Breast Tomosynthesis in Screening - Benefits and Challenges

Johnson, Kristin

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KRISTIN JOHNSON
DEPARTMENT OF TRANSLATIONAL MEDICINE | FACULTY OF MEDICINE | LUND UNIVERSITY

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Benefits and Challenges

Kristin Johnson M.D.

LUND
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DOCTORAL DISSERTATION

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Abstract

Background: Mammography has limited sensitivity in screening. Breast tomosynthesis, a form of pseudo-3D mammography, could potentially complement or replace mammography due to its ability to reduce the effects of overlapping tissue.

Aim: To investigate the use and potential benefits and negative side effects of breast tomosynthesis in screening.

Methods: The Malmö Breast Tomosynthesis Screening Trial was a prospective population-based, paired trial comparing stand-alone one-view breast tomosynthesis with standard two-view mammography in the screening programme in the city of Malmö, Sweden. The images were double-read and scored in two separate reading arms. Measures of diagnostic accuracy, tumour characteristics and false-positive recall rates were assessed. The interval cancer rate in the trial was compared with that in an age-matched contemporary control group screened with mammography.

Results: In total 21 691 women, aged 40 to 74, were invited to participate, 14 848 of which were included in the final analyses (mean age 57 years). The detection rate and sensitivity were higher in breast tomosynthesis than in mammography: 8.7 per 1000 screened women vs. 6.5 per 1000 screened women (95% confidence interval (CI) 7.3-10.3 vs. 5.2-7.9; p<0.0001) and 81.1% vs. 60.4% (95% CI: 74.2-86.9 vs. 52.3-68.0), respectively. The specificity of breast tomosynthesis was lower than mammography: 97.2% vs. 98.1% (95% CI: 97.0-97.5 vs. 97.9-98.3). The tumour characteristics of the additional breast cancers detected with breast tomosynthesis only were in general similar to those of tumours detected in mammography screening. The interval cancer rate in breast tomosynthesis screening was lower in the control group: 1.6 per 1000 screened women, compared to 2.8 per 1000 screened women in those screened with mammography with age-adjusted odds ratio, 0.6 (95% CI: 0.3-0.9); p=0.02. The false-positive recall rate was higher in breast tomosynthesis than in mammography: 1.6% (95% CI: 1.4-1.8) vs. 0.8% (95% CI: 0.7-1.0).

Conclusions: Breast tomosynthesis can play an important role in screening due to earlier detection and, more importantly, a reduced interval cancer rate, with an acceptable rate of false positives, compared to standard mammography screening. Further studies are needed to evaluate if benefits are sustained in consecutive breast tomosynthesis screening rounds.

Key words: Mammography, breast tomosynthesis, breast cancer, screening

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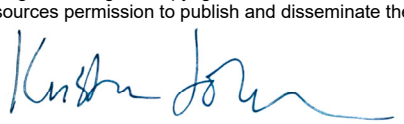
Signature  Date 2022-12-12

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Kristin Johnson M.D.

LUND
UNIVERSITY

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Faculty of Medicine
Department of Translational Medicine, Radiology Diagnostics
Lund University, Sweden

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To my family

Contents

List of papers

This thesis is based on the following papers, which will be referred to in the thesis by their Roman numerals, I-IV. The papers are appended at the end of the thesis.

I. One-view breast tomosynthesis versus two-view mammography in the Malmö Breast Tomosynthesis Screening Trial (MBTST): a prospective, population-based, diagnostic accuracy study
Zackrisson S, Lang K, Rosso A, **Johnson K**, Dustler M, Fornvik D, Fornvik H, Sartor H, Timberg P, Tingberg A and Andersson I
Lancet Oncology. 2018. 19(11):1493-1503

II. Tumor characteristics and molecular subtypes in breast cancer screening with digital breast tomosynthesis – Results from the population-based Malmö Breast Tomosynthesis Screening Trial
Johnson K, Zackrisson S, Rosso A, Sartor H, Saal L, Andersson I and Lång K
Radiology. 2019. 293(2): 273-281

III. Interval breast cancer rates and tumor characteristics in the prospective population-based Malmö Breast Tomosynthesis Screening Trial (MBTST)
Johnson K, Lång K, Ikeda D, Åkesson A, Andersson I and Zackrisson S
Radiology. 2021. 229(3): 559-564

IV. False positive recalls in the Malmö Breast Tomosynthesis Screening Trial
Johnson K, Olinder J, Rosso A, Andersson I, Lång K and Zackrisson S
Submitted

Thesis at a glance

Study	Question	Method	Results and Conclusions
I	How accurate is one-view breast tomosynthesis compared to standard two-view mammography in breast cancer screening?	Prospective paired Malmö Breast Tomosynthesis Screening Trial (MBTST) with 14 848 participating women, examined with breast tomosynthesis and mammography on one screening occasion.	Thirty-four percent higher cancer detection rate with one-view breast tomosynthesis compared to two-view mammography. One-view breast tomosynthesis is a feasible screening method.
II	Do the tumour characteristics of breast cancers detected with breast tomosynthesis differ from breast cancers detected with mammography?	The tumour characteristics of additional cancers detected with only breast tomosynthesis were compared to the tumour characteristics of cancers detected with mammography.	The tumour characteristics in the two groups were similar, suggesting that breast tomosynthesis would not necessarily change the panorama of tumour characteristics of screen-detected breast cancer.
III	Is the interval cancer rate reduced after screening with breast tomosynthesis compared to screening with mammography?	The interval cancer rate in the MBTST was compared with the interval cancer rate in an age-matched contemporary control group screened with mammography.	The interval cancer rate after screening with breast tomosynthesis was significantly reduced compared to the control group, and might translate into screening benefits.
IV	What is the false-positive recall rate in breast tomosynthesis compared to that in mammography, and what is the radiographic appearance of false-positive findings?	The false-positive recall rates in the MBTST were compared and false-positive findings were classified according to radiographic appearance.	A higher false-positive recall rate was found with breast tomosynthesis than with mammography, mainly due to more stellate findings, especially during the first year of the trial.

Abstract

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Screening med 3D-mammografi

Bröstcancer är den vanligaste cancerformen hos kvinnor i världen och i Sverige drabbas fler än var tionde kvinna någon gång under sin livstid. Tidig upptäckt av bröstcancer leder ofta till en bättre prognos och ökad chans till överlevnad. Syftet med screening är att upptäcka bröstcancer innan den har hunnit ge symptom. I Sverige erbjuds alla kvinnor mellan 40 och 74 år att delta i bröstcancerscreening. Bland kvinnor i det åldersintervallet är ca två tredjedelar av bröstcancerfallen diagnosticerade med hjälp av screening. Undersökningen som genomförs i screeningen är mammografi, dvs röntgen av brösten, och ger en tvådimensionell bild av bröstet. Bröst har olika utseende på mammografi-bilder, bland annat beroende på hur mycket körtelvävnad som bröstet innehåller. Körtelvävnad, men även cancer, är vitt på bilden vilket gör att cancer kan skymmas av normal körtelvävnad och är då svårare att upptäcka. Med 3D-mammografi, även kallat brösttomosyntes, tas flera bilder av bröstet med en röntgenapparat som rör sig i en båge ovanför bröstet. Eftersom bilderna tas från olika vinklar kan den skymmande effekten från normal bröstkörtelvävnad minska när man skapar 3D-bilderna. Därför har 3D-mammografi föreslagits som ett alternativ för att förbättra upptäckt av bröstcancer i screening.

Syftet med studierna i den här avhandlingen är att utvärdera 3D-mammografi jämfört med vanlig mammografi i bröstcancerscreening. När en ny metod ska utvärderas i screening är det många aspekter som man behöver ta med i beräkningarna. Ett viktigt mått på om den nya metoden, 3D-mammografi, är bättre än den gamla, mammografi, är andelen cancerfall som upptäcks med respektive metod. Det är också viktigt att ta reda på vilka typer av bröstcancer som metoderna hjälper till att diagnosticera, eftersom olika typer av bröstcancer har olika prognos. Ett sätt att undersöka om 3D-mammografi diagnosticerar bröstcancer som är snabbväxande och mer elakartad är att utvärdera det som kallas för intervallcancer, cancer som diagnosticeras mellan screeningtillfällen, eftersom de typerna av bröstcancer ofta har sämre prognos.

Något annat som ofta beräknas är andelen kvinnor där röntgenläkarna har sett misstänkta förändringar på mammografi-bilden och som då återkallas från screeningen för att genomgå fler undersökningar. För fyra av fem återkallade kvinnor visar undersökningarna att de misstänkta förändringarna är ofarliga, så kallade falskt positiva återkallningar. Det är värdefullt att hålla andelen falskt

positiva återkallningar på en låg nivå eftersom kvinnorna som drabbas blir oroliga och kanske inte vill komma tillbaka till screeningen.

Under åren 2010 till 2015 genomfördes en stor studie i Malmö där vanlig mammografi jämfördes med 3D-mammografi i screening. Studien heter Malmö Breast Tomosynthesis Screening Trial (MBTST). I MBTST undersöktes ca 15 000 kvinnor med både vanlig mammografi och 3D-mammografi. Bilderna granskades i två så kallade granskningsarmar, en för 3D-mammografi och en för mammografi. De som granskade bilderna var röntgenläkare med särskild inriktning mot diagnostik av bröstcancer. Andelen diagnosticerade fall av bröstcancer var fler med 3D-mammografi, 8,7 per 1000 kvinnor, än med mammografi, 6,5 per 1000 kvinnor.

De cancerfall som upptäcktes med hjälp av 3D-mammografi var fördelade mellan olika typer av bröstcancer, både cancer med god prognos och cancer med sämre prognos. Det fanns inga tydliga skillnader mellan fördelningen av cancertyper bland de cancerfallen jämfört med de cancerfall som upptäcktes med hjälp av mammografi. Andelen fall av intervallcancer var lägre efter screening med 3D-mammografi än i en grupp kvinnor som screenades med mammografi under samma tidsperiod vilket tolkas som att 3D-mammografi hjälper till att hitta snabbväxande bröstcancer som annars hade orsakat symptom. Det var en högre andel falskt positiva återkallningar med 3D-mammografi än med mammografi, men de falskt positiva återkallningarna sjönk under studiens gång, troligen för att röntgenläkarna fick mer erfarenhet, och andelen falskt positiva återkallningar höll sig sammantaget på en acceptabel nivå.

Resultaten i avhandlingen tyder på att 3D-mammografi i bröstcancerscreening ger flera fördelar jämfört med vanlig mammografi. 3D-mammografi kan ersätta eller komplettera mammografi i screening, men är också en metod som skulle kunna användas för kvinnor som löper högre risk att drabbas av bröstcancer. En utmaning inför framtiden är bristen på de röntgenläkare som granskar bilderna i screening och där undersöks det om artificiell intelligens vara en hjälp.

Abbreviations

AI	Artificial intelligence
BI-RADS	Breast Imaging Reporting and Data System
CC	Craniocaudal
CEM	Contrast-enhanced mammography
CI	Confidence interval
HER2	Human epidermal growth factor receptor 2
MBTST	Malmö Breast Tomosynthesis Screening Trial
MLO	Mediolateral oblique
MRI	Magnetic resonance imaging
OR	Odds ratio
RCT	Randomised controlled trial
RIS	Radiology information system
SD	Standard deviation
TNM	Tumour node metastases

Introduction and aims

When the work on this thesis was initiated in 2016, investigations of the potential of tomosynthesis in screening for breast cancer had just begun, and results had been reported from only a few prospective trials (1-3). The reason for the interest in breast tomosynthesis as a new screening modality is the limited sensitivity of the standard screening modality mammography. Studies have shown that 16-30% of cancers can remain undetected in mammography screening, mainly due to overlapping fibroglandular tissue obscuring the cancer (4). Furthermore, the sensitivity can be lower in breasts with a higher amount of fibroglandular tissue, so-called dense breasts (4). In tomosynthesis, low-dose images of the breast are acquired from different angles generating a stack of images that the radiologist can scroll through. The aim of breast tomosynthesis is to improve the diagnostic accuracy by reducing the effects of overlapping tissue (5).

In order to determine whether a new screening modality is superior to the existing method, it is important to compare its diagnostic accuracy to that of the standard modality. However, not only detection rates and sensitivity are of interest when evaluating a new screening modality. The additional cancers detected with the new modality should be those that would have progressed during the woman's lifetime and become symptomatic. This can be investigated by studying the tumour characteristics of the additionally identified cancers and by measuring interval cancer rates, i.e., the rate of cancers diagnosed between screening occasions (6). A low rate of false-positive recalls, i.e., high specificity, is also of importance in screening, as recalls can cause distress and lead to lower re-attendance (7, 8).

The Malmö Breast Tomosynthesis Screening Trial (MBTST) is a prospective population-based, paired trial comparing one-view breast tomosynthesis with standard two-view mammography. The trial included 14 848 women, aged 40 to 74 years, from the screening population in Malmö, Sweden from 2010 to 2015.

The studies described in this thesis focus on the performance of breast tomosynthesis in screening, in terms of screening performance measurements, the subtypes of breast cancer that are detected, screening efficacy, and false-positive recalls in the MBTST. The overall aim of the research presented in this thesis was to investigate potential benefits and challenges of breast tomosynthesis in breast cancer screening.

The specific aims of the studies presented in the papers were:

I. to prospectively investigate the accuracy of one-view breast tomosynthesis and compare it with standard two-view mammography in population screening,

II. to describe the tumour characteristics in detail, including molecular subtypes, of additional cancers detected with breast tomosynthesis compared with those detected with mammography in screening,

III. to compare the interval cancer rate in a prospective breast tomosynthesis screening trial with that in a contemporary mammography-screened control group, and to describe the characteristics of the interval cancers, and

IV. to analyse false-positive recall rates, false-positive biopsy rates and radiographic appearances of false positives in breast tomosynthesis screening and compare them to those in mammography screening.

Breast cancer and breast imaging

Breast cancer

Breast cancer is the most common form of cancer affecting women. In 2020, 2.3 million women worldwide were diagnosed with breast cancer, which corresponds to 11.7% of global cancer diagnoses in women, and in that year, 685 000 women died as a result of breast cancer (9). In the same year, 7570 women in Sweden were diagnosed with breast cancer. One in ten Swedish women will develop breast cancer before the age of 75, and the 10-year survival rate is 86%. About 60% of breast cancers in Sweden are detected through breast cancer screening with mammography (10).

The strongest risk factor for breast cancer is female gender, followed by increasing age. Other risk factors are postmenopausal obesity (11), high breast density (12), family history of breast cancer (13), high alcohol consumption (14), post-menopausal hormone replacement therapy (15) and reproduction patterns, i.e., early menarche, late menopause, no or few children and less breast feeding (11). Women who are carriers of the breast cancer gene 1 (BRCA1) or breast cancer gene 2 (BRCA2) have a very high risk of developing breast cancer before the age of 70; 65% and 45%, respectively (16).

Breast cancer types

Breast cancer is a heterogeneous disease, both in terms of biological profile and clinical manifestation, and can be divided into many different subgroups based on various characteristics. Breast cancer is either non-invasive, i.e., in situ, or invasive. In situ cancers are limited to the ducts or lobules, and have not yet acquired the ability to invade the basal membrane (Figure 1).

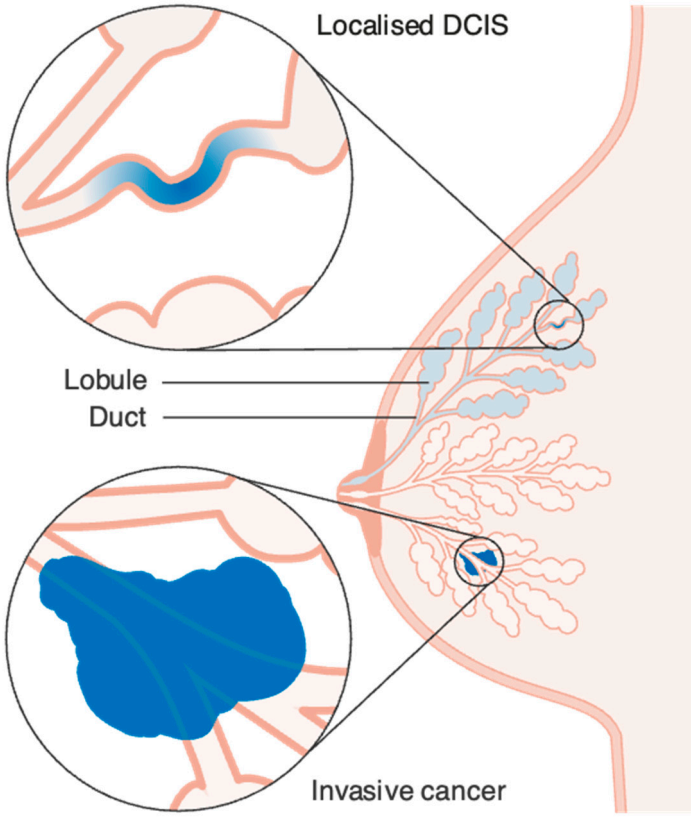

Figure 1: Ductal carcinoma in situ and invasive ductal carcinoma. Schematic illustration of a breast showing the ducts and lobules. Cancer cells are located within the duct in ductal carcinoma in situ (DCIS). The cancer cells have invaded the basal membrane and infiltrate the surrounding tissue in invasive ductal carcinoma. (Image courtesy of Cancer Research UK/Wikimedia Commons).

Staging

The tumour–node–metastases system (TNM) is a classification system for invasive cancer widely used for treatment planning and prognosis estimation (17). T represents tumour size, N lymph node status and M distant metastases. In breast cancer, T is categorised into five groups: Tis (in situ), T1 ≤20 mm; T2: 21-50 mm; T3: >50 mm and T4: skin or muscular involvement (irrespective of size). Axillary lymph node status is divided into four groups: no positive lymph nodes, 1 to 3 positive lymph nodes, 4 to 9 positive lymph nodes and 10 or more positive lymph nodes. A positive lymph node is defined as a micro- or macrometastasis in the node. Metastases are classified as M0, no distant metastases or M1 distant metastases.

Tumour grade

The Nottingham histological grade is a grading system that provides a measure of tumour cell differentiation in the microscope. The pathologist grades the tumours in each of the three categories: tubule formation, nuclear pleomorphism and mitotic count. Invasive cancers are then categorized as I, II or III based on the grading. A high histological grade indicates a worse prognosis compared with a low histological grade. In situ cancers are categorised according to nuclear grade only (18).

Histological subtypes

Breast cancer is also divided into different subtypes based on its origin in the breast. The most common histological type is ductal invasive carcinoma, also known as invasive breast carcinoma of no special type, which originates in the cells in the ducts (Figure 1). This type accounts for about 80% of invasive carcinomas. Invasive lobular carcinoma, which originates in the milk-producing lobules, is less common, accounting for about 15%. The remaining 5% consists of less common breast cancer types (19), for example, tubular carcinomas, which have an excellent prognosis (20). Invasive lobular carcinomas are more difficult to detect in mammography images than invasive ductal carcinoma as their growth pattern is more diffuse (21). In situ carcinomas are divided into ductal carcinoma in situ and lobular carcinoma in situ, the latter is in general considered a high-risk lesion, and is not assigned a T status within the TNM classification (17).

Molecular subtypes

Perou and Sörlie developed a method of categorising breast cancers based on their genetic alterations (22). Four intrinsic subtypes of breast cancer were identified: luminal A, luminal B, human epidermal growth factor 2 (HER2)-enriched and basal-like. The luminal subtypes both express the oestrogen and progesterone hormone receptors. The HER2-enriched subtype does not express hormone receptors, but instead has an amplified expression of the HER2 receptor. Basal-like cancers express neither hormone receptors nor HER2.

Genetic analysis is time consuming and expensive. It is therefore still common in clinical routine to use a surrogate system based on immunohistochemical and fluorescence in situ hybridization as part of the routine pathological work-up of breast specimens. The St Gallen surrogate molecular subtype categorisation is based on the presence of the oestrogen receptor, the progesterone receptor and the HER2 and Ki-67 statuses (23). Ki-67 is a proliferation marker that is measured by counting the mitotic rate in the tumour. The subtypes are: luminal A-like, luminal B-like HER2-negative, luminal B-like HER2-positive, HER2-positive and triple-negative. The luminal subtypes, especially luminal A-like, have in general a more favourable prognosis, whereas the triple-negative subtype has the least favourable (23, 24). There are, however, discrepancies between the results obtained with gene

expression analysis and immunohistochemical markers; gene expression markers being suggested to better predict the prognosis (25). Figure 2 shows an overview of the subtypes of breast cancer in relation to histological parameters, prognosis and treatment options.

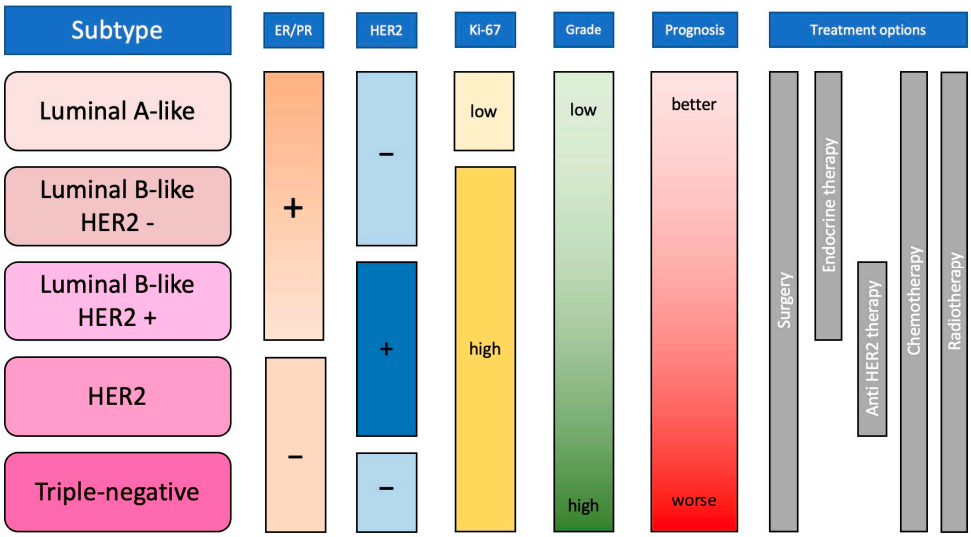

Figure 2: Subtype overview. A simplified overview of surrogate molecular subtypes, histological parameters, prognosis and treatment options in invasive breast cancer. HER2 = human epidermal growth factor type 2, HER2 - = HER2 negative, HER2 + = HER2 positive, ER = oestrogen receptor, PR = progesterone receptor.

Screen-detected breast cancer

Women with screen-detected breast cancer have in general a more favourable prognosis than women with symptomatic cancers (26). This is attributed to earlier detection, smaller tumour size and less lymph node involvement (27). It has also been shown that screen-detected cancers are more often luminal A-like than clinically detected cancers. The number of diagnosed ductal carcinoma in situ increased dramatically after the implementation of mammography screening (28).

Breast cancer treatment

The recommended treatment for breast cancer depends, for example, on tumour characteristics, lymph node status, distant metastases, general health status and the patient's own preference. The Swedish National Treatment Guidelines, based on current evidence, are used by clinicians for guidance (29).

Surgery

Breast surgery is offered to almost all women with breast cancer. Mastectomy involves removal of the whole breast, whereas in breast-conserving surgery only the tumour and surrounding tissue are removed, and as much of the remaining breast tissue as possible is spared. A sentinel node biopsy is performed if there are no known cytology-verified lymph node metastases before surgery. A radioactive isotope is injected near the cancer to identify the first draining lymph node/nodes. The sentinel node/nodes are then removed and analysed by a pathologist during surgery. Axillary lymph node dissection is performed if there are metastases in the sentinel node or if lymph node metastases have been previously verified (29).

Other treatment

Other treatment options include anti-hormonal drugs, targeted therapy, chemotherapy and radiotherapy. The purpose of postoperative pharmaceutical therapy is to eliminate micrometastatic disease and thus reduce the risk of relapse. Anti-oestrogen drugs are commonly used to treat luminal-like cancers. Anti HER2 therapy specifically targets the HER2 protein, and is used in the treatment of HER2-positive breast cancer (29, 30). Neoadjuvant treatment, i.e., treatment before surgery, is offered to women with cancers that have more aggressive biological profiles and/or advanced TNM-status (30). In cases of distant metastases resulting from breast cancer the treatment has palliative intention (29).

Breast density

Breast density, i.e., the amount of fibroglandular tissue in the breast, affects both the risk and diagnosis of breast cancer. The risk of developing breast cancer increases with increasing density (12), but the biological reason for this is unknown. It has been suggested that the higher proportions of epithelial cells, non-epithelial cells and connective tissue in dense breasts promote the acquisition of mutations in epithelial cells (31). Dense breasts are more common in younger women, and the amount of fibroglandular tissue generally decreases post-menopause (32). Hormone replacement therapy, nulliparity and high age at first birth are associated with higher breast density (33).

Fibroglandular tissue is white on mammography images as this kind of tissue absorbs X-ray photons to a higher degree than the surrounding fatty tissue, potentially obscuring tumours as they also appear white. The sensitivity of mammography screening is thus lower in women with very dense breasts, and can be less than 50% (4). Mammographic breast density is most commonly classified visually by radiologists according to the 4-grade Breast Imaging Reporting and Data System (BI-RADS) system (34). The density assessment in the MBTST was based on BI-RADS 4th Edition (Figure 3). More emphasis was given to the masking effects

of dense tissue and percentage estimations were removed in the current BI-RADS 5th Edition: A: the breasts are almost entirely fatty, B: there are scattered areas of fibroglandular density, C: the breasts are heterogeneously dense which may obscure small masses and D: the breasts are extremely dense which lowers the sensitivity of mammography (34, 35). Other methods of categorization can be used, such as computer-based automated density assessment (36).

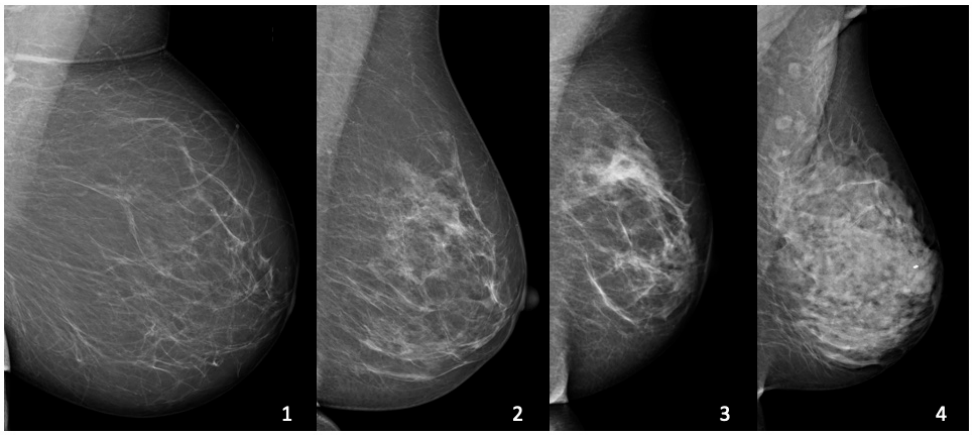

Figure 3: Breast density categories. The four breast density categories according to the Breast Imaging Reporting and Data System, 4th Edition (35). 1: Almost entirely fatty, <25% fibroglandular tissue, 2: scattered fibroglandular densities, 25-50% fibroglandular tissue, 3: heterogeneously dense, 51-75% fibroglandular tissue, 4: extemely dense, > 75% fibroglandular tissue.

Breast imaging

The basic principle in diagnosing breast cancer is triple diagnostics: clinical examination, imaging and tissue sampling. The clinical examination is performed by palpation of the breasts and axillae. Several imaging methods can be applied to women suspected of having breast cancer: mammography, contrast-enhanced mammography (CEM), breast tomosynthesis, ultrasound and magnetic resonance imaging (MRI) are commonly used. A tissue sample is usually obtained by fine-needle aspiration or core-needle biopsy.

Mammography

Mammographic images are obtained using an X-ray emitting tube and a detector, with the breast in between. The X-ray tube generates photons that either pass through the breast or interact with it, depending on the tissue. Fatty tissue has low density, and a large proportion of the photons pass through to the detector,

generating dark pixels. Denser tissues, such as tumours and glandular tissue, absorb photons to a higher degree resulting in bright pixels. The breast is compressed with a compression paddle to improve image quality by separating breast structures and reduce motion, and to reduce the radiation dose. Compression is a source of discomfort and pain and has been linked to less re-attendance in screening (37). Standard procedure in mammography screening is to use two projections per breast, the craniocaudal view (CC) and the mediolateral oblique (MLO) view. In the latter view the breast is compressed in an oblique plane that includes part of the pectoralis muscle. Mammography was previously based on analogue-film technology where the detector converted X-rays to light reaching a film that was chemically developed. The contrast and the brightness in the images were fixed when the film had been exposed. Digital mammography has electronic detectors which allows the degree of contrast and brightness to be manipulated through post-processing (38). The shift to digital technique has reduced radiation dose by 25 to 30% and has improved the diagnostic performance, especially in young women with dense breasts (39).

Contrast-enhanced mammography

Mammography can also be performed using an iodine-based contrast agent, so-called contrast-enhanced mammography (CEM). Most breast cancers have increased vascularity and vessel leakage, and the contrast agent makes them easier to detect. Images are obtained approximately two minutes after administering the contrast agent, using a dual-energy technique that generates a low-energy image similar to a conventional mammography image, and a recombined image showing areas of contrast enhancement. CEM is mainly used as a work-up tool when evaluating suspicious lesions (40), but has also been discussed as a potential supplemental screening tool in women with intermediate risk of developing breast cancer (41). The few, mainly small and retrospective, studies performed so far have shown that CEM has a higher sensitivity than conventional mammography (41). CEM has also been highlighted as an affordable and faster alternative to MRI in screening of women at high risk (41).

Mammographic appearance

Suspicious findings in mammography images are classified according to their appearance. Mammographic appearances are described in a standardized manner according to the BI-RADS Atlas 2013 (34). Factors such as shape, margins, lesion density, asymmetries, architectural distorsion and calcifications are assessed. Associated factors, such as nipple retraction or skin thickening, can also be signs of malignancy. Figure 4 shows some typical mammographic appearances. These have prognostic value as they can be linked to different cancer subtypes. Ductal carcinoma in situ is associated with microcalcifications that are normally clearly visible. Spiculated/stellate appearance is indicative of luminal A-like cancer and hence a

more favourable prognosis (42, 43). The subtype with the least favourable prognosis, the triple-negative subtype, is often round or oval, sometimes with circumscribed margins (42, 43).

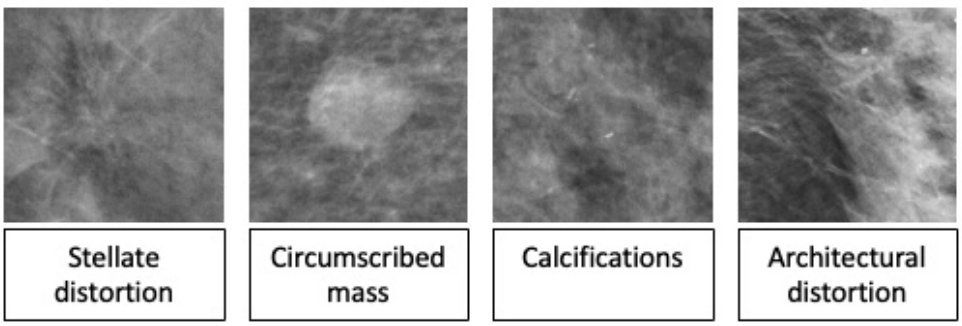

Figure 4: Radiographic appearances. Four examples of appearances in mammography images.

Artificial intelligence in screening

Image reading is laborious, and there is a general shortage of breast radiologists in the world. This has led to an increased interest in the use of artificial intelligence (AI) in mammography reading. Recent retrospective studies have shown promising results, with sensitivity and specificity comparable to those of breast radiologists (44, 45). One study using data from the MBTST showed that an AI mammography tool could retrospectively detect almost half of the cancers that were detected with DBT alone on the corresponding mammography screening examinations (46).

Breast tomosynthesis

Breast tomosynthesis is a development of the two-dimensional mammography technique, where the X-ray tube is rotated above the breast, generating multiple low-dose images (Figure 5). These images are reconstructed into an image volume presented as a stack of slices, similar to three-dimensional imaging techniques, which is why breast tomosynthesis is sometimes called 3D mammography. The third dimension helps reduce the effect of tissue that may obscure a possible cancer and may reduce the number of psudolesions from overlapping tissue. This is the basis of the original question, if breast tomosynthesis would be superior to mammography in detecting breast cancer, especially in dense breasts where the sensitivity of mammography is low (4). The added third dimension also diminishes the need for separation of breast structures and hence the compression force can be reduced with maintained image quality (47).

Breast tomosynthesis systems are nowadays digital, as for mammography systems. Various breast tomosynthesis systems are available with different acquisition angles

(15 to 50 degrees), X-ray tube movement ("step-and-shoot", where the tube stops for each exposure, or "continuous") and numbers of projection images (usually 11 to 25) (48). Narrow-angle tomosynthesis systems have been shown to better visualise microcalcifications (49), whereas wide-angle systems better depict masses. The tomosynthesis system used in the MBTST was a combined mammography and tomosynthesis machine (Siemens Mammomat Inspiration, Erlangen, Germany). The acquisition angle was 50 degrees, and the images were acquired continuously in 25 projections over 25 seconds. Image reconstructions were made through a filtered back projection algorithm. For a standard 53-mm-thick breast model, the average glandular dose was estimated to be 1.6 mGy for one-view tomosynthesis, compared to 2.4 mGy for two-view mammography (Paper I).

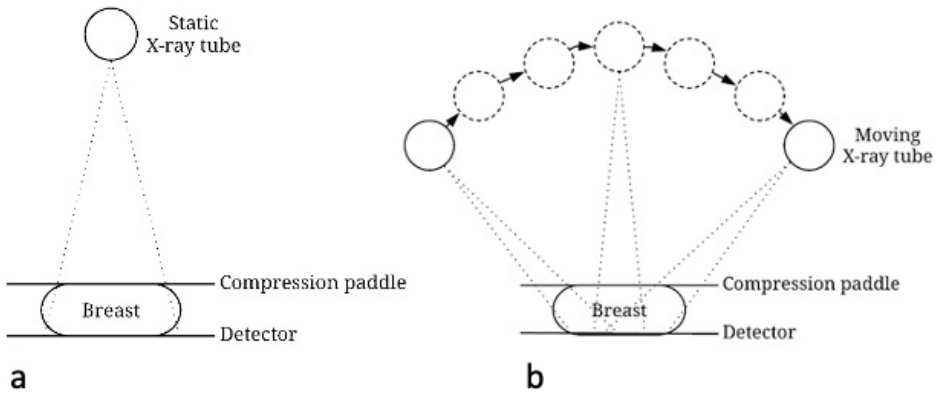

Figure 5: Mammography and breast tomosynthesis. Schematic figures illustrating a): mammography with a static X-ray tube and b): breast tomosynthesis, where the X-ray tube moves in an arc over the breast, generating several low-dose images. (Image courtesy of Sofia Wiberg.)

Synthesised mammography are mammography images reconstructed from the tomosynthesis image volume. The synthesised images can be combined with breast tomosynthesis, instead of standard mammography, to maintain a low radiation dose. The combination of breast tomosynthesis and synthesised mammography has been shown to have similar screening performance as breast tomosynthesis in combination with standard mammography (50).

One disadvantage of breast tomosynthesis is that the image reading time is approximately two to four times longer than for mammography images (51, 52). An average reading time of 77 seconds was reported in one study of two-view breast tomosynthesis vs. 33 seconds for two-view mammography (51). In the present work, one-view breast tomosynthesis was compared with two-view mammography, and it has been estimated that the reading time for one-view breast tomosynthesis in a screening setting is about 30 seconds (53).

Breast tomosynthesis screening trials

The MBTST, presented in this thesis, is one of several prospective screening trials comparing breast tomosynthesis with mammography. In some trials two-view breast tomosynthesis has been compared with two-view mammography (1, 52) while in others breast tomosynthesis has been used in combination with synthesised mammography (54-57). Three of the trials were randomised controlled trials (RCTs), i.e., women were randomly assigned to either mammography and breast tomosynthesis or mammography screening (52, 56, 57). In all trials except the MBTST, two-view breast tomosynthesis (MLO and CC) was used. The mammography examinations in all trials were two-view (MLO and CC). All trials except the randomised controlled To-Be trial (56) have shown significantly higher breast cancer detection rates with breast tomosynthesis in combination with mammography (standard or synthesised). A large RCT, the Tomosynthesis Mammographic Imaging Screening Trial (TMIST), comparing breast tomosynthesis with mammography, is ongoing in the United States, and planned to include 165 000 women (58).

Breast tomosynthesis screening studies

Several retrospective breast tomosynthesis screening studies have been performed, mostly in the United States. A meta-analysis performed by Marinovich et al., in which the cancer detection rates of 13 retrospective studies, where the number of participants ranged from 524 to 173 633 (59-71) were pooled, showed an increase in detection rate with the addition of breast tomosynthesis (5.7 per 1000 screened) compared to mammography (4.5 per 1000 screened) (72).

Ultrasound

Breast ultrasound is commonly used in the work-up of suspected breast cancer, for example, in women recalled after screening. The axillae are normally examined at the same time. Fine-needle aspiration and core needle biopsies are often performed with guidance from ultrasound.

Ultrasound in screening

Women with a very high risk of developing breast cancer, for example, carriers of mutations in the BRCA1 and BRCA2 genes, are offered high-risk screening in which ultrasound supplements mammography (29) to increase the sensitivity (73).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a non-radiating imaging modality using a strong magnet, magnetic gradients and radio waves to generate images. An intra-

venous contrast agent containing gadolinium is administered in breast MRI, and the contrast enhancement pattern is an important factor when analysing lesions (74). Indications for MRI in breast cancer work-up include for example ill-defined tumours at mammography and ultrasound, invasive lobular carcinomas and discrepancy in clinical presentation and imaging (29).

Magnetic resonance imaging in screening

MRI is used in screening of high-risk women in Sweden (29) as a supplement to mammography, but is not included in the screening programmes for average-risk women. The sensitivity of contrast-enhanced MRI in screening is high, between 81 and 100% in women with an average to high risk of breast cancer (75). In the Dutch randomised controlled Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial, published in 2019, MRI was compared with mammography in the screening of women with very dense breasts, showing a significantly reduced interval cancer rate after screening with MRI (76). However, the use of MRI as a potential screening tool has several drawbacks, such as the high cost, high rate of false positives (i.e., low specificity), the need for administration of an intravenous contrast agent, and time-consuming image acquisition and reading (75). A great deal of effort is being devoted to finding feasible MRI procedures, for example, using abbreviated protocols and diffusion-weighted imaging instead of contrast agents (77).

Breast cancer screening and statistics

The overall aim of breast cancer screening is to reduce mortality due to breast cancer. Pioneering RCTs, where women were randomly assigned to either mammography screening or no screening, performed in Sweden in the 1980s showed a 20% to 34% reduction in breast cancer mortality in women screened with film screen mammography compared to non-screened control groups (78, 79). These findings led to the introduction of population-based screening programmes in many parts of the world. Current European Union guidelines recommend regular screening in women aged 45 to 74 years (80).

The Swedish screening programme for breast cancer

The population-based mammography screening program has been fully implemented in Sweden since 1997 (81). The National Board of Health and Welfare recommendations stipulate that women aged 40 to 74 years should be invited to screening at 18- to 24-month intervals. The shorter interval is applied to women aged 40 to 54 years in many regions of Sweden. The overall attendance rate in 2017-2018 was just over 80% (82).

Women are invited to screening by letter. Those who choose not to attend continue to receive invitations. The screening examination is performed by a radiographer who also collects clinical information, including breast symptoms and previous breast surgery. The images are read independently by two breast radiologists, so-called double reading, forming the basis for the decision to recall the woman for further examination or not. Previous breast images, if any, are used for comparison. Borderline cases are typically discussed at a consensus meeting where two or more breast radiologists reassess the images and the decision to recall the woman or not. Women with findings that cannot be considered benign are recalled by letter for further investigation. A woman may also be recalled if she reports symptoms at the screening visit, such as a lump in the breast, even if mammography findings are judged as normal or benign. Women who are not recalled receive information by post that their screening examination showed no sign of malignancy. Those who are recalled undergo work up, usually including additional mammography views and ultrasound. Breast tomosynthesis can also be used in the work up. A biopsy of suspicious findings is performed if deemed necessary (83).

False-positive recalls

Women recalled due to suspicious findings on mammography screening, but where no cancer is found during work-up or before next screening are classified as false-positive recalls. False-positive findings can include normal glandular tissue, benign cysts, benign calcifications, radial scars and fibroadenomas (84). Some women who are subjected to false-positive recall experience long-lasting anxiety (7, 85). Studies have also shown that they may be less likely to attend future screening rounds (8). It is therefore important to keep the false-positive recall rate at a low level. However, it is also known that women who have had a false-positive recall have a higher probability of developing breast cancer later in life (86).

Interval cancers

Interval breast cancers are cancers diagnosed after screening negative for malignancy (which may include assessment), but before the next scheduled screening occasion, as defined by the European Union guidelines (87). Most interval cancers are diagnosed due to symptoms, normally a lump in the breast. Interval cancers generally have a more aggressive biological profile and a less favourable prognosis than screen-detected breast cancer (88, 89). The rate of interval cancer in screening can be used as a surrogate measure of breast cancer mortality when evaluating screening efficacy. A low rate of interval cancer indicates that screening captures fast-growing breast cancers that would otherwise have presented within the screening interval (6, 90).

Overdiagnosis

Overdiagnosis is another potential problem associated with screening. Over-diagnosis in breast cancer screening is defined as the diagnosis of a breast cancer which, if not diagnosed, would not have caused any harm during the lifetime of the woman. However, at the level of the individual woman it can never be verified whether a she has been overdiagnosed. Some women thus experience the anxiety of a cancer diagnosis and treatment, with potential negative side effects, with no benefit (91). It is likely that less aggressive screen-detected breast cancers, such as ductal carcinoma in situ, especially low-grade, and luminal A-like breast cancers, could contribute to overdiagnosis since it is known that they in general have excellent prognosis (24, 26, 92). Overdiagnosis increases with age (93).

It is very difficult to measure the rate of overdiagnosis. RCTs with a very long follow-up and large sample sizes in which a screened group is compared to a non-screened group have been suggested as a way to estimate overdiagnosis. In the Malmö Mammographic Screening Trial initiated in 1976, screened women were

compared to an unscreened control group, aged 55 to 69 years at randomisation, and the rate of overdiagnosis was found to be 10% 15 years after the end of trial (94). However, such trial is not feasible anymore as mammography screening is widely implemented and it would be unethical not to offer screening (95). Other pioneering screening trials offered screening to the women in the non-screened control groups after the trials had been completed, and they can therefore not be used for direct calculations (91). Thus, calculations of overdiagnosis are based on modelling and the estimates are dependent on the study design (95). According to a comprehensive review from 2012, the rate of overdiagnosis was estimated to 5-15% on a population level and 15-25% from the individual woman's perspective (91). The same review led to the conclusion that "screening reduces breast cancer mortality but some over-diagnosis occurs" (91).

Screening biases

Several factors influence screening outcome and constitute potential biases. Two of the most commonly mentioned are lead time and length time biases.

Lead time is the time between the detection of breast cancer by screening and the time at which the breast cancer would have been diagnosed clinically, if not detected by screening. In other words, the lead time is the time by which the diagnosis is "brought forward" by screening. This means that women with screen-detected cancers might appear to have a longer survival than those with clinically detected cancers, whereas the difference in survival can instead be explained by the lead time bias (96).

As slow-growing cancers are asymptomatic for a longer period than rapidly growing cancers, they are more likely to be detected on a screening occasion. A rapidly growing cancer is asymptomatic for a shorter period, and is therefore more likely to present as a symptomatic cancer than a slow-growing one. This leads to a length time bias, i.e., overrepresentation of slow-growing cancers detected by screening, resulting in the overestimation of survival as a result of screening (96).

Screening controversies

Opinions vary as to whether the benefit of breast cancer screening outweigh its harm. Pioneering RCTs have been criticised for suboptimal randomisation and misclassification of cause of death (97). New targeted breast cancer treatment has improved breast cancer survival since mammography screening was first implemented, and the question of whether screening is still needed has been raised (98). Overdiagnosis is also the subject of debate; the rates of overdiagnosis being claimed to be both over- and underestimated (99).

Statistics

Measurement of diagnostic accuracy

Diagnostic accuracy is a measure of the ability of a test to both detect a specific condition and to exclude the same condition. To be able to measure the diagnostic accuracy, a gold standard i.e., the best available examination to decide whether a subject has the condition or not, is needed for comparison. The sum of screening detected and interval cancers is used as gold standard in screening trials.

Sensitivity and specificity

Sensitivity describes how good the test is in correctly detecting the condition i.e., the true positive rate (number of true positives/ (number of true positives and false negatives)), while specificity describes the ability of a test to correctly identify people who do not have the condition, i.e., the true negative rate (number of true negatives/ (number of true negatives and false positives)) (Figure 6). A high specificity in breast cancer screening means that the rate of false positives is low and implies a low probability of recalling women who do not have breast cancer.

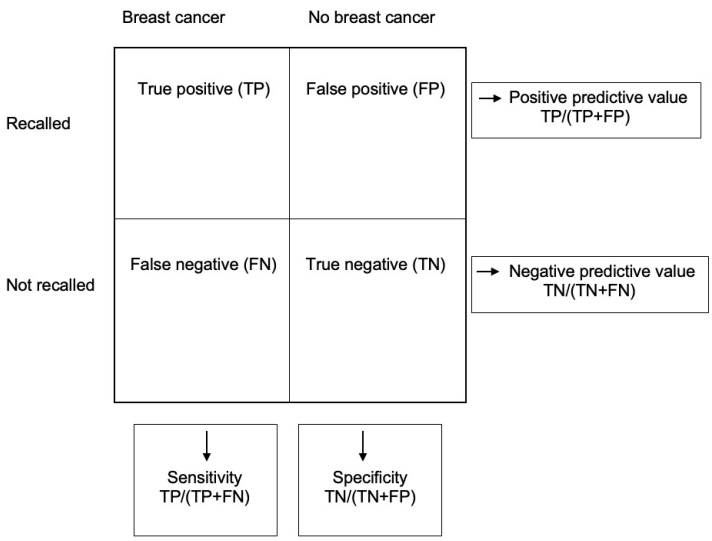

Figure 6: Measurement of diagnostic accuracy. A 2 x 2 contingency table, here using breast cancer screening as an example.

Positive and negative predictive values

Positive and negative predictive values describe the proportion of positive and negative test results. In contrast to sensitivity and specificity, they are impacted by

the prevalence of a condition. The positive predictive value (number of true positives/ (number of true positives and false positives)) describes how probable it is that a positive test result is truly positive. The negative predictive value (number of true negatives/ (number of true negatives and false negatives)) describes the probability of a negative test result being truly negative (Figure 6).

Screening measures

Several other important measures must be calculated when evaluating a new screening modality, in addition to the measures of diagnostic accuracy. The detection rate (detected cancers/screened women) describes the proportion of cancers detected by a screening modality. The recall rate describes the proportion of women participating in screening who are recalled due to suspicious findings (recalled women/screened women), and the false-positive recall rate is the proportion of recalled women where work-up shows no cancer (false positives/screened women).

The recall rates in Sweden are around 3% (100), which is well below the acceptable level of <5%, and in line with the desirable level of <3%, in subsequent screening examinations according to the European Union guidelines (101). The recall rates in the United States are higher, around 10% (102), and this should be considered when interpreting results from different parts of the world as they cannot be directly compared.

Statistical tests

McNemar's test

McNemar's non-parametric test is used to compare measures of diagnostic accuracy such as sensitivity and specificity in two diagnostic tests that have been applied to the same individuals. McNemar's test is a χ^2 test for paired nominal data and tests the null hypothesis that there are no differences in accuracy between the two diagnostic tests. The proportions are tabulated in a diagnostic accuracy 2 x 2 contingency table and generates a p-value (103).

Pearson's χ^2 test

Pearson's χ^2 test is used to test the independence between the binary variable of exposure to a diagnostic test (for example breast tomosynthesis) and the binary variable of the test result. The outcomes of each variable are assumed to be independent of each other. The exposure and outcome variables can be arranged in a 2 x 2 contingency table, where the test examines the association between the row variable and the column variable. The test compares the value in each of the four

squares to the expected value if there were no association between the exposure and the outcome (104).

Logistic regression

Logistic regression is used for the analysis of binary outcome variables in two or more exposure groups. The analysis estimates the odds ratio (OR) which is a measure of association between outcome and exposure. One of the exposure groups is chosen as the reference. Logistic regression models can accommodate covariates to adjust for potential confounding (104). Conditional ORs are used when there are fixed values in a third (or more) variable.

Summary of the studies

Subjects and methods

All studies were approved by the Regional Ethics Review Board at Lund University and the local Radiation Safety Board at Skåne University Hospital, Malmö, Sweden. In statistical analyses generating p-values, the value indicating statistical significance was set at ≤0.05 in all studies.

The Malmö Breast Tomosynthesis Screening Trial

The trial was designed to investigate measures of screening performance such as the sensitivity and specificity of breast cancer detection, detection rates and recall rates of one-view breast tomosynthesis in comparison with two-view mammography (Paper I). The MBTST was a prospective paired population-based trial in the breast cancer screening population in Malmö, Sweden. A random selection of women aged 40 to 74 years old, were invited to participate by letter. Exclusion criteria were pregnancy and/or lack of knowledge in Swedish or English. Participating women gave their written consent and underwent trial screening at Unilabs Breast Centre in Malmö from February 2010 to January 2015. All the participants underwent one-view (MLO view) digital breast tomosynthesis and standard two-view (MLO and CC view) digital mammography on one screening occasion, hence each woman was her own control. The equipment used in the trial was a combined mammography and tomosynthesis machine, Mammomat Inspiration (Siemens Healthcare GmbH, Erlangen, Germany), with a wide tomosynthesis angle (50^{o}).

The images from each modality were read by two breast radiologists, and a total of seven radiologists were involved in a double-blinded procedure. The mammography and tomosynthesis images were read using two different procedures (reading arms), each consisting of three steps, as outlined in Figure 7 below. The tomosynthesis images were read as follows: Step 1, one-view tomosynthesis alone, plus Step 2, the current CC mammography view, and finally, Step 3 images from any previous mammography examinations. The mammography images were read as follows: Step 1, the current mammography examination in the MLO and CC views, plus Step 2, images from any previous mammography examinations, and finally in Step 3, the breast density was categorised (according to the BI-RADS 4^{th} Edition categories, 1:

<25%, 2: 25-50%, 3: 51-75%, 4: >75% fibroglandular tissue) (Figure 3). In each step, the radiologist scored the images on a 5-step scale, from 1 (normal) to 5 (high suspicion of malignancy). Examinations with a score of 3 or higher were discussed at a consensus meeting, when the decision was made to recall the woman for further investigation or not. A woman could be recalled based on findings from breast tomosynthesis alone, mammography alone, a combination of both modalities, or due to self-reported symptoms.

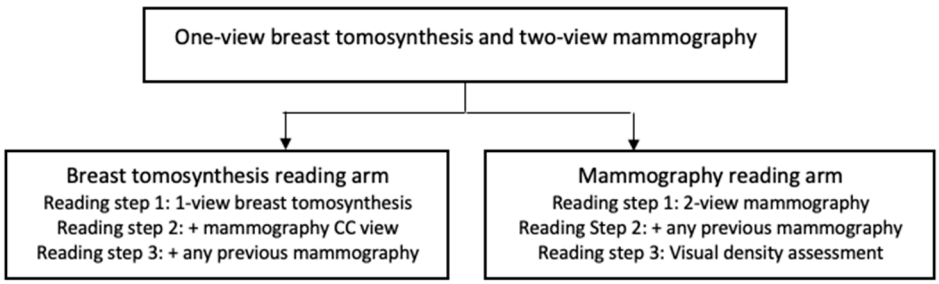

Figure 7: Reading procedure. Flow chart showing the reading procedures in the Malmö Breast Tomosynthesis Screening Trial. Any previous mammography examination could be screening examinations and/or clinical examinations, if available. CC = craniocaudal.

Screen-detected breast cancers, interval breast cancers and false-positive recalls were identified through the Radiology Information System (RIS) and the Swedish Cancer Registry South.

Statistical analysis

Detection rates and false-positive recall rates were calculated per 1000 screened women, and recall rates per 100 screened women, with 95% CIs. Comparisons of detection rates and recall rates between reading arms were performed with McNemar's test. Sensitivity, specificity, positive predictive values and negative predictive values were calculated as described in Figure 6.

Tumour characteristics of cancers in breast tomosynthesis screening

The characteristics of the tumours detected only in Step 1 of the breast tomosynthesis image readings were analysed and compared to the characteristics of the cancers detected with mammography in the MBTST (Steps 1 and 2 of the mammography image readings and Steps 2 and 3 of the breast tomosynthesis image readings) and presented in Paper II. Tumour characteristics such as size, histological type, hormone receptor status and proliferation status were retrieved from pathology reports. Invasive cancers were classified according to St Gallen molecular subtypes: luminal A-like, luminal B-like HER2-negative, luminal B-like HER2-positive,

HER2-positive, and triple-negative (Figure 8). The radiographic appearance of invasive cancers was assessed and classified into the following subgroups: spiculated mass, circumscribed mass, architectural distortion, microcalcifications and nonvisible.

Statistical analysis

Pearson's χ^2 test was applied to compare the exposure (breast tomosynthesis and mammography) to outcome (different tumour characteristics and the radiographic appearance category of a spiculated mass). Radiographic appearances of luminal A-like cancers and non-luminal A-like cancers were compared by number and percentages.

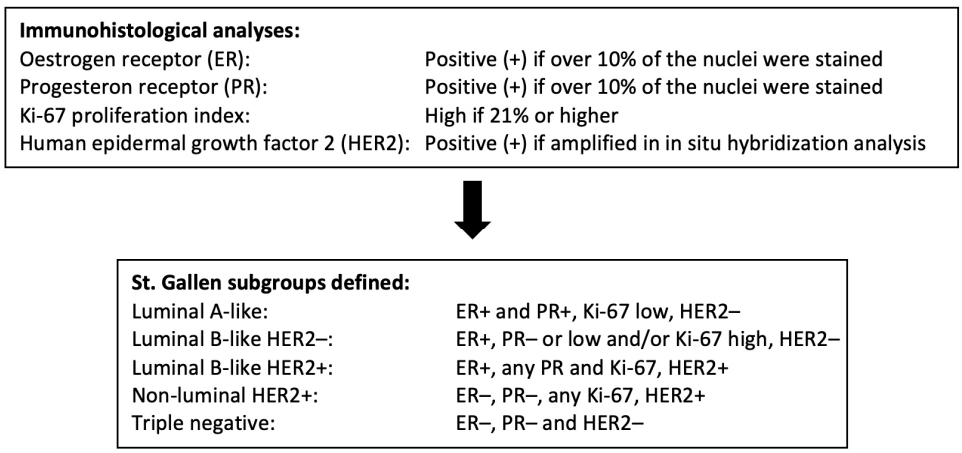

Figure 8: Definitions of the St Gallen subtypes. Categorisation is based on immunohistochemical and in situ hybridization analyses. The definitions are used in the analyses in Paper II and III.

Interval cancers in screening with breast tomosynthesis

The main focus of the study presented in Paper III was to compare the interval cancer rate in the MBTST with that in a contemporary control group. A total of 96 037 screening examinations were performed at the same clinic, Unilabs Breast Centre, in Malmö during the same time period as the MBTST, 2010-2015, identified through RIS. One screening occasion per woman was selected at random, generating 43 769 screened women. Two unique age- and screening-date-matched controls were selected for 13 639 women in the MBTST, generating a control group of 26 738 women (Figure 9). Interval cancers in the MBTST and in the control group were identified through the Swedish Cancer Registry South.

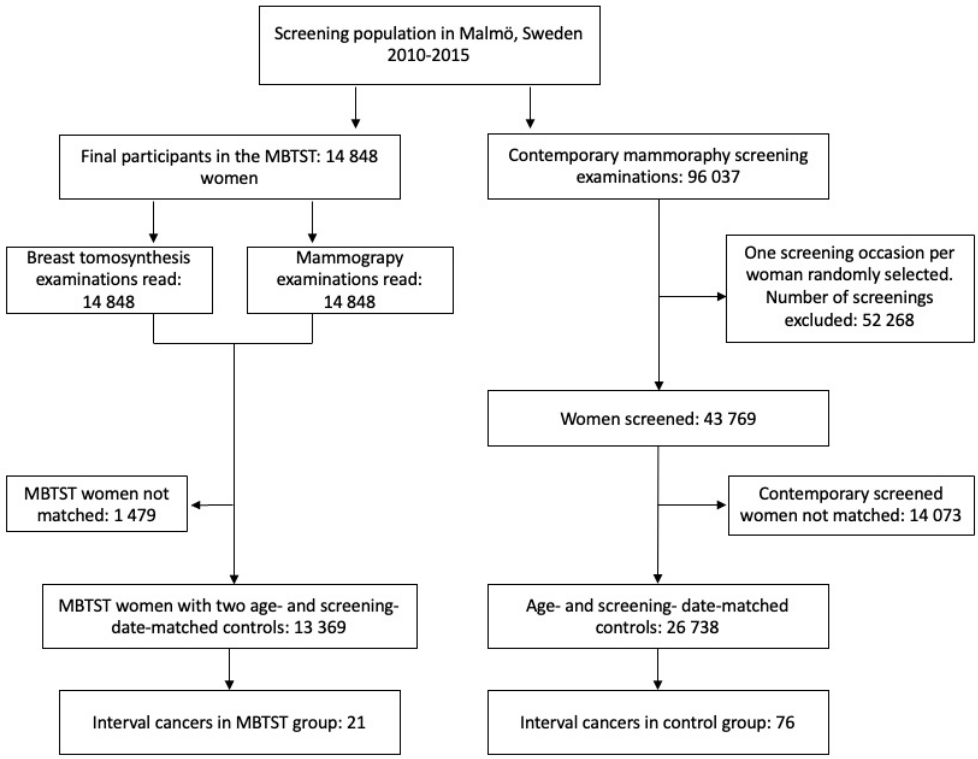

Figure 9: Flow chart. Trial design, trial participants and results in Paper III. MBTST = Malmö Breast Tomosynthesis Screening Trial

The tumour characteristics of the interval cancers in the MBTST and of the interval and screen-detected cancers in the control group were retrieved from pathology reports. As in Paper II, invasive cancers were classified according to St Gallen molecular subtypes (Figure 8).

Statistical analysis

Interval cancer rates and detection rates were expressed as the number of cancers per 1000 screened women, and 95% CIs were calculated. Some analyses were stratified by age, 40-54 and 55-74 years. The relation between the interval cancer rate in the MBTST and that in the control group was analysed using conditional logistic regression, with the age- and screening-date-matched control group as reference. The tumour characteristics of the interval cancers in the MBTST and in the control group were compared by number and percentages.

False-positive recalls

False-positive recalls were the subject of the study presented in Paper IV. Women recalled, but not diagnosed with breast cancer, i.e., false-positive recalls, were identified through the RIS and the Swedish Cancer Registry South. The number of biopsies and the outcome of biopsies (fine-needle aspiration or core needle biopsy) were assessed by reviewing pathology reports. The radiographic appearance of the images in cases of false-positive recalls was assessed by reviewing radiology reports, and classified into seven groups: stellate distortion, circumscribed mass, indistinct density, architectural distortion, focal asymmetry, calcifications and other. Comparisons of false-positive recall rates, biopsy rates and radiographic appearances were made between breast tomosynthesis, mammography, and breast tomosynthesis + mammography, both over the whole period of the MBTST and comparing the first year of the trial with years 2-5.

Statistical analysis

False-positive recall rates were calculated as false-positive recalls per 100 screened women (%) and false-positive biopsy rates as biopsies per 100 false-positive recalls (%) in total, and in the reading arms. 95 % CIs were calculated for rates. Radiographic appearances of the tumours were compared by number and percentages.

Results

Screening performance of breast tomosynthesis in screening

The results of the screening performance measures in the MBTST were presented in Paper I. In total, 21 691 women were invited to participate in the MBTST. Of these, 14 851 gave their written consent and underwent examinations. Three women later withdrew their consent, giving a final number of 14 848 women in the analyses. The mean age at inclusion was 57 years, range 40 to 76 years (standard deviation (SD 10)). Information on breast density was available for 13 907 women. There were 2319 (17%) women in BI-RADS density category 1, 5386 (39%) in category 2, 4949 in category 3 (36%) and 1253 (9%) in category 4. The women in the MBTST were followed at least until their next screening. In total, 139 breast cancers were detected in 137 women (two bilateral cancers), 42 of which were detected in the breast tomosynthesis images only, 8 in the mammography images only, and 89 in both. A total of 22 interval cancers were identified. Screening measure outcomes are presented in Table 1.

Table 1: Screening measure outcomes in Paper I
Measures are expressed per 100 women (%) unless otherwise specified, with 95% CIs.

	Breast tomosynthesis	Mammography	p-value
Sensitivity, %	81.1 (74.2-86.9)	60.4 (52.3-68.0)	
Specificity, %	97.2 (97.0-97.5)	98.1 (97.9-98.3)	
Cancer detection rate, *per 1000 screened women*	8.7 (7.3-10.3)	6.5 (5.2-7.9)	<0.0001
Recall rate, %	3.6 (3.3-3.9)	2.5 (2.2-2.8)	<0.0001
Positive predictive value, %	24.1 (20.5-28.0)	25.9 (21.6-30.7)	
Negative predictive value, %	99.8 (99.7-99.9)	99.6 (99.4-99.7)	

The mean glandular dose was lower in one-view digital breast tomosynthesis (2.3 mGy, ± 0.7) than in two-view digital mammography (2.7 mGy, ± 0.8). The mean compression force in the MLO projection with breast tomosynthesis was 71 N (± 21) and in the MLO projection with mammography 118 N (± 24).

Similar tumour characteristics with breast tomosynthesis and mammography

Detailed tumour characteristics of the breast cancers detected in the MBTST were presented in Paper II. Of the 139 breast cancers detected, 118 were invasive and 21 were ductal carcinomas in situ. Forty cancers, 37 of which were invasive, were detected in Step 1 in the breast tomosynthesis image reading arm and these constituted the additional cancers (i.e., those not detected with mammography). A total of 99 cancers were detected by mammography, either when reading the mammography images, or in Steps 2 or 3 in the breast tomosynthesis reading arm, 81 of which were invasive.

Tumour characteristics were available for most cancers. No clinically relevant or statistically significant differences were seen in the distribution of cancers 20 mm or smaller between cancers detected with breast tomosynthesis and cancers detected with mammography (86% [31 of 36] vs. 85% [68 of 80], respectively; p = 0.88), negative lymph node status (75% [27 of 36] vs. 73% [59 of 80], respectively; p = 0.89) or low histological grade (grade 1; 42% [15 of 36] vs. 40% [32 of 80], respectively; p = 0.87). A trend was observed towards a higher proportion of invasive lobular cancers in the additional cancers detected with breast tomosynthesis than in the cancers detected with mammography (30% [11 of 37] vs. 17% [14 of 81], respectively; p = 0.13).

The distribution of luminal A-like cancers was also similar with breast tomosynthesis and mammography (53% [19 of 36] vs. 46% [37 of 81], respectively; p = 0.48), positive progesterone receptor status (69% [25 of 36] vs. 74% [59 of 80], respectively; p = 0.63) and low proliferation status (Ki-67≤ 20%; 58% [21 of 36] vs. 57% [46 of 81], respectively; p = 0.88). Three of eight triple-negative cancers, the subtype with the least favourable prognosis, were detected only with breast tomosynthesis.

The radiographic appearance of the majority of the additional cancers detected with breast tomosynthesis was a spiculated mass: 14 luminal A-like (77 % [14 of 19]) and 13 non-luminal A-like tumours (74% [13 of 17]). The spiculated mass appearance of luminal A-like cancers did not differ from that of non-luminal A-like cancers (84% [46 of 55] vs. 72% [44 of 61], respectively; p = 0.14). Figure 10 shows a cancer detected only with breast tomosynthesis.

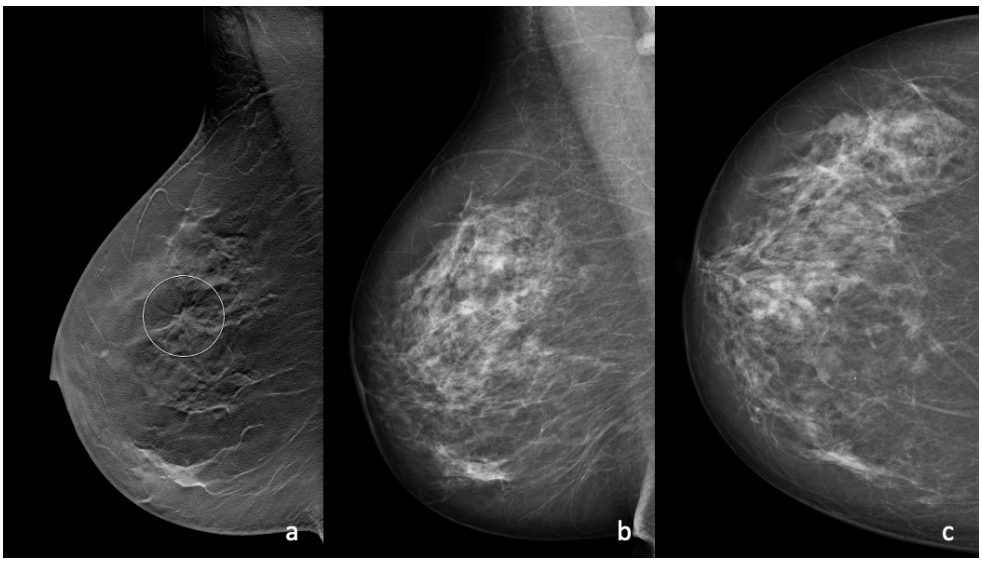

Figure 10: Images of a breast cancer detected with breast tomosynthesis only. A 55-year-old woman who was diagnosed with a 13 mm invasive ductal, node-negative, luminal B-like, HER2 negative breast cancer. a) The breast tomosynthesis image in the MLO view, the stellate tumour encircled. b) and c) Mammography images in the MLO and CC views, respectively.

Reduced interval cancer rate in breast tomosynthesis screening

Interval cancer rates in the MBTST and a matched control group were compared in Paper III. Twenty-one interval cancers were diagnosed in the MBTST group and 76 interval cancers were diagnosed in the control group (Figure 9). The mean age was 56 years (SD 10) in both the MBTST group and the control group. The interval cancer rate in the MBTST was 1.6 per 1000 screened women (21 of 13 369; 95% CI: 1.0-2.4), and 2.8 per 1000 screened women in the control group (76 of 26 738; 95% CI: 2.2-3.6); conditional OR 0.6 (95% CI: 0.3-0.9); p = 0.02), meaning that the odds of interval cancer were 40% lower in the MBTST group than in the matched control group.

The interval cancer rate in women aged younger than 55 years at screening was 1.3 per 1000 screened women (8 of 6289; 95% CI: 0.6-2.5) in the MBTST compared with 2.6 per 1000 screened women in the control group (33 of 12 541 (95% CI: 1.8-3.7); conditional OR 0.5 (95% CI: 0.2-1.1); p = 0.07). In women aged 55 years or older at screening, the interval cancer rate in the MBTST was 1.8 per 1000 screened women (13 of 7080; 95% CI: 1.0-3.1) compared with 3.0 per 1000 screened women in the control group (43 of 14 197; 95% CI: 2.2-4.1); conditional odds ratio, 0.6 (95% CI: 0.3-1.1); p = 0.11).

Of the 21 interval cancers diagnosed in the MBTST, 90% (19 of 21) were invasive, compared with 95% (72 of 76) in the control group. The mean size of invasive tumours, after excluding tumours receiving neo-adjuvant treatment, was 15 mm (SD 7) in the MBTST group and 20 mm (SD 10) in the control group. A large proportion of the invasive interval cancers consisted of invasive ductal carcinomas in both the MBTST and the control group (90% [17 of 19] and 80% [58 of 72], respectively). The invasive interval cancers in both the MBTST and the control group exhibited in general high (>20%) Ki-67 values (63% [12 of 19] and 75% [54 of 72]), and low proportions of luminal A-like subtype cancers (26% [5 of 19] and 17% [12 of 72]), respectively.

False-positive recall rate reduced over time

The aim of the study in Paper IV was to evaluate false-positive recall rates, false-positive biopsy rates and radiographic appearance of false-positive recalls in the MBTST. The mean age at screening of the women with false-positive recalls was 53 years (SD 9.7). The overall false-positive recall rate was 3.5% (514 of 14 848, 95% CI: 3.3-3.8) in total, 1.6% (244 of 14 848, 95% CI: 1.4-1.8) in the breast tomosynthesis reading arm, 0.8% (121 of 14 848, 95% CI: 0.7-1.0) in the mammography reading arm and 1.0% (149 of 14 848, 95% CI: 0.9-1.1) in both reading arms. The false-positive recall rate in the breast tomosynthesis reading arm was higher during the first year of the MBTST, 2.6% (38 of 1480, 95% CI: 1.8-3.5) and then stabilized at about 1.5% (206 of 13 368, 95% CI: 1.3-1.8). The false-positive recall rate in the mammography reading arm varied between 0.5 and 1% throughout the MBTST.

The most common radiographic appearance among the false-positive recalls in the breast tomosynthesis reading arm only was a stellate distortion, 37.3% (91 of 244), whereas the most common radiographic appearance in the mammography reading arm only was a circumscribed mass, 29.8% (36 of 121). In false positives recalled in both the breast tomosynthesis and mammography reading arm, the most common reason for recall was symptoms, 38.3% (57 of 149). Normal breast tissue was the dominant work-up outcome in both the breast tomosynthesis reading arm, 57.0% (139 of 244) and in the mammography reading arm, 50.4% (61 of 121). Figure 11 shows images from a false-positive recall.

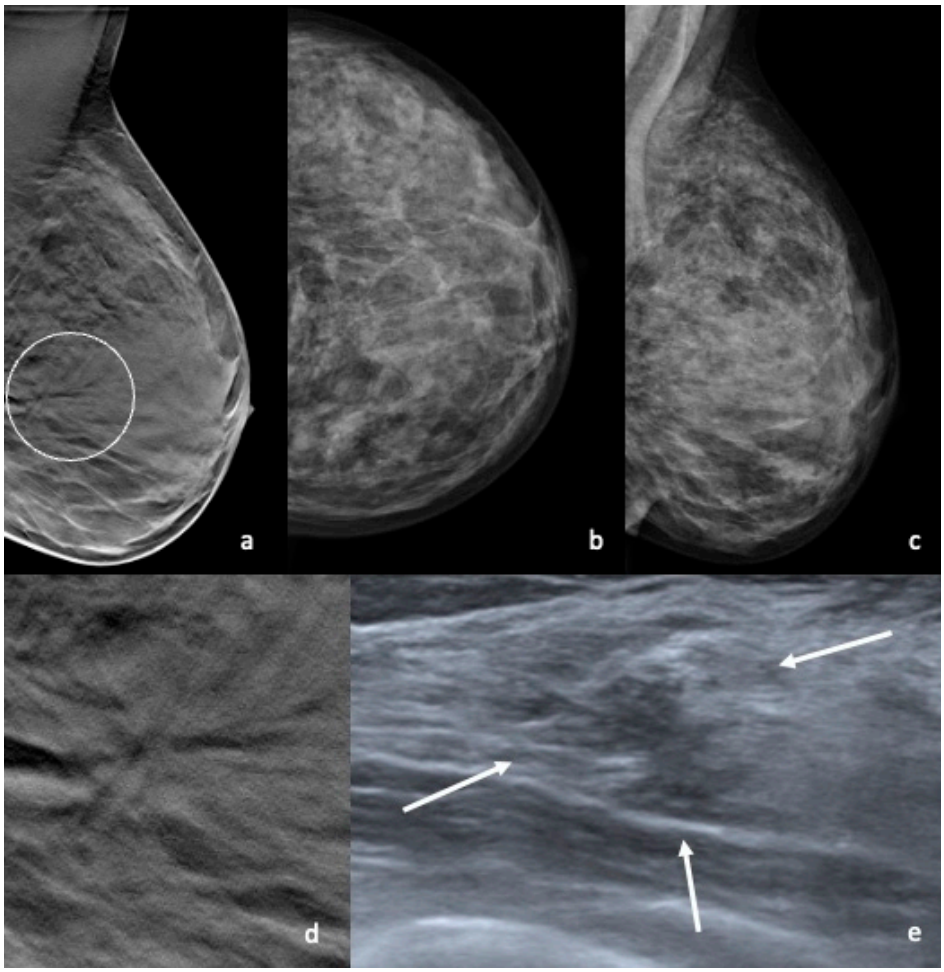

Figure 11: Images from the breast of a false-positive recalled woman. A 48-year-old woman was recalled due to a stellate distortion in the breast tomosynthesis reading arm. a) One-view breast tomosynthesis (MLO) image with the distortion encircled. b) and c) Mammography screening images in the MLO and CC views. d) Enlargement of the false-positive finding in the breast tomosynthesis image. e) Ultrasound image showing a diffuse irregular lesion (arrows). Core needle biopsy confirmed a radial scar.

The false-positive biopsy rate in the breast tomosynthesis reading arm only was lower during the first year, 16% (6 of 38, 95% CI: 6-31), than during years 2 to 5, 32.0% (66 of 206, 95% CI: 25.7-38.9). The most common radiographic appearance leading to a false-positive recall based on the breast tomosynthesis reading arm only during the first year of the MBTST was a stellate distortion, 50% (19 of 38), however, the proportion of stellate distortions was lower during years 2 to 5, 35.0% (72 of 206).

Discussion

The results presented in this thesis show an improvement in breast cancer detection rate with breast tomosynthesis compared with mammography. The additional cancers detected only with breast tomosynthesis showed a similar distribution of cancer subtypes to those identified with mammography. The interval cancer rate was lower with breast tomosynthesis screening than in a contemporary matched control group, screened with mammography. Finally, breast tomosynthesis was associated with a higher false-positive recall rate.

Screening with breast tomosynthesis

Cancer screening is a complex intervention in which healthy individuals are examined in order to detect asymptomatic cancer early, with the overall aim of reducing cancer mortality. The method used should be sensitive, specific, fast, cost-effective and acceptable to the individuals that are examined.

One-view breast tomosynthesis was found to have a 34% higher breast cancer detection rate than two-view mammography (Paper I). This is in line with the results of other prospective trials also showing an increase in detection rate with breast tomosynthesis (1, 54, 57, 105, 106). However, no improvement was seen in the randomised controlled To-Be trial (56). The MBTST is the only trial to explore one-view breast tomosynthesis as a stand-alone modality. In all other trials, the addition of two-view breast tomosynthesis to mammography and/or synthesised mammography to two-view mammography was compared. Furthermore, different breast tomosynthesis machines have been used with different acquisition angles, X-ray tube movements and number of images, making direct comparisons difficult. Age and screening intervals also vary between the trials. Nevertheless, there is convincing evidence that breast tomosynthesis detects more breast cancers than mammography. Table 2 presents an overview of the prospective trials and detection rates found in the literature.

Table 2: Overview of prospective breast tomosynthesis screening trials
All examinations were two-view unless otherwise stated. Differences in the detection rates using the two modalities are statistically significant, except for the To-Be trial.

Trial, publication year	Participants (N)	Trial design	Detection rate BT, per 1000 screened women	Detection rate M, per 1000 screened women
STORM, 2013	7 292	Paired, BT + M vs. M	8.1	5.3
STORM-2, 2016	9 677	Paired, BT + M and BT + sM vs. M	8.5*, 8.8**	6.3
MBTST, 2018	14 848	Paired, 1-view BT vs. M	8.7	6.5
Verona DBT pilot, 2018	34 071	BT + sM vs. previous M screening round	9.2	5.2
OTST, 2019	24 301	Paired, BT + M and BT + sM vs. M	7.6	9.6
To-Be, 2019	28 749	RCT, BT + sM vs. M	6.6	6.1
TOSYMA, 2022	99 689	RCT, BT + sM vs. M	7.1	4.8
RETomo, 2022	26 877	RCT, BT + M vs. M	7.6	4.5

BT = breast tomosynthesis, M = mammography, sM = synthesised mammography, RCT = randomised controlled trial. *BT + M vs. M, **BT + sM vs. M.

The recall rate was higher in the breast tomosynthesis reading arm (3.6%) compared with the mammography reading arm (2.5%) but still well below the recommended acceptable levels in European guidelines. They state that the recall rate in prevalence screening should be <7% and in subsequent screening <5% (101).

Studies on the characteristics of tumours detected with breast tomosynthesis screening have in general shown that they have favourable properties, such as smaller size, lower grade, oestrogen receptor positivity and fewer lymph node metastases (105, 107-110). The present study on tumour characteristics (Paper II) showed that cancers detected only with breast tomosynthesis had similar properties to those detected with mammography, which is in line with the results of the randomised controlled To-Be and TOSYMA trials (56, 57). However, the majority of the cancers in the present study were small and oestrogen receptor positive, as reported in other studies. The trial design with breast tomosynthesis as stand-alone modality could partly explain the difference in results. The sample sizes in subgroups of all these trials, including the MBTST, are small and not statistically powered to compare differences, and a larger true consistency in tumour characteristics between the studies cannot be ruled out.

The fact that the interval cancer rate was found to be lower with breast tomosynthesis screening than with mammography in the current work (Paper III) is an important indicator that screening detects relevant cancers that would otherwise have become symptomatic before the next screening occasion. However, the MBTST is the only breast tomosynthesis screening trial so far to show an overall reduced interval cancer rate compared to mammography. The results of the randomised controlled Reggio Emilia Tomosynthesis trial suggested a reduced interval cancer rate in women aged 45 to 49 years, but the number of participants in

that age interval was small, (5053 in experimental arm and 5103 in control arm) (111). Whereas RCTs use dedicated control groups for comparison, other trials have used data from previous screening rounds (55, 112) or, similar to the control group presented in Paper III, contemporarily screened women as controls (113).

The false-positive recall rate in several other trials comparing breast tomosynthesis with mammography was lower with breast tomosynthesis, as opposed to what was seen in the MBTST. The false-positive recall rate in the breast tomosynthesis reading arm in the MBTST was low in comparison with other trials, only the To-Be trial showed a lower false-positive recall rate with breast tomosynthesis (Table 3). Detailed data on false-positive recalls in breast tomosynthesis screening is so far limited. Only one other trial, the To-Be trial, has reported radiographic appearances of false positives in breast tomosynthesis screening. The most common radiographic appearance of false-positive recalls with DBT in that trial was asymmetry, 28.9%, which is different from the MBTST where only 0.4% showed focal asymmetry. Spiculated masses were uncommon, only 0.6%, whereas stellate distortions were very common in the MBTST, 36.9%. The inconsistent results are likely to be explained by different definitions of appearances, different readers, various screening populations and that the examinations were performed on different machines.

Table 3: Overview of false-positive recall rates in breast tomosynthesis screening trials

Trial, publication year	Participants (N)	Trial design	Total FP recall rate, % BT	Total FP recall rate, % M
STORM, 2013	7 292	Paired, BT + M vs. M	3.5	4.4
STORM-2, 2016	9 677	Paired, BT + M and BT + sM vs. M	4.0*, 4.5**	3.4
MBTST, 2018	14 848	Paired, 1-view BT vs. M	2.6	1.8
OTST, 2019	24 301	Paired, BT + M and BT + sM vs. M	2.4	2.1
To-Be, 2019	28 749	RCT, BT + sM vs. M	2.4	3.4
TOSYMA, 2022	99 689	RCT, BT + sM vs. M	4.1	4.4
RETomo, 2022	26 877	RCT, BT + M vs. M	3.1	3.4

FP = false positives, BT = breast tomosynthesis, M = mammography, sM = synthesised mammography, RCT = randomised controlled trial. *BT + M vs. M, **BT + sM vs. M.

Limitations of the Malmö Breast Tomosynthesis Screening Trial

There were three reading steps in the breast tomosynthesis reading arm. The reason for including the mammography image in the CC view in Step 2 was to ascertain the value it added to the one-view MLO projection in breast tomosynthesis. Previous mammography images, if available, were included in Step 3. The images read in the breast tomosynthesis reading arm are thus not only tomosynthesis images. However, 40 out of 42 of the cancers detected only in that reading arm were detected in reading Step 1.

The decision to recall a woman or not when the image score was 3 or higher, was made at a consensus meeting, where all the images from the MBTST trial and any previous examinations were available. The recall rate in the mammography reading arm could have been reduced as suspect lesions in the mammography images could have been judged as benign if no corresponding findings were visible in the breast tomosynthesis images. The recall rate found in the MBTST (Paper I) may not apply in other screening settings with different reading routines.

Individual characteristics, such as body mass index and menopause status, are not recorded in the Swedish breast cancer screening programme, and were therefore not assessed in the MBTST. A high body mass index is known to be a risk factor for breast cancer, and menopause status affects breast density and thus breast cancer risk (11). Including these would have added more information in subgroup analysis. The results were stratified into two age-groups, 40 to 54 and ≥55 to 74 years of age as a surrogate for menopausal status in Paper III. Most women older than 54 years are likely to be menopausal, however, the women in the lower age group will have different menopausal statuses. Breast density is also not assessed by radiologists or by software in the normal screening programme. This was done in the MBTST as part of the mammography reading arm, but not in the control group, described in Paper III, as it was retrospectively defined. It would have been advantageous to be able to stratify cancer detection and interval cancer rates based on breast density. The age stratification compensates for the lack of breast density assessment to some extent, but is less accurate.

The images obtained in the MBTST were read by four breast radiologists, two in each reading arm. When comparing the interval cancer rate in the MBTST to that in the control group (Paper III) where two readers read each image as part of the regular screening programme, it is possible that the sensitivity was higher in the MBTST group than in the control group. This might have had an effect on the interval cancer rate in the trial that is not attributable to breast tomosynthesis itself.

The radiographic appearances of false-positive recalls (Paper IV) were retrieved from breast tomosynthesis and mammography reports to understand the clinical reason for recall. This limits the comparability between studies on radiographic appearances in breast tomosynthesis screening as the definitions used were not standardized. The appearances were also not clearly written out in some reports and for those images the appearances were retrospectively reviewed. The true reason for recall and the reason for recall in the study might therefore not be the same.

Methodological considerations

The highest level of scientific evidence in screening trials is obtained in RCTs where participants are randomised either to the exposure group or the control group. Breast cancer has a low prevalence, making it necessary to have very large study samples, and when breast cancer mortality is used as a measure of screening efficacy, the trials are very time-consuming (6). Paired trials have therefore been suggested as an efficient and adequate way to evaluate a new screening method (90).

Almost all trials performed so far have analysed breast tomosynthesis in one screening round, as was the case in the MBTST. When using a more sensitive screening method in a population for the first time it is to be expected that the new method will detect more cancers, among them slow-growing ones that might have been detected later with the conventional method, this is called the prevalence effect, and is closely related to both lead time and length time biases. In the mammography screening round following the MBTST the proportion of luminal A-like cancers was reduced (unpublished data), supporting the theory that cancers detected with breast tomosynthesis are at early, less aggressive stages. Retrospective studies have shown sustained favourable outcomes of screening with breast tomosynthesis over multiple screening rounds (114, 115) and one prospective trial, the Verona DBT pilot (116), has also shown sustained favourable outcomes in one subsequent round, but the lack of more prospective studies on repeated breast tomosynthesis screening rounds is a general limitation in this research field. This reduces our ability to fully understand how the implementation of breast tomosynthesis in screening would affect detection rates over time.

There will be a selection bias in all studies in which subjects are invited to participate. The women who chose to participate in the MBTST might have differed from those who chose not to participate, in aspects such as age, socio-economic status and general interest in health (117). Declining participants are accounted for in RCTs, which is a strength of this design. There is also an inherent selection bias in breast screening itself, as it has been shown that women who choose to participate generally have a higher socio-economic status (118).

The paired design in the MBTST means that each woman is her own control when measuring the diagnostic accuracy, but a control group is needed when comparing the interval cancer rate in breast tomosynthesis screening with that in mammography screening. The mammography control group (Paper III) was not specifically defined in the MBTST design, which limited the possibility of assessing risk factors and limiting biases. Statistical analysis using logistic regression and age-weighted comparisons can limit biases, but a pre-specified control group would have improved the study.

The MBTST was powered for measurements of diagnostic accuracy, but not for subgroup analyses. Some subgroup analyses are presented in Papers II-IV, where statistical tests have been performed, but the subgroups are mainly compared by number and percentages. Differences and similarities between subgroups should therefore be interpreted with caution due to the small sample sizes.

The European Union guidelines on breast cancer screening and diagnosis recommend screening from the age of 45 (80). However, the Swedish mammography screening programme includes women from the age of 40, in contrast to most other European screening programmes. Younger women generally have denser breasts, and a lower risk of developing breast cancer, however, if they do, it is often more aggressive than in older women (10, 32, 119). This will affect screening and the interpretation of the results in the MBTST. For example, since the sensitivity of mammography is lower in dense breasts, the inclusion of younger women will affect the overall cancer detection rate.

Conclusions

The overall conclusion drawn from the research presented in this thesis is that tomosynthesis can play a role in breast cancer screening as it provides several benefits.

- Breast cancer screening with one-view digital breast tomosynthesis had a higher sensitivity but a slightly lower specificity for breast cancer detection than two-view digital mammography (Paper I).
- Breast tomosynthesis in screening might not alter the predictive and prognostic profile of screen-detected cancers (Paper II).
- Breast tomosynthesis screening contributes to the earlier detection of cancers that would otherwise have become symptomatic before the next screening round (Paper III).
- Breast tomosynthesis has an acceptable false-positive recall rate. (Paper IV).

Future perspectives

The results presented in this thesis will be useful in the future as breast tomosynthesis is successively implemented in different breast screening programmes. The breast cancer screening programme in Sweden is currently being evaluated by the National Board of Health and Welfare, and it has been suggested in the European Union guidelines that breast tomosynthesis is an option for women with dense breasts (120).

The general lack of breast radiologists in the world has increased the need for solutions in screening image reading. The addition of breast tomosynthesis would increase the reading time, further emphasizing the need for new reading strategies. AI offers a possible solution, and has been the subject of discussion for a while. Studies have shown that the performance of AI mammography software is similar to that of breast radiologists in detecting breast cancer (44, 45, 121, 122). However, the studies performed so far on the diagnostic accuracy of AI have some limitations. One is that they have mostly been carried out on enriched materials, where the proportion of images showing cancer is higher than in screening. Also, all the studies performed to date have been retrospective (123). Moreover, there are few studies evaluating AI in breast tomosynthesis image reading. There are four ongoing Swedish prospective AI mammography screening trials: Mammography Screening with Artificial Intelligence (MASAI) (ClinicalTrials.gov NCT04838756), Artificial Intelligence in Breast Cancer Screening in Region Östergötland Linköping (AI-ROL) (ClinicalTrials.gov NCT05048095), ScreenTrust CAD (NCT04778670) and ScreenTrust MRI (NCT04832594).

Personalised screening is another possible future strategy in breast cancer screening (124). The life-time risk of developing breast cancer varies, and it may be more effective to screen women with average to high-risk with a more sensitive, but also more resource-demanding, modality than mammography. Breast tomosynthesis could be used, for example, to screen women with dense breasts (125).

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THE OVERALL AIM of the research in this thesis was to investigate potential benefits and challenges of breast tomosynthesis in breast cancer screening. The studies focus on the performance of breast tomosynthesis in screening, in terms of screening performance measurements, the subtypes of breast cancer that are detected, screening efficacy, and false-positive recalls.

KRISTIN JOHNSON, M.D., is a radiologist and is currently working at Skåne University Hospital in Sweden.

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