening regio is momenteel 73%. Ondanks dat meer dan 20% van de kankers wordt gemist, dienen vrouwen zelden een schadeclaim in. Met een verhoging van de sensitiviteit van screeningsmammografie zal waarschijnlijk het aantal gemiste kankers dalen. Wij zagen dat kanker detectie waarschijnlijk toeneemt als mammogrammen standaard in 2 richtingen worden gemaakt, niet alleen in de eerste maar ook in de volgende screening rondes. De resultaten van onze studie hebben inmiddels geleid tot een (tijdelijke) verandering van het screeningsbeleid in Nederland; tegenwoordig ondergaat iedere vrouw bij de borstkankerscreening een mammogram in 2 richtingen en men verwacht dat dit beleid zal worden gecontinueerd in de toekomst. Daarnaast hebben we ontdekt dat vrouwen met een benigne borstoperatie in de voorgeschiedenis een significant lagere screenings sensitiviteit hebben dan vrouwen zonder eerdere borstoperatie. Dit is het gevolg van postoperatieve veranderingen. Op dit moment geeft ongeveer 7% van de vrouwen in de zuidelijke screening regio aan een eerdere benigne mammaoperatie te hebben gehad. In de afgelopen jaren zijn voor diagnostiek van mammalaesies de chirurgische biopten echter grotendeels vervangen door percutane naald biopten. Daarom verwacht ik dat het aantal vrouwen met een eerdere benigne operatie in de voorgeschiedenis zal afnemen in de toekomst. De lagere sensitiviteit van screeningsmammografie na een eerdere benigne borstoperatie is mogelijk gelijk aan de sensitiviteit na een behandeling voor borstkanker. Als verdere studies onze bevindingen kunnen bevestigen, dan moeten vrouwen die een eerdere benigne operatie hebben ondergaan hiervan op de hoogte worden gebracht en we moeten we zelfs overwegen of we deze vrouwen geen tweejaarlijks klinisch mammografisch onderzoek moeten aanbieden in plaats van de standaard screening. Dit zal de zorgkosten doen stijgen, maar ook het screeningsresultaat doen verbeteren en klinische mammografie zal waarschijnlijk lijden tot een hogere tumordetectie in vrouwen met een status na eerdere benigne mammaoperatie. Tot slot zal de verhoging van de screeningskosten slechts van tijdelijke aard zijn vanwege de te verwachten daling van het aantal vrouwen met een status na benigne mammaoperatie in de toekomst.

Dankwoord



Eindelijk ligt hier dan het proefschrift waar ik de afgelopen jaren zo druk mee bezig ben geweest. De laatste loodjes wegen zeker het zwaarst en het afgelopen jaar was hectisch, maar gelukkig waren er veel mensen waarop ik heb kunnen rekenen en ik wil graag iedereen bedanken die heeft geholpen om mijn promotie tot een goed einde te brengen!

Allereerst mijn promotor, Jan Willem Coebergh. Je bent een inspirerende persoonlijkheid vol anekdotes en vol humor. Het vooroordeel dat professoren verstrooid kunnen zijn werd zo nu en dan bevestigd, maar ik was ook iedere keer weer onder de indruk van je uitgebreide kennis van alle zaken die te maken hebben met de borstkanker screening en (borst)kanker in het algemeen. Ook over allerlei niet-kanker gerelateerde onderwerpen kon ik veel van je leren. Bedankt!

Mijn copromotor Lucien Duijm verdient eveneens een mooie plek in dit dankwoord. Lucien, jij hebt me enthousiast weten te maken voor wetenschappelijk onderzoek en zonder jou was dit proefschrift er niet geweest. Ik wil je heel erg bedanken voor het vertrouwen dat je in me had en alle tijd die je in het onderzoek hebt gestoken. Het was niet altijd makkelijk om te voldoen aan je verwachtingen, maar volgens mij heb ik het er aardig vanaf gebracht. Ik voel me zeer vereerd om je eerste promovenda te mogen zijn en met jouw passie voor onderzoek zullen er ongetwijfeld nog velen volgen!

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De leden van de leescommissie prof.dr.dr. Giard, prof.dr. den Heeten en prof.dr. Klijn hebben allen de tijd genomen om mijn proefschrift aandachtig door te nemen. Ik wil u allen hartelijk danken voor de inhoudelijke beoordeling van mijn proefschrift!

Wikke en Joost, mijn paranimfen, tevens mijn collega's en onderzoeksmaatjes; het was heerlijk om met jullie te discussiëren over de mammascreening en om samen te mopperen over lastige vragen van reviewers. Het was fijn om met z'n drieën in hetzelfde schuitje te zitten! Wikke, het einde van jouw promotietraject is ook nabij. Ik vind het ontzettend knap dat je altijd vriendelijk en rustig weet te blijven, ondanks alle hectiek. Je moet nog heel even bikkelen, accepteren dat er maar 24 uur in een dag zit en nog heel even aanhoren dat je weinig tijd aan het gezin besteedt, zeer binnenkort heb je je boekje af en heb je weer zeeën van tijd! Joost, ook jouw promotie komt in zicht en ik dank je voor je hulp bij statistische vraagstukken, het toepassen van reference manager bij mijn laatste artikel (wat scheelt het veel tijd als je dat niet allemaal handmatig hoeft te doen!) en bedankt voor het presenteren van mijn praatje in Wenen toen ik net was bevallen. Ik vind het nog altijd spijtig dat ik niet in de kitscherige Versaci-kamer in Wenen heb kunnen slapen, maar de foto's die je me stuurde maakten veel goed. Wikke en Joost, fijn dat jullie op 6 juni naast me staan, met jullie samen zie ik de verdediging vol vertrouwen tegemoet!

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Adri Voogd, je was co-auteur bij meerdere artikelen, maar was ook altijd beschikbaar voor advies. Bedankt voor je altijd snelle reacties en de tijd die je hebt besteed aan het beoordelen van mijn teksten. Ook hield je me op de hoogte van onderzoek op mamma-gebied door me regelmatig interessante artikelen te sturen. Bedankt!

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Laurens en Emily, kleine boefjes. Jullie kwamen snel achter elkaar op de wereld en ons leven is sindsdien op een heerlijke manier veranderd. Rustig op de bank zitten is er niet meer bij, maar daar hebben we veel knuffels en liefde voor teruggekregen. Alsof jullie meteen doorhadden dat papa en mama het erg druk hadden, sliepen jullie beiden vlot na de geboorte al door en Laurens was het afgelopen jaar ook zeer behulpzaam met stofzuigen en andere huishoudelijke klusjes. Als ik het erg druk had wisten jullie me regelmatig op te vrolijken met mooie tekeningen (op de muur of de bank), kusjes en knuffels. Jullie krijgen een hele dikke kus van mama!

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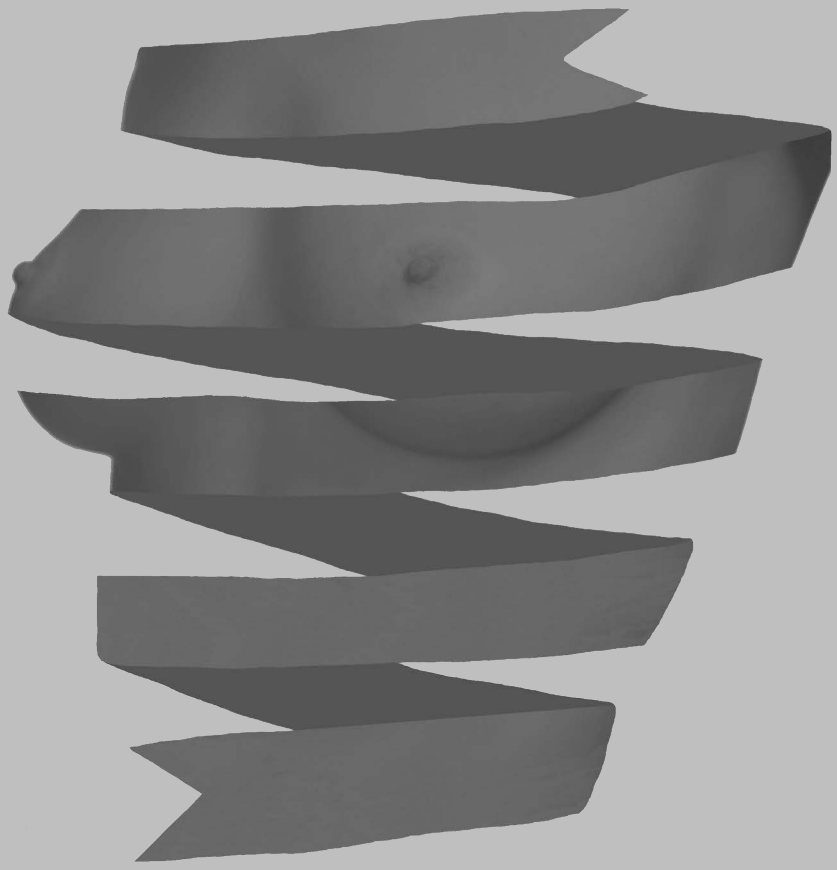
Curriculum Vitae



Vivian van Breest Smallenburg werd geboren op 30 mei 1980 te Groningen. In 1998 behaalde ze haar gymnasium diploma aan het Preadinius gymnasium te Groningen. Ze werd meteen ingeloot voor de studie geneeskunde, maar ze moest eerst nog een certificaat scheikunde halen. Na het behalen van het certificaat startte ze in 1999 met de studie geneeskunde aan de Rijksuniversiteit Groningen. Tijdens deze studie liep ze coschappen in verscheidene ziekenhuizen, waaronder het Universitair Medisch Centrum Groningen, het St. Elisabeth hospitaal te Curaçao en het Jeroen Bosch ziekenhuis te 's-Hertogenbosch. Haar afstudeeronderzoek (Is bij IVF en ICSI een dosisverhoging gonadotrofinen bij matige responders zinvol?) verrichtte ze op de afdeling fertiliteit van het Jeroen Bosch ziekenhuis. Na het behalen van het artsexamen in 2005 startte ze als arts-assistent op de afdeling obstetrie en gynaecologie van het Jeroen Bosch ziekenhuis. Na een jaar verruilde ze deze baan voor een baan als arts-assistent op de afdeling chirurgie, eveneens in het Jeroen Bosch ziekenhuis. Uiteindelijk begon ze medio 2007 aan de opleiding tot radioloog in het Catharina ziekenhuis te Eindhoven. Tijdens deze opleiding kwam ze in aanraking met wetenschappelijk onderzoek en de Nederlandse borstkankerscreening en in 2009 startte ze het onderzoek dat resulteerde in dit proefschrift. Begin 2013 heeft ze haar opleiding tot radioloog afgerond en momenteel is ze in het Catharina ziekenhuis als radioloog werkzaam. Ze woont samen met Alexander en heeft twee kinderen, Laurens en Emily.