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BEYOND MAMMOGRAPHY: AN EVALUATION OF COMPLEMENTARY MODALITIES IN BREAST IMAGING

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Beyond mammography: An evaluation of complementary modalities in breast imaging

Thesis for Doctoral degree (Ph.D.)

By

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To my family, through blood or love.

"Curtsey while you're thinking what to say. It saves time".

Lewis Carroll

Through the Looking-Glass

Popular science summary of the thesis

There is a greater likelihood of surviving breast cancer if the cancer is detected early and the tumour is relatively small and less aggressive. Mammography is an x-ray examination of the breast which may be used to identify early breast cancer (screening). The reliability of the method in detecting breast cancer is decreased among women who have a large proportion of glandular and connective tissue in their breasts compared to women who have a large proportion of fatty tissue. These women would benefit from additional imaging methods such as ultrasound or magnetic resonance imaging (MRI). One major hindrance to such an approach is the drastic increase in cost for each extra detected cancer. We therefore tested some alternative methods that may potentially be less costly. We compared a new ultrasound method (ABVS) to a traditional ultrasound examination and found that it had a similar ability to detect breast cancer. We also tested if adding infrared imaging to mammography screening would increase our ability to find more breast cancers. In one study, we compared a hypothetical situation with an MRI examination of 5 minutes instead of 30 minutes and found that the shorter examination was sufficient for finding the same proportion of breast cancers. The true cost of each extra detected breast cancer by using these methods has to be further studied in screening settings.

Abstract

Breast cancer is the main cause of cancer death among women worldwide and the goal of mammography screening is to reduce breast cancer-specific mortality. The reduction of the sensitivity of mammography for detecting cancer among women with dense breasts requires the use of complementary methods for this subset of women. Three of the projects in this thesis examine the performance of such complementary methods and a fourth study investigates the association between the biomarker BPE (background parenchymal enhancement) and risk factors for breast cancer.

In study 1, we prospectively compared the sensitivity and specificity of Automated Breast Volume Scanner (ABVS) with handheld ultrasound for detection of breast cancer among women with a suspicious mammographic finding who were recalled after attending the population-based mammography screening program. We performed both methods on 113 women and found 26 malignant lesions. Analysis was performed in two categories: breasts with a suspicious screening mammography and breasts with a negative screening mammography. In the first category (n=118) the sensitivity of both methods was 88% (p=1.0), the specificity of handheld ultrasound was 93.5 % and ABVS was 89.2%. The difference in specificity was not statistically significant (p=0.29). For breasts without a suspicious mammographic finding, the sensitivity of handheld ultrasound and ABVS was 100% (p=1.0), the specificity was 100% and 94.1% respectively. The difference in specificity was statistically significant (p=0.03). In summary, ABVS has similar sensitivity to handheld ultrasound, but lower specificity in breasts with a negative mammogram.

In study 2, we explored the incremental cancer detection rate when adding a three-dimensional infrared imaging (3DIRI) score to screening mammography among women with dense breasts (Volpara volumetric density >6 % on the previous mammography examination) who attended the population-based mammography screening program. Women with a negative mammogram and positive 3DIRI score were triaged for a DCE-MRI examination to verify the presence of cancer. Of 1727 participants, 7 women had a mammography-detected breast cancer. Among women with a negative mammogram and a positive infrared imaging (n=219), an additional 6 cancers in 5 women were detected on MRI resulting in an incremental cancer detection rate of 22.5 per 1000. Among women with a negative mammography and infrared examination, one woman was diagnosed with breast cancer during the two-year follow-up. The study does not provide information on the proportion of cancers that might have been detected had MRI been performed among women with a negative mammogram and 3DIRI score. Consequently, this study does not shed light on the diagnostic accuracy of infrared imaging or whether using an infrared risk score is the optimal method for identifying women who would benefit from additional imaging modalities.

In study 3, we used MRI examinations of study 2 among women without breast cancer (n=214) to explore the association between BPE at DCE-MRI and a large array of risk factors for breast cancer. Thanks to the Karma database, we had unique access to data from self-reporting questionnaires on risk factors. BPE and mammographic density were assessed visually by three radiologists and BPE was further dichotomized into low and high. We created categorical variables for other risk factors. We calculated the univariable associations between BPE and each risk factor and fitted an adjusted logistic regression model. In the adjusted model, we found a negative association with age (p=0.002), and a positive association with BMI (p=0.03). There was a statistically significant association with systemic progesterone (p=0.03) but since only five participants used progesterone preparations, the result is uncertain. Although the likelihood for high BPE increased with increase in mammographic density, the association was not statistically significant (p=0.23). We were able to confirm earlier findings that BPE is associated with age, BMI and progesterone, but we could not find an association with other risk factors for breast cancer.

In study 4, we compared the diagnostic accuracy, reading-time, and inter-rater agreement of an abbreviated protocol (aMRI) to the routine full protocol (fMRI) of contrast-enhanced breast MRI. The MRI examinations were performed before biopsy and among women who were not part of a surveillance program due to an increased familial risk of breast cancer. Analysis was performed on a per breast basis. Aggregated across three readers, the sensitivity and specificity were 93.0% and 91.7% for aMRI, and 92.0% and 94.3% for the fMRI. Using a generalized estimating equations approach to compare the two protocols, the difference in sensitivity was not statistically significant (p=0.840), and the difference in specificity was significant (p=0.003). There was a statistically significant difference in average reading time of 67 seconds for aMRI and 126 seconds for the fMRI (p= 0.000). The inter-rater agreement was 0.79 for aMRI and 0.83 for fMRI. We were able to demonstrate that the abbreviated protocol has similar sensitivity to the full protocol even if MRI is performed before biopsy and the images lack telltale signs of malignancy.

In conclusion, this thesis provides new knowledge about the biomarker BPE, broadens our knowledge on the diagnostic accuracy of two different imaging modalities and highlights the importance of good study design for diagnostic accuracy studies.

List of scientific papers

I **Roxanna Hellgren**, Paul Dickman, Karin Leifland, Ariel Saracco, Per Hall, Fuat Celebioglu

Comparison of handheld ultrasound and automated breast ultrasound in women recalled after mammography screening

Acta Radiologica 2017;58:515-520.

II **Roxanna Hellgren**, Ann Sundbom, Kamila Czene, David Izhaky, Per Hall, Paul Dickman

Does three-dimensional functional infrared imaging improve breast cancer detection based on digital mammography in women with dense breasts?

European Radiology 2019;29:6227-6235.

III **Roxanna Hellgren**, Ariel Saracco, Fredrik Strand, Mikael Eriksson, Ann Sundbom, Per Hall, Paul Dickman

The association between breast cancer risk factors and background parenchymal enhancement at dynamic contrast-enhanced breast MRI

Acta Radiologica 2020;61:1600-1607.

IV **Roxanna Hellgren**, Ernst Tolocka, Ariel Saracco, Brigitte Wilczek, Ann Sundbom, Per Hall, Paul Dickman

Comparing the diagnostic accuracy, reading time and inter-rater agreement of breast MRI abbreviated and full protocol: a multi-reader study

Manuscript.

Contents

List of abbreviations

DCIS	Ductal carcinoma in situ
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor
SNP	Single nucleotide polymorphism
BRCA	Breast cancer gene
BI-RADS	Breast imaging reporting and data system
BPE	Background parenchymal enhancement
DCE-MRI	Dynamic contrast-enhanced MRI
fMRI	MRI full protocol
aMRI	MRI abbreviated protocol
KARMA	Karolinska mammography project for risk prediction of breast cancer
ABVS	Automated breast volume scanner
3DIRI	Three-dimensional infrared imaging
AI	Artificial intelligence
ROC	Receiver operating characteristic
MET	Metabolic equivalent of task
BMI	Body mass index

1 Introduction

This thesis gives an account of why early detection is an important endeavor for reducing the physical and psychological burden of breast cancer, why screening mammography does not benefit all women, and how we can identify this subset of women. It also gives an in depth presentation of other imaging modalities that play a key role in cancer detection. Three of the four studies presented in this thesis have investigated methods that could potentially be cost-effective additions to mammography screening. The fourth study has investigated the association of risk factors for breast cancer with background parenchymal enhancement, a biomarker that can be measured at contrast enhanced breast MRI.

2 Literature review

2.1 The global burden of breast cancer

Breast cancer is a physical, emotional and financial burden on women and families worldwide. It is a leading cause of cancer death among women in Sweden and globally [1]. According to the World Health organization, breast cancer accounted for 627 000 deaths worldwide in 2018 [2]. In Sweden in the same year, almost 8000 new cases were reported and 1407 died of breast cancer [3]. It is more likely for a woman to be diagnosed with breast cancer in high income countries (1 in 11 women) than in low income countries (1 in 38 women) [1]. At the same time, data from the International Agency for Research on Cancer (IARC) shows that the estimated age-standardised mortality rate for breast cancer per 100 000 was lowest in high income countries [4]. Figures 1 & 2 show global estimated age-standardized incidence and mortality rates per 100 000.

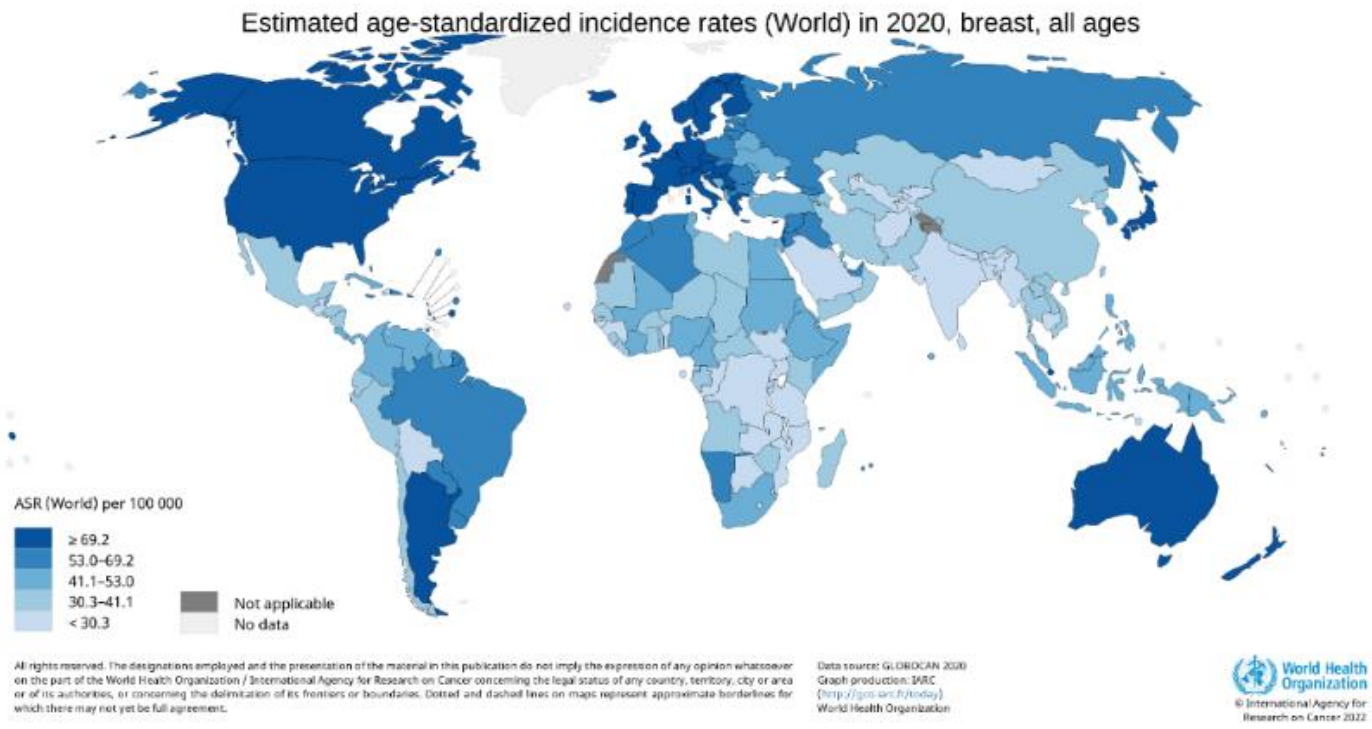

Figure 1. Estimated age-standardized incidence rates in 2020 worldwide for breast cancer.

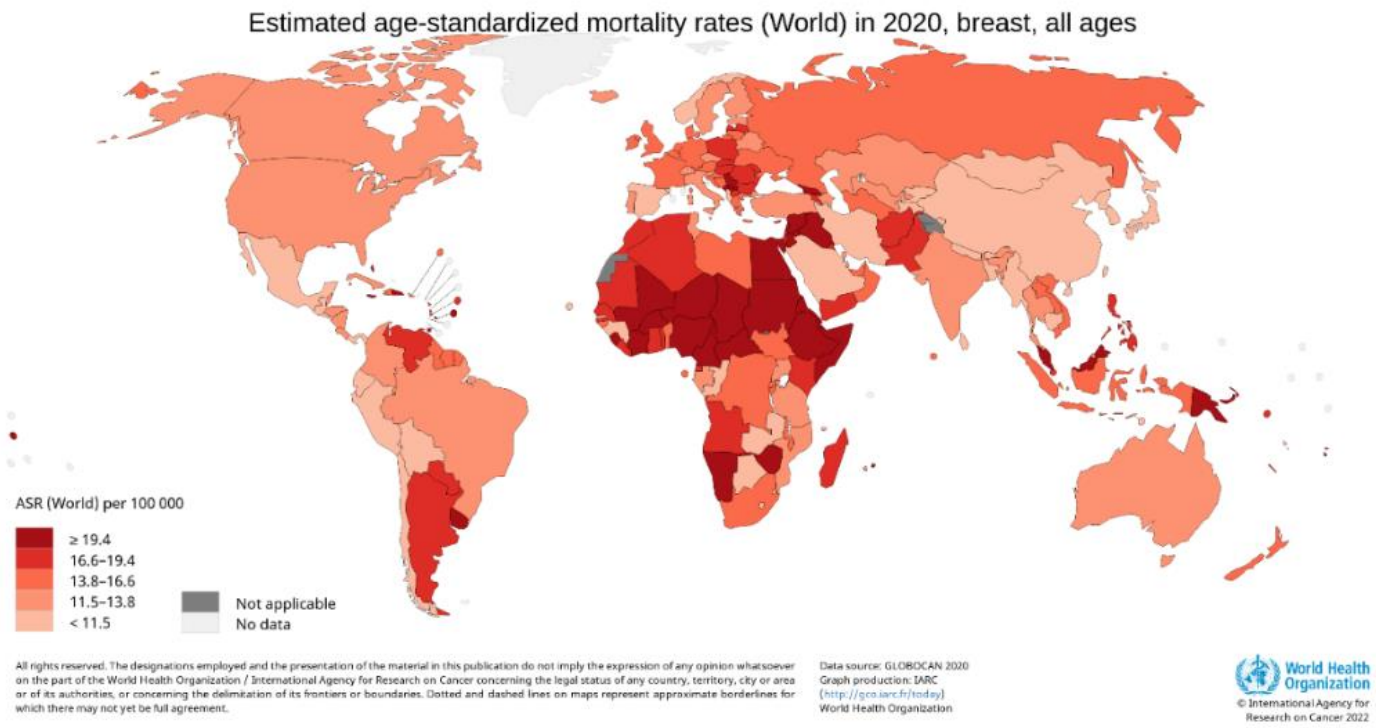

Figure 2. Estimated age-standardized mortality rates worldwide in 2020 for breast cancer.

The highest mortality rate was reported from Fiji, with an age-standardised mortality rate of 36.9 and an incidence rate of 63.4 [4]. In Sweden, the age-standardised mortality rate was 11.4 and incidence rate was 89.8. Many Swedish women are diagnosed with breast cancer, but the majority will not die from the disease (Figure 3).

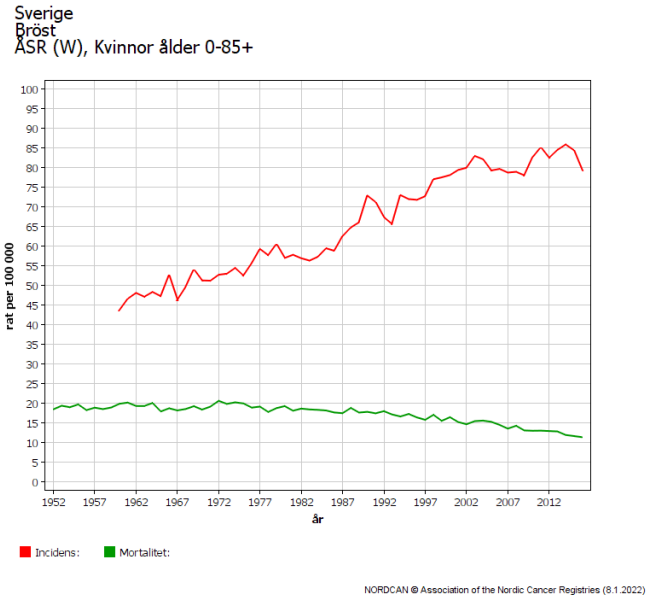

Figure 3. Estimates of Swedish incidence and mortality rates per 100 000.

The high incidence rate is attributed not only to lifestyle factors that increase the risk of developing breast cancer, but also differences in reporting between countries. A study on the degree of reporting to the Swedish Cancer Register, found an underreporting of only 3.7 % compared to hospital records [5]. There is likely a higher degree of underreporting in countries where scarce health care resources are not used for reporting and monitoring disease. The low mortality rate in high-income countries is attributed not only to improvement in cancer therapy, but also early detection by screening. This can be illustrated by comparing breast cancer specific mortality rates of Sweden to its neighbour Denmark (Figure 4) where national screening was implemented decades later [6, 7].

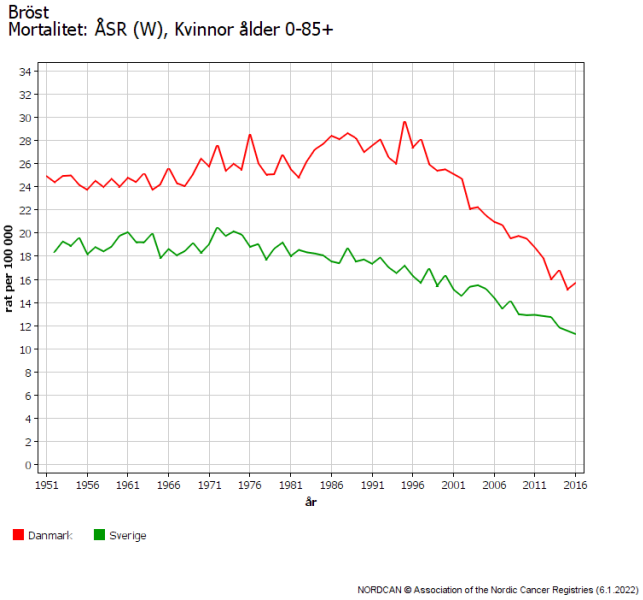

Figure 4. Estimates of mortality rates of Denmark and Sweden per 100 000.

2.2 Biological predictors of outcome

Breast cancer is a heterogeneous disease with different therapeutic response and outcome. The two most important underlying factors are anatomic stage and tumour characteristics.

2.2.1 Anatomic stage

According to the National Cancer Institute Surveillance Epidemiology and End Results Program, the 5 year relative survival by stage at diagnosis is 98.6 for localised breast cancer and 25.9 for patients with distant metastasis [8]. A study of 173 797 Dutch patients comparing a patient cohort between the years 1999-2005 with a patient cohort between the years 2006-2012 found that survival is still influenced by tumour stage at the time of diagnosis despite improvements in therapy [9]. A study comparing the breast cancer

survival and stage at diagnosis of several countries including Sweden for the years 2000-2007 came to the same conclusion [7].

2.2.1.1 TNM classification

TNM classification 8th edition is published by the Union for International Cancer Control (UICC). It is an international tool to classify cancer disease extent which is important in prognosis and treatment decision making [10]. T category describes the primary tumour site and size and in the case of multifocal malignancy, the size of the largest invasive tumour. N category describes the regional lymph node involvement. For breast cancer, the regional lymph nodes are the nodes in the axilla (levels I-III), and internal mammary lymph nodes. Level I is infero-lateral to pectoralis minor, level II is behind the pectoralis minor, and level III is supero-medial to the pectoralis muscle. M category describes distant metastatic spread. Table 1 describes the TNM classification. Combinations of the TNM categories informs us of the stage of disease which is outlined in Table 2.

Category	***Description***
T category	
TX	*Primary tumour cannot be assessed*
T0	*No evidence of primary tumour*
Tis (DCIS)	*Ductal carcinoma in situ*
Tis (Paget)	*Paget disease not associated with invasive carcinoma*
T1	*Tumour size less than or equal to 20 mm*
T2	*Tumour size greater than 20 mm but less than or equal to 50 mm*
T3	*Tumour size greater than 50 mm*
T4	*Tumour with direct extension to the chest wall and/or skin with macroscopic changes*
N category	
NX	*Regional lymph nodes cannot be assessed*
N0	*No regional nodal metastasis*
N1	*Metastasis to movable ipsilateral level I and/or level II axillary nodes*
N2	*Metastasis to fixed or matted ipsilateral level I and/or level II axillary nodes, or metastases to ipsilateral internal mammary nodes without axillary metastasis*

N3	*Metastases to ipsilateral level III axillary nodes with or without level I and/or level II axillary metastases; or metastases to ipsilateral internal mammary lymph nodes with level I and/or level II axillary metastases or metastases to ipsilateral supra-clavicular nodes*
M category	
M0	*No clinical or imaging evidence of distant metastases*
M1	*Distant metastases on the basis of clinical or imaging findings*

Table 1. TNM classification for breast cancer.

Stage	*TNM descriptors*
0	*Tis, N0, M0*
IA	*T1, N0, M0*
IB	*T0, N1 (micrometastases), M0*
	T1, N1 (micrometastases), M0
IIA	*T0, N1, M0*
	T1, N1, M0
	T2, N0, M0
IIB	*T2, N0, M0*
	T3, N0, M0
IIIA	*T0, N2, M0*
	T1, N2, M0
	T2, N2, M0
	T3, N2, M0
IIIB	*T4, N0, M0*
	T4, N1, M0
	T4, N2, M0
IIIC	*Any T, N3, M0*
IV	*Any T, Any N, M1*

Table 2. Staging of breast cancer.

2.2.2 Tumour characteristics

Breast neoplasm can develop from different components of the breast. The majority of breast cancers are carcinomas that arise from epithelial cells lining the lobules and ducts. Sarcomas are very rare in the breasts and arise from the stromal components (myofibroblasts and blood vessel cells). Carcinomas are divided into two main categories:

carcinoma in situ and invasive carcinoma. The classification of tumours is based on tumour microscopic morphology and the use of immunohistochemistry.

2.2.2.1 Ductal carcinoma in situ (DCIS)

Ductal carcinoma in situ is treated as a pre-invasive disease within intact lobules with the potential of breaking through the basement membrane and invading the stroma. DCIS is classified into three nuclear grades and the grading system is based on nuclear proliferation, mitotic activity and architecture. A review estimated that 14-53% of DCIS may progress to invasion over a period of 10 years or more. The same study also reported undiagnosed DCIS in autopsy studies to be 9% suggesting that there is a large reservoir of DCIS in the population that never becomes manifest [11]. One meta-analysis showed an association between the diagnosis of high nuclear grade DCIS at preoperative core needle biopsy and detection of invasive disease in the surgical specimen [12]. Retrospective studies have shown an association between high nuclear grade and local recurrence [13]. Based on survival rates and three-dimensional histology, Tabar et al. suggest that what today is labelled "invasive ductal carcinoma" has its origin in the acini and should be termed "*acinar* adenocarcinoma of the breast" and that what is classified as high grade "carcinoma in situ" is a form of invasive carcinoma with origin from the major ducts and should be termed "*ductal* adenocarcinoma of the breast" [14].

2.2.2.2 Invasive carcinoma

In invasive carcinomas the cancerous cells have broken through the basal membrane of lobules and infiltrated the surrounding tissue. According to the World Health Organization (WHO) classification of tumours of the breast 5th edition, invasive carcinomas are divided into two main subtypes: 1) tumour of no special type (NST, previously named invasive ductal carcinoma) which constitute about 70% of tumours and 2) tumour of special type. Tumour of no special type is a default classification when the tumour lacks special features. Tumours of special type have special features and these include invasive lobular carcinoma which constitutes circa 20% of breast cancers, and the rarer mucinous, tubular, medullar, and metaplastic tumours.

The Nottingham Histologic score further divides tumours into three grades (Grade I, II, and III). The grade system reflects the degree of architectural and cellular deviation from normal tissue and how rapidly the tumour cells proliferate. The pathologist gives a score for three characteristics: tubule formation, nuclear pleomorphism and mitotic activity. Each characteristic is given a score from 1 to 3, with a score of 3 being most abnormal. This gives a total score of minimum 3 and maximum 9. Grade I tumours have a score of 3-5 and are well differentiated. Grade II tumours have a score of 6-7 and are moderately differentiated. Grade III tumours have a score of 8-9 and are poorly differentiated [15].

2.2.3 Immunohistochemistry and predictive markers

There are four immune-histochemical biomarkers that are measured routinely in the analysis of breast cancer. The analyses are done on formalin-fixed, paraffin-embedded breast cancer tissue. These biomarkers give predictive information for adjuvant treatment strategies [15].

2.2.3.1 The estrogen receptor (ER)

Estrogen receptors are found in the cell nucleus and are involved in the processes of gene transcription, carcinogenesis, proliferation and apoptosis [16]. About 75% of tumours of the breast have an overexpression of estrogen receptors (ER) in the cell nucleus [17].

2.2.3.2 The progesterone receptor (PR)

Progesterone receptors also belong to the steroid hormone nuclear receptor family. Estrogen receptor positive breast cancer may or may not have an overexpression of progesterone receptors. Clinically, the PR is a positive prognostic factor [18].

2.2.3.3 HER2

Human epidermal growth factor receptor 2 (HER2) is found on the surface of cells and promotes cell growth. It is expressed in normal tissue and many types of cancers. In 10-20% of breast cancers, there is an overproduction of the HER2 receptor as a result of gene amplification [19]. The overproduction of HER2 is associated with higher recurrence rate [20, 21]. It is assessed with immunohistochemistry, but when the results are undecided, a complimentary analysis is done with fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH).

2.2.3.4 Ki-67

Ki-67 is a protein found in the nucleus of dividing cells and is therefore a marker for proliferation. Ki-67 can be used to further stratify patients into different prognostic groups. The marker however suffers from lower analytic validity [22] and the thresholds for low, intermediary and high are specific for each pathology laboratory. The International Ki67 in Breast Cancer Working Group recommends proper tissue handling before analysis, a standardized visual scoring method, and quality control programs. The marker is used to determine if a patient will benefit from adjuvant chemotherapy among patients with estrogen receptor positive and HER2-negative tumours [23].

2.2.4 Intrinsic molecular subtyping

Analysis of expression of combinations of genes in tumour cells provides genomic subtypes that have prognostic implications. For this purpose, there are several commercially available tests such as Oncotype DX Recurrence Score, MammaPrint, Endopredict, Breast Cancer Index, and Prosigna.

The genomic subtypes include luminal A (typically low grade, strongly ER/PR positive, HER2-negative and have low proliferation), luminal B (typically ER positive, PR low, high grade and have high proliferation), HER2-enriched luminal, HER2-enriched (non-luminal) and Basal-like [24-26].

2.3 Breast cancer treatment

In Europe, it is recommended that patients be treated in units by a multidisciplinary team specialized in breast cancer, consisting of at least medical oncologists, breast surgeons, radiation oncologists, breast radiologists, breast pathologists and breast nurses [27]. The breast unit should have or be able to refer patients for reconstructive surgery, genetic counseling, physiotherapy and psychological support. A specialized nurse should be designated to the patient for support and information throughout the treatment.

2.3.1 Loco-regional therapy

2.3.1.1 Breast conserving therapy

The first documentation of breast cancer surgery is from the 1890's [28]. At the time, extensive and "radical mastectomy" involved removal of the breast, underlying chest muscles and all axillary lymph nodes. Today, surgeons aim to remove the cancer with negative margins while preserving healthy tissue. The Society of Surgical Oncology guidelines defines a negative margin for invasive cancer as having no tumour cells on the margin of the surgical specimen (no tumour on ink) [29]. For carcinoma in situ the desirable margin is 2 mm or more [30, 31]. The tumour extent does not play a role in decision making as long as the criteria for complete tumour excision with negative margins and good cosmetic result can be met [32-34]. A meta-analysis based on 33 studies, found that the odds ratio of local recurrence was 2.44 for positive versus negative margins while the distance of tumour to margin had no significant effect [35]. Several clinical trials have shown better breast specific survival rates after breast conserving

surgery and radiotherapy compared to mastectomy, even after adjustment for patient and tumour characteristics [9, 36-40]. Even in cases of large tumours, breast conserving surgery can be performed after preoperative chemotherapy and down-staging [41]. Oncoplastic procedures such as expander implants or autologous tissue flaps, remodelling of the breast, and reduction of the contralateral breast can further enhance the cosmetic result.

2.3.1.2 Radiotherapy

Radiotherapy is standard treatment procedure after breast conserving therapy and after mastectomy and axillary dissection with positive node status. Radiotherapy after breast conserving surgery reduces the risk of local recurrence rates by 50% and improves breast cancer specific survival [42-44]. A meta-analysis of seventeen randomised trials, found that radiotherapy after breast conserving surgery reduced the 10 year risk of any first recurrence (both loco-regional and distant) from 35.0% to 19.3% and reduced the 15 year risk of breast cancer death from 25.2% to 21.4% compared to women who did not receive radiotherapy [45].

2.3.1.3 Mastectomy with or without radiotherapy

In the following situations, mastectomy is the first choice of treatment: inflammatory breast cancer or other T4 tumour, large tumours that progress during neo-adjuvant treatment, local recurrence after earlier breast conserving surgery and radiotherapy, multi-centric tumours where an acceptable cosmetic result cannot be achieved with breast conserving surgery, positive margins after a second surgery and multiple resections, contra-indications for postoperative radiotherapy, patient request, or in women with high risk of a new tumour in the same breast. Women with breast cancer and germline gene mutation with high penetrance such as BRCA1 and BRCA2 are recommended to undergo bilateral mastectomy.

Complimentary radiotherapy is administered to the chest wall and regional lymph nodes even in the case of mastectomy if there is extensive cancer burden in the breast (positive resection margins, T3, or T4 tumour) or axillary macro-metastasis. A meta-analysis of 8135 patients in 22 randomised trials found that for node positive patients, radiotherapy reduces risk of recurrence and breast cancer mortality [46].

2.3.1.4 Axillary surgery

It is important to establish the presence of lymph node metastases for staging and treatment. The removal of all lymph nodes (axillary dissection) has a sensitivity close to 100%, but is associated with a high morbidity [47]. Pre-operative clinical examination has low accuracy [48] while pre-operative ultrasound has a better performance. In a meta-analysis, pre-operative ultrasound had a sensitivity of 79.6% and a specificity of 98.3% [49].

The removal of sentinel nodes (the first 1-4 nodes in the lymphatic drainage of the breast) is standard procedure in apparently node negative invasive breast cancer and carcinoma in situ with the risk of invasion underestimation (palpable mass, high grade, large extent). The method has proven to be reliable with high sensitivity [50-55], equivalent survival rates compared to axillary dissection [56], and reduced arm morbidity [57]. The lymph nodes are classified as negative (no cancer cells), isolated tumour cells (cancer cells less than or equal to 0.2 mm/200 cells), micro-metastasis (greater than 0.2/200 cells and equal to or less than 2.0 mm) or macro-metastasis (greater than 2.0 mm). Axillary dissection if performed after the confirmation of macro-metastases, but has not proven to have added clinical value in cases of micro-metastases or isolated tumour cells [58, 59].

Today, if there is clinical evidence of less than four lymph node metastases and clinical complete response after neo-adjuvant therapy, targeted axillary dissection (TAD) may be performed. In this procedure, only the biopsy-verified lymph node metastases and sentinel nodes are removed. A recent systemic review and pooled analysis showed that the false negative rate of TAD was 5.18% and that the method is acceptable for staging after neo-adjuvant chemotherapy [60].

2.3.2 Systemic therapy

2.3.2.1 Endocrine therapy

In estrogen receptor (ER) positive breast cancer, the use of adjuvant endocrine therapy substantially reduces the 5-year risk of recurrence and 15-year breast cancer mortality rates [18, 61]. Generally, all patients with ER positive (ER+) breast cancer receive anti-hormonal therapy, either tamoxifen (a selective estrogen receptor modulator) or aromatase inhibitors that block the production of estrogen. The threshold for ER positivity is arbitrary. While some clinics consider 1% or more of tumour cells demonstrating nuclear staining as ER+, a more common threshold is 10%. One study found that patients with 1-

9% ER positivity did not seem to benefit from endocrine therapy and had similar outcome to ER negative (ER-) patients [62].

2.3.2.2 Targeted therapy for HER2-positive breast cancer

HER2 is an oncogene that is amplified in 10-20% of primary breast cancer and these tumours have a worse prognosis. Adding anti-HER2 treatment to HER2 positive breast cancer patients greatly improves clinical outcome. Trastuzumab is a humanised monoclonal antibody that targets the HER2 receptor and is most commonly used in treatment of HER2-positive primary breast cancer. In a meta-analysis of eight studies involving 11991 patients, the hazard ratio for overall survival was 0.66 and disease-free survival 0.60 for patients with trastuzumab-containing regimens [63].

2.3.2.3 Targeted therapy for women with germline BRCA mutation

PARP inhibitors are developed for targeted cancer therapy in patients with germline BRCA1 and BRCA2 mutation. They inhibit the enzyme poly ADP ribose polymerase (PARP), causing damage to the DNA and cell death. A randomized trial found that adjuvant Olaparib was associated with improved overall survival compared to placebo [64].

2.3.2.4 Chemotherapy

Adjuvant chemotherapy is recommended for patients with HER2-positive breast cancer, triple-negative breast cancer (ER, PR, and HER2 negative), HER2-negative luminal B breast cancer, node positive breast cancer or young age (under 35). Chemotherapy should be initiated soon after surgery and ideally no later than 4 weeks. The most frequently used regimens contain anthracyclines and taxanes. The addition of taxanes and its sequential use together with anthracyclines allows for a lower total dose of anthracyclines as well as better survival outcome. A meta-analysis of long term outcome of 123 trials with 100 000 patients reported a reduction of breast cancer specific mortality by 13% for regimens including taxanes compared to regimens without taxanes [65]. Cyclophosphamide/methotrexate/5-fluorouracil (CMF) can be administered as an alternative for patients who do not tolerate anthracyclines and taxanes.

2.3.2.5 Neo-adjuvant systemic therapy

Chemotherapy should be considered prior to surgery in patients whose health status allows for chemotherapy and one of the situations in table 3.

1	*locally advanced and technically inoperable breast cancer*
2	*triple negative breast cancer or HER2+ breast cancer with tumour size greater than 20 mm*
3	*positive axillary lymph node and if clinical data would indicate post-operative chemotherapy*
4	*if clinical data would indicate post-operative chemotherapy and breast conserving surgery can be performed after down staging of breast tumour*

Table 3. Criteria for neo-adjuvant chemotherapy

The remission of breast tumour and axillary lymph nodes during neo-adjuvant chemotherapy are prognostic indicators. Patients with complete pathologic response (absence of residual tumour in the breast and axilla) have the most favourable outcome [66]. For patients without complete pathological response, the residual cancer is reported according to the Residual Cancer Burden classification [67, 68] with categories RBC 0 to 3. A pooled analysis of 5295 patients from 12 studies published in 2022, found that the risk of recurrence increased with the extent of residual disease regardless of breast cancer subtype [69].

2.3.3 Management of occult breast cancer

In occult breast cancer there is axillary lymph node metastasis without identifiable primary tumour in the breast. This constitutes 0.3-1 % of all breast cancer patients [70]. Patients are treated with axillary lymph node dissection, as well as radiotherapy and chemotherapy when tumour burden and characteristics requires such treatment.

2.4 Maturation of the female breast

Human breasts contain parenchyma (lobules and ducts) and stroma (fibrous tissue and fat) that are developed from the embryonic ectoderm and mesoderm respectively. Breast development begins in the 5th week of intrauterine life with the development of the primary mammary bud. The mammary bud continues to develop and branch and finally builds the 15-20 lactiferous ducts that extend from lobules to the nipple and are present at birth. At puberty, under the influence of estrogen, the female breast undergoes further development of both the parenchyma (more branching of the ducts) and stroma (more fibrous and fatty tissue). The primary ducts branch into segmental, sub-segmental and terminal ductules. The terminal ductules, ending in a cluster of secretory cells, with the surrounding interlobular stroma make up the smallest unit in the breast [71]. During

pregnancy and lactation, under the influence of progesterone and prolactin, the breasts undergo further ductal branching and epithelial proliferation and differentiate into lactating lobules [72]. At weaning, the secretory epithelial cells undergo apoptosis and the adipocytes become more differentiated [73]. This phenomenon is the basis of fatty involution and is protective against breast cancer.

2.5 Risk factors for breast cancer

2.5.1 Gender and age

The two greatest risk factors for breast cancer are gender and age. Breast cancer affects almost only women, with sporadic cases among men. In Sweden, only approximately 60 men are diagnosed with breast cancer annually [74]. This disease also mainly affects post-menopausal women and the disease is rare among women under 40 years of age. The median age for breast cancer in Sweden is 64 years [74].

2.5.2 Mammographic Density

Mammographic density is the proportion of the radio-opaque fibroglandular tissue (glands, ducts and fibrous connective tissue) observed on a mammogram. Figure 5 illustrates a schematic image of structures in the breast and how they appear on a mammogram.

The proportion of fibroglandular and fatty tissue in the breasts vary among women, consequently there are variations in mammographic density among individuals, as illustrated in Figure 6. Women with the highest density have a four to six times increased risk of developing breast cancer compared to women with the lowest density [75, 76]. Many risk factors for breast cancer are associated with mammographic density. A cohort study of over 30 000 mainly Caucasian women found that young age, lean body, having a family history of breast cancer, hormone replacement therapy, and alcohol consumption were associated with high mammographic density, while being physically active, young age at first birth, multi-parity and longer breast feeding were associated with lower density [77]. Genome studies have also shown that at a proportion of variance in mammographic density is explained by genetic variation [78].

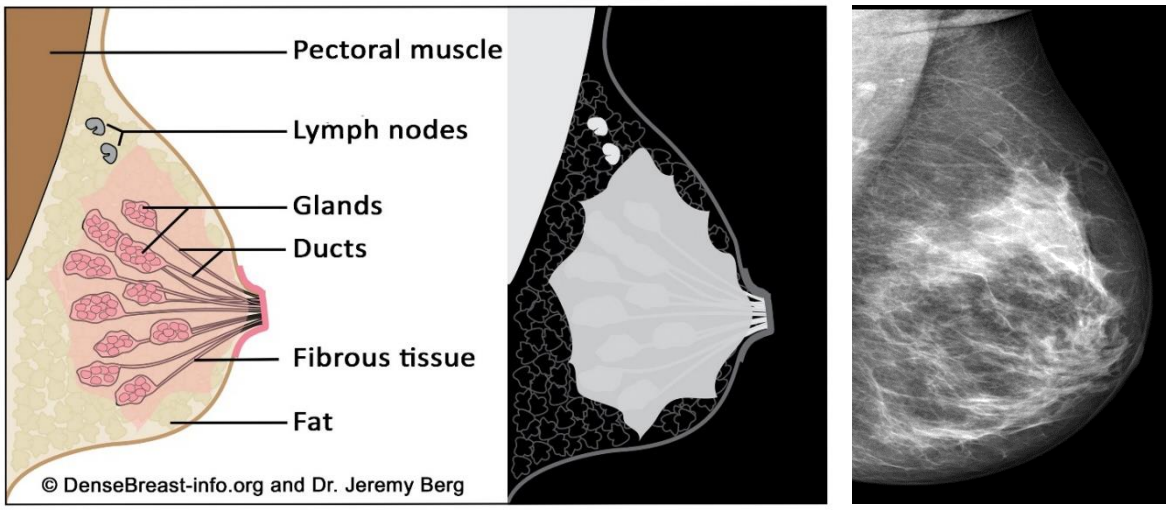

Figure 5. Schematic image of the breast and comparison with a mammogram.

2.5.2.1 Measurement of mammographic density

Since the start of mammography, extensive work has been done to measure density. There are several modes for measuring density, the traditional mode has been visual assessment by the radiologist and the use of a standardized classification system. Such classification systems include the American College of Radiology BI-RADS [79], Wolfe [80], and Tabar [81].The most widely used classification system has been BI-RADS and it classifies the breasts into four beast composition categories: a. the breasts are almost entirely fatty, b. there are scattered areas of fibro-glandular density, c. the breasts are heterogeneously dense which may obscure small masses, d. the breasts are extremely dense which lowers the sensitivity of mammography [79]. Figure 6 illustrates the different breast composition categories a-d according to BI-RADS.

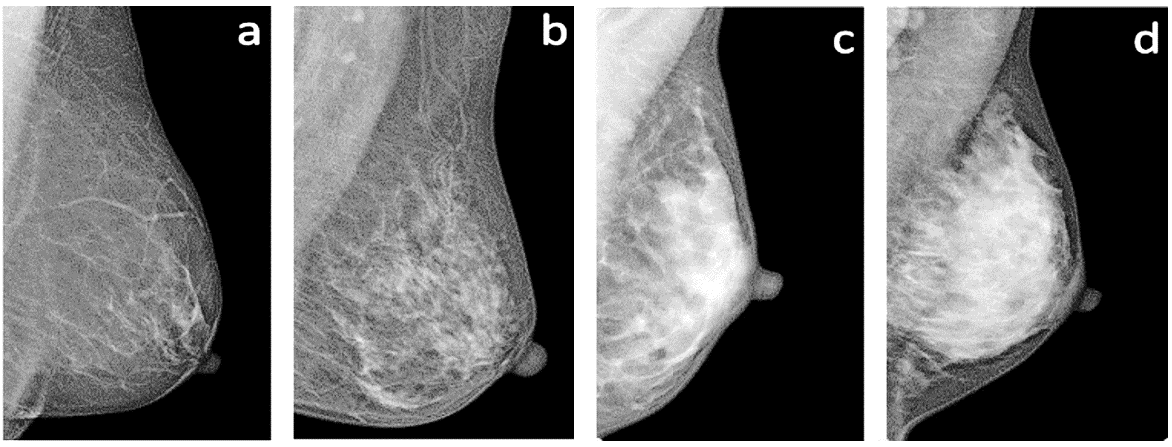

Figure 6. Breast composition categories according to BI-RADS.

After switching from film to digital mammography, several commercially available programs such as Quantra, Volpara, and Stratus [82-84] provide digital automated measurements. The latest advancement has been taken by vendors that now offer software programs that are built into the mammography equipment and measure density based on the absorbed amount of x-ray.

2.5.3 Radiation

Ionizing radiation of the breasts causes mutations in the breast tissue that can lead to breast cancer. Japanese teenagers that had been exposed to high doses of radiation during World War II, were twice as likely to develop breast cancer [85]. Also women who have undergone radiation therapy of the mediastinum for treatment of Hodgkins lymphoma are five times more likely to develop breast cancer compared to women who have not had radiation therapy [86].

2.5.4 Genetic factors

The risk of breast cancer is doubled if a woman has a first-degree relative (mother, sister, or daughter) with breast cancer [87]. Inheritable susceptibilities for developing breast cancer accounts for 15-20 % of incident breast cancer [88].The heritable predisposition is of two kind. There may be a germline gene mutation which hinders the cell's normal repair mechanism, or variations in the DNA known as SNPs (single nucleotide polymorphism).

The two gene mutations with the highest penetrance are BRCA1, BRCA2. A meta-analysis reported mean cumulative risk at the age of 70 to be 57% for BRCA1 and 49% for BRCA2 mutation carriers [89]. PALB2, CHEK2, ATM, and TP53 are other gene mutations with high penetrance. Overall 5-10% of breast cancers are associated with a gene mutation.

SNPs occur both within genes and also in chromosomal loci with no known genes. This is also referred to as "low-penetrance breast cancer susceptibility polymorphisms". Hundreds of SNPs, with low penetrance have been identified [90]. SNPs account for more of the familial risk of breast cancer than high risk genes. Genetic counselling centres may screen women with a family history of breast cancer for gene mutations and SNPs. This generates a polygenetic risk score that can be added to a risk score model [91].

There are also differences in the incidence of subtypes of breast cancer among different ethnicities. For example, American data show that triple negative breast cancer, the

subtype with the worst prognosis, is more common among non-Hispanic black women [92].

2.5.5 Reproductive factors

Early menarche and late onset of menopause increase the risk of developing breast cancer [85]. Women with first childbirth after the age of 30 have twice the risk of developing breast cancer compared to those with first childbirth before the age of 20 [85]. Parity and breast feeding decrease the risk of breast cancer. An analysis based on pooled data from 47 epidemiological studies showed that the relative risk of breast cancer decreased by 4.3% for every 12 months of breastfeeding and 7.0% for each birth [93]. Another meta-analysis found that nulliparous women had a 30% increased risk of breast cancer compared to parous women, and that women giving first birth after the age of 35 had a 40% increased risk compared to those with first birth before the age of 20 [94].

2.5.6 Menopausal hormone therapy

There is an association between high levels of estrogen and breast cancer [95] and high levels of endogenous estrogen is the proposed mechanism for the increased risk of breast cancer in obesity [96]. The risk of breast cancer is greater for preparations with a combination of both estrogen and progesterone than for preparations that only contain estrogen. The risk applies mainly to estrogen receptor positive and low grade cancers [97]. A meta-analysis from 2000 showed that the use of menopausal hormone therapy for 10 years between the age of 50 and 60 by 1000 women increased the rate of breast cancer from 63 to 69 cancers [98]. Published in 2022, a prospective cohort study of over 44000 women age 55-74 found a hazard ratio of 1.42 for current users and 0.96 for former users compared to the never users in the adjusted model [99]. A meta-analysis published in 2022 with data from 19 randomized controlled trials and 8 prospective observational studies among women who initiate hormone therapy before the age of 60 has shown significant reduction of all-cause mortality with a relative risk around 0.70 [100]. Consequently, the use of hormone therapy should be considered wisely and women should not per default be discouraged from its use.

2.5.7 Lifestyle factors

In a pooled analysis of prospective cohort studies, premenopausal women with BMI over 31 had a relative risk of breast cancer of 0.54 compared to women with BMI under 21. However, in postmenopausal women the relative risk of breast cancer was 1.26 for women

with BMI over 28 [101]. This suggests that high BMI is protective for premenopausal women, but is a risk factor for postmenopausal women.

The World Cancer Research Fund/American Institute for Cancer Research regularly analyses and reports on cancer prevention research related to diet, weight and physical activity. The organisation reports that there is strong evidence that consuming alcohol increases the risk of breast cancer (pre and post-menopause) while being physically active decreases the risk. There is also strong evidence that high birth weight and length increases the risk of breast cancer [102]. There is also a modest association between smoking and breast cancer [103].

2.5.8 Previous breast disease

Compared to women with no prior history, women with prior invasive breast carcinoma have a relative risk of 6.8 to develop a new cancer. For prior diagnosis of ductal carcinoma in situ, the relative risk is 17.3. and for lobular carcinoma in situ 16.4 [86]. The relative risk of developing breast cancer is 4-5 for women with earlier diagnosis of atypical ductal hyperplasia [85].

2.5.9 Background parenchymal enhancement at MRI

Background parenchymal enhancement (BPE) is the proportion of fibro-glandular tissue that enhances after gadolinium contrast injection in breast MRI. Normal fibro-glandular tissue usually has a slow and persistent contrast uptake with a symmetrical distribution between the breasts [104]. BPE is hormone sensitive, it varies during the menstrual cycle, is generally low in postmenopausal women, and decreases with anti-oestrogen medication and bilateral salpingo-oophorectomy [105-111]. According to the American College of Radiology BI-RADS 5the edition, it is classified as a) minimal, b) mild, c) moderate, and d) marked [79]. Figure 7 shows different categories of BPE according to the BI-RADS classification.

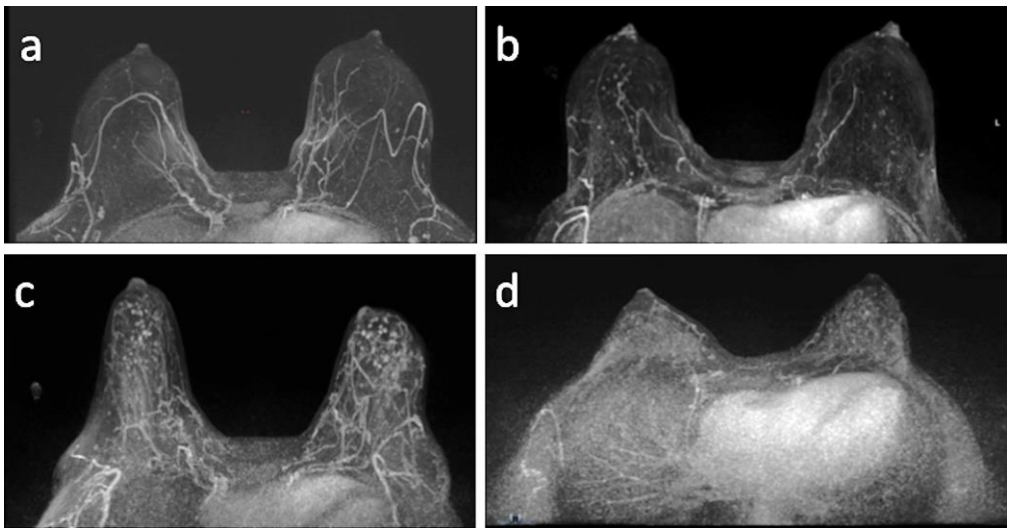

Figure 7. BPE categories according to BI-RADS.

A meta-analysis published in 2019 including eighteen studies with a total of 1910 women with breast cancer and 2541 controls found a higher level of BPE was associated with breast cancer in high risk women, but not among women with average risk [112].

2.6 Clinical risk assessment

2.6.1 Indications for genetic testing

According to the Swedish guidelines [113], having a germline genetic mutation should be suspected if a first-degree relative has a positive test or one of the criteria listed in table 4.

	Criteria
1	*Breast cancer under the age of 40*
2	*Breast cancer under the age of 50 and one other family member with breast cancer, ovarial cancer, tubar cancer, prostate cancer under age 65 or pancreatic cancer*
3	*Breast cancer under the age of 60 and two family members with breast cancer, ovarial cancer, tubar cancer, prostate cancer under age 65, or pancreatic cancer*
4	*Triple negative breast cancer (according to current Swedish guidelines, for patients under the age of 60)*
5	*Male breast cancer*
6	*Tubo-ovarian cancer and primary peritoneal carcinomatosis*

Table 4. Criteria for genetic testing

2.6.2 Clinical risk assessment models

Clinical risk assessment models may determine an individual's short term or life-time risk of breast cancer that can highlight the need for genetic testing and more comprehensive surveillance. Well established models include the Gail model, the Tyrer-Cuzik model, the Claus model, and BOADICEA. An analysis of the Gail and Tyrer-Cuzik model in the Nurses' Health Study, found that both models suffered from over-prediction among the higher-risk women and under-prediction among the lower-risk women [114]. A recent validation study in a cohort of over 66 000 women for a multifactorial BOADICEA model found that the model is well calibrated in predicting the risks for women with low risk and high risk [115]. Different risk factors that can be incorporated into the model include questionnaire-based risk factors, family history, mammographic density, genetic analysis, and a polygenic risk score. One limitation of these models is the risk of inaccuracy of self-reported family history. Although a Finnish study found that information on first- and second-degree relatives was usually quite accurate [116], retrieving information may be difficult or impossible for women who have lost contact with their family of origin.

2.7 Primary prevention

2.7.1 Prophylactic mastectomy

Surgical removal of the breasts reduces the risk of developing breast cancer by at least 90% both in women with a family history of breast cancer [117] and in women with BRCA1 and BRCA2 mutation [118]. A meta-analysis of four prospective studies showed a substantial risk reduction with hazard ratio of 0.06 (95 % CI 0.01-0.41) for BRCA1 and BRCA2 mutation carriers [119].

2.7.2 Chemoprevention

There are two main types of breast cancer preventive drugs: selective estrogen receptor modulators (such as tamoxifen and reloxifene) and aromatase inhibitors (such as exemestane and anastrozole). A 2019 evidence report and systematic review for the US Preventive Services Task Force for medication to reduce the risk of developing breast cancer showed a pooled relative risk of 0.69 for tamoxifen, 0.44 for raloxifene and 0.45 for aromatase inhibitors exemestane and anastrozole [120]. A recent Cochrane review also found a risk ratio of 0.68% for Tamoxifen and 0.47 for aromatase inhibitors [121]. One study of tamoxifen showed that the protective effect of the drug lasted several years after the treatment period [122]. The effectiveness of these drugs are set off against the adverse effects and difficulty with compliance.

The most serious adverse effects are higher incidence of endometrial carcinoma and thromboembolism. Less harmful adverse effects that impact the most on treatment adherence are vasomotor symptoms (hot flashes, cold sweats and night sweats), sexual symptoms (reduced libido), and musculoskeletal pain [123]. Using reduction in mammographic density as a proxy for treatment effectiveness, one randomised controlled trial found that pre-menopausal women had a non-inferior mammographic density reduction and significantly less severe symptoms when given tamoxifen 2.5 mg instead of the standard dose of 20 mg [124].

2.8 Secondary prevention

2.8.1 Mammography screening

In 1913, a German surgeon who conducted x-ray examinations of mastectomies laid the foundations for clinical mammography and subsequent screening for detection of early breast cancer [125]. The disease is eligible for screening according to the criteria published by Wilson and Jungner in 1968 [126]. The criteria states that the disease should be an important health problem with a latent stage, the test (mammography) should be acceptable to the population, and there must be an acceptable treatment. The first large scale randomised screening trial was performed in 1966 in New York with 30 000 women aged 40-64 in each arm [127]. Thereafter, several population based randomised controlled trials were conducted [128-136].

2.8.2 Benefits and Harms

Harris et al. have proposed that net benefits should be calculated in determining the value of a screening program [137]. The net benefits are calculated as the magnitude of benefits (probability of adverse outcome without screening, identifying all people who would suffer the adverse health outcome, and magnitude of incremental health benefit from screening) minus the magnitude of harms (frequency and experience of false positive tests, frequency and experience of overdiagnosis, and harms of receiving an earlier diagnosis).

A Cochrane database systemic review of screening trials published in 2013 gave a very negative review of mammography screening. The authors suggested that some mammography screening trials suffered from misclassification of cause of death that would favour screening while trivializing its harms. They found three trials with adequate randomization and these trials did not show a significant reduction in breast cancer mortality [138]. However, a meta-analysis published in 2016 to update U.S. Preventive

Services Task Force recommendations analysed not only screening trials, but also observational studies. The pooled results gave a relative risk for breast cancer mortality of 0.92 (age 39-49), 0.86 (age 50-59), 0.67 (age 60-69) and 0.80 (age 70-74) in the trials and a risk reduction of 25-31% for women 50-69 years in observational studies [139]. The results led to a recommendation for mammography screening in the United States. Several observational studies on mortality rates before and after screening in European countries have also shown results in favour of screening [140, 141]. Even Denmark, a country that was negatively influenced by the Cochrane report, finally implemented nationwide screening after two regions that had pioneered population-based screening in the 1990s showed a decrease in breast cancer mortality of 22-25% compared to regions that had not implemented screening [6].

There are two harmful items that are inherently present in every screening program, namely overdiagnosis and false positive test results. Both situations cause emotional and/or physical harm to women and take resources from healthcare without yielding any benefit to the individual. Overdiagnosis is the proportion of indolent screen-detected breast cancers that might never had been diagnosed in the absence of screening. In order to overcome this negative aspect, the challenge is to reduce overtreatment by identifying women who do not benefit from extensive therapeutic measures. A false positive test requires workup, and possibly biopsy or even surgery for a benign finding.

2.8.3 Participation in screening

A successful screening program requires not only acceptance of the test but also a broad participation by the target population. A recent systemic review has for example shown that a reduction of screening during the Covid pandemic resulted in a reduction in proportion of screen-detected breast cancers and lower proportion of early stage cancer at diagnosis [142].

Multiple studies have identified socio-economic status, level of education, and cultural background as factors that affect participation rates [143-146]. An analysis of the WHO's Study on Global Ageing and Adult Health (SAGE) with data from India, China, Mexico, Russia and South Africa found that having high socioeconomic status was positively associated with breast cancer screening [147]. A European study found that participation in screening was less likely among individuals with low income and educational level and individuals born outside of the European Union [148]. A systemic review of European surveillance programs for women with increased risk of breast cancer showed that even such programs fail to actively seek out and include women with other ethnic origins [149].

2.8.4 Interval cancers

Mammography screening has shown to be a cost-effective method that reduces breast cancer specific mortality [150]. A proportion of attendees will present with a clinically detected breast cancer between two screening intervals, so called interval cancers. Several studies have shown that the risk of interval cancer increases with increase in mammographic density [151-153]. In other words, women with the highest density that already have a greater risk of developing breast cancer are less likely to benefit from screening. A pooled analysis of interval cancer rates in six European countries, revealed that interval cancers compromised 28% of the total of screen-detected + interval cancers [154]. The main concern is not so much overdiagnosis as it is underdiagnosis, since a proportion of women participating in screening still perish from breast cancer.

2.8.5 Mammographic predictors of interval cancer and personalised screening

As mentioned earlier, women with the highest breast density have a higher risk of both developing breast cancer and receiving a false negative screening mammogram. These women have limited benefit of the "one size fits all" approach with age-based mammography screening. In the Dutch Dense Trial, women with the highest breast density were randomised to undergo breast MRI in the intervention arm [155]. In the intervention arm of the European MyPeBS trial, risk stratification is partly based on breast density and women with the highest risk will receive mammography and MRI annually [156]. In the British multi-centre BRAID trial, women with dense breasts are randomised into standard care, or supplementary imaging by either automated breast ultrasound, contrast enhanced spectral mammography, or abbreviated breast MRI [157].

Although density is a key factor for false negative screening, newly developed deep learning models have shown even higher predictive value than only density-based models [158]. One model using participants from the Karma cohort (Karolinska Mammography Project for Risk Prediction of Breast Cancer) identifies women at the risk of being diagnosed with breast cancer within two years using mammographic features and age. Additional risk factors such as life-style factors, family history and polygenic risk score only slightly improve this model's performance [159].

2.8.6 Artificial intelligence (AI) for detection

With advancements in machine learning and an increasing demand for imaging procedures, many AI computer-aided detection algorithms have emerged for detection of breast cancer. AI could potentially decrease a radiologist's workload by removing the need to read AI negative images and increase a radiologist's sensitivity when combined

[160, 161]. The numerous commercially available AI computer-aided detection algorithms may vary in sensitivity for detection of breast cancer. For example, in a retrospective evaluation by Salim et al. three different algorithms were evaluated and sensitivity was calculated at 81.9% for AI-1, 67.0% for AI-2, 67.4% for AI-3 [161]. Before implementation, during its use, and after each upgrade, the promised performance has to be evaluated on a representative sample of the population. In addition, the professional and scientific community must have a consensus on acceptable levels of test performance. Substituting a radiologist with AI requires the trust and acceptance of citizens, and legal accountability needs to be clarified. These challenges cannot be undertaken by individual radiology departments and necessitate co-ordination by national agencies [160].

2.9 Design and measures of diagnostic accuracy studies

Sensitivity is defined as the proportion of subjects with a disease that have a positive test result. Specificity is defined as the proportion of subjects without the disease that have a negative test result. Positive predictive value is the probability of a test positive subject having the disease. Negative predictive value is the probability of a test negative subject not having the disease. Predictive values depend on the prevalence of the disease in the evaluated population. Sensitivity and specificity are independent of prevalence [162]. Studies of diagnostic accuracy of a test should be designed so that they are easily identified and the results should be reproducible. Consequently, adherence to a relevant guideline is such as STARD (Standards for reporting of diagnostic accuracy studies) [163] is highly recommended.

2.10 Complementary imaging modalities

2.10.1 Tomosynthesis

In this new mammography technology, the x-ray tube rotates to take multiple images at different angels. The images are then reconstructed into a series of slices through the breast. This reduces the problem of overlapping in the 2D mammogram. Tomosynthesis has higher specificity as well. This is because suspicious areas caused by overlapping of normal structures can be resolved by looking at individual slices. In a meta-analysis published in 2020 that included 38 studies reporting on 488,099 patients (13,923 with breast cancer) found a pooled sensitivity of 0.88 for tomosynthesis and 0.79 for mammography, specificity of 0.84 for tomosynthesis and 0.79 for mammography [164]. In summary, tomosynthesis has higher accuracy compared than standard mammography and is easy to implement since it can be performed on already existing mammography

equipment and interpreted on existing workstations. The negative aspect of this examination is a doubling of the ionizing radiation dose and interpretation time.

2.10.2 Hand held ultrasound

Ultrasound imaging uses high frequency sound waves, to create detailed images of the underlying breast tissue. By holding the probe in one's hand and moving it over an area of interest, the area can be scanned in real time. The method is well tolerated by women and uses no ionizing radiation. The reliability of ultrasound is, however, dependent on the person performing the examination since the whole breast is not documented and the examination cannot be double read. Traditionally, handheld ultrasound has been used both for diagnostic purposes and as an additional screening tool in women with dense breasts.

A 2002 study by Kolb et al. illustrated that when screening women with dense breasts, handheld ultrasound increased the detection of non-palpable invasive cancers by 42% [165]. The main result of this study has been replicated by other researchers [166-168]. A systemic review found that, among women with high density, ultrasound after a negative mammography screening accounted for 22.5 % of the total number of detected cancers [169]. The negative impact of ultrasound was the large number of biopsy rates and false positives, the positive predictive value (PPV) of biopsy due to ultrasound was as low as 8.4-13.7. This low PPV, together with the time needed to scan the breasts by a trained and experienced radiologist or sonographer considerably lowers the cost-effectiveness of the method as a screening tool. [169].

2.10.3 "Automated" breast ultrasound

In order to standardize breast ultrasound and make the method reproducible and double readable, an ultrasound scanner has been developed that scans a large area of the breast in one sweep. This method is generally called automated ultrasound, although different vendors have adapted variations of the term. On average, three sweeps are acquired for each breast and each sweep takes one minute. The acquisition can be performed by a radiology technician. A software program then creates reconstructions of the original images in the coronal and sagittal plane and the images can be reviewed at a later time from a work station by a radiologist. Several studies have compared the accuracy of the method with traditional hand held ultrasound [170-176]. A meta-analysis in 2019 found a pooled sensitivity of 0.93 and specificity of 0.86 for automated and sensitivity of 0.90 and specificity of 0.82 for handheld ultrasound [177].

The method has also been evaluated as an adjunct to screening [178, 179]. The multicentre SomoInsight study that included 15 318 women with dense breasts found that the addition of automated ultrasound to mammography increased cancer detection rate by 25%. However, the recall rate was also increased to 28%. In a Swedish study, Wilczek et al. reported that the addition of automated ultrasound did increase cancer detection rate, and nearly doubled the recall rate. There have been attempts to integrate computer aided detection programs that would improve reading time [180].

2.10.4 Full protocol dynamic contrast-enhanced MRI (DCE-MRI)

Magnetic resonance imaging uses a strong magnetic field and radio waves to create high resolution images of soft tissues. Gadolinium contrast is administered intravenously to further enhance a malignant lesion. Due to neovascularization of malignant tumours and increased permeability of these vessels, the contrast medium leaks out of the vessels and is accumulated in the extracellular matrix [181]. Because of the same abnormal properties of these vessels, contrast medium is also rapidly washed out. The difference in contrast medium kinetics helps in differentiating between malignant and benign lesions. A routine breast MRI protocol must contain a dynamic series with one pre-contrast and several post-contrast acquisitions [182].

The sensitivity of MRI is significantly higher than mammography and the method was first performed and studied among women with increased lifetime risk of breast cancer [183-189]. Several of these studies also showed that MRI was more likely to detect invasive cancers. Regular MRI screening among BRCA mutation carriers detects cancers at a more favourable stage [190-193]. A meta-analysis of prospective studies comparing DCE-MRI to mammography in women at very high risk found a sensitivity of 0.39 for mammography compared to 0.77 for DCE-MRI [194]. It also found a high false positive recall and biopsy rate for DCE-MRI (13.7% and 3.9%) compared to mammography (5.3% and 1.5%). The false positive rates were highest in the first round [194].

MRI maintains the same high sensitivity even among women with average risk of breast cancer. In a study among women of average risk and different degrees of density, Kuhl et al. found that MRI resulted in an incremental cancer detection rate of 22.6 per 1000 women in the first round without any interval cancers, and 6.9 per 1000 in the subsequent rounds [195]. In the Dutch DENSE Trial, women with the highest density in the population-based screening program were invited to undergo breast MRI after a negative mammogram [155]. For women who actually underwent an MRI examination, the incremental cancer detection rate was 16.5 per 1000 and the interval cancer rate was 0.8 per 1000 compared to 5 per 1000 in the control arm. In the same study, the false positive rate was 79.8 per 1000. However, in the second round of MRI examinations, the

incremental cancer detection rate was 5.8 per 1000 screening examinations and the false positive rate dropped from 79.8 to 26.3 per 1000 [196].

Issues that have to be taken into consideration with MRI are contra-indications for MRI, the unclear clinical impact of gadolinium retention, and cost. MRI is contra-indicated for those with pregnancy, allergy to gadolinium-based contrast agents, MRI-incompatible internal devices, severe renal insufficiency, and severe claustrophobia. In the DENSE Trial, 0.1 % of women had an adverse event or serious adverse event [155]. There is evidence of gadolinium retention in human organs including the brain. Although gadolinium contrast has been used in the last thirty years without documented long term effects, cautious use is advised [197].

Because of the high cost of the MRI equipment and relatively long acquisition and reading time, an MRI examination greatly exceeds the cost of a mammogram. The lower specificity escalates the costs even more. An analysis of the cost-effectiveness of MRI, using data from the DENSE Trial, has established that MRI screening in women with extremely dense breast (circa 10% of the total population) every four years is cost-effective with a cost of € 22 000 per QALY (Quality-adjusted life year). The cost-effective analysis is sensitive to the unit cost of an MRI examination. Shorter acquisition and reading time and reduction of false-positives would increase the cost-effectiveness of this modality [198]. One multicentre study found that, when double-reading by two radiologists, MRI sensitivity increased by 7% to 91% while the specificity dropped by 7% to 81% [199]. If double-reading was applied in a wide-spread screening setting, the additional cost for reading would certainly impact on cost-effectiveness.

2.10.5 Abbreviated protocol contrast-enhanced magnetic resonance imaging

The advocates of MRI have proposed an abbreviated acquisition protocol that reduces acquisition and reading time, thereby reducing the total cost. In 2014, Kuhl et al. proposed an abbreviated protocol consisting of the first post-contrast subtracted images and its MIP. The sensitivity and specificity of the abbreviated protocol was equivalent to that of the full protocol [200]. Since then, several studies have compared the accuracy of the two protocols without a universal definition of the abbreviated protocol and studies have large protocol variations [201]. Additionally, there is a large variation in study populations: women with increased lifetime risk of breast cancer who undergo MRI surveillance [200, 202-205], women with a biopsy-confirmed breast cancer [206, 207], women with a personal history of breast cancer [208], mixed study populations [209-212] and unselected women of average risk [213]. Despite all these variations, all studies have found both similar sensitivity and specificity [200, 203, 205, 210, 212, 214-217] except for two studies by Chen et al. that found lower specificity [218, 219].

The first prospective multicentre trial to add an abbreviated MRI protocol to mammography in screening of women of average risk and with dense breasts was the ECOG-ACRIN 1141 trial. The results published in 2020 by Weinstein et al. showed an incremental cancer detection rate of 27.4 per 1000 [220].

2.10.6 Other techniques using magnetic resonance

There are different applications of magnetic resonance imaging that would not require intravenous contrast injection. These methods include diffusion weighted imagining and MRI spectroscopy [221, 222].

Diffusion weighted imaging measures the differences in the magnitude of diffusion of water molecules within tissue. Since diffusion of water molecules is restricted in a malignant tumour, there will be an intrinsic contrast between normal/benign tissue and a malignant lesion. Using different b-values, (gradients used to generate diffusion-weighted images), a software program can automatically calculate the apparent diffusion coefficient (ADC) value. Using a dedicated software program, quantitative ADC measures can be attained for a given region of interest (ROI). Low ADC values are usually associated with malignant lesion and high ADC values are associated with benign lesions and normal breast tissue [223]. A meta-analysis by Baxter et al. with 6791 breast lesions in total found a pooled sensitivity of 89% and specificity of 82% for ADC [224].

MRI spectroscopy measures the metabolites specific to malignant tumours. Presently, the use of this method for breast cancer diagnosis is limited to research and may gain clinical value with a more wide spread use of higher field strength MRI equipment [225]. There are also studies to mathematically optimize MRI spectroscopy for breast diagnosis [226].

2.10.7 Contrast-enhanced spectral mammography (CESM)

The concept of contrast-enhanced spectral mammography is somewhat similar to an abbreviated MRI. First, iodine-based contrast medium is injected intravenously, then two x-ray examinations are performed within seconds of each other using different energy levels. Image acquisition is the same as for a standard mammography. The result is a standard mammogram and a subtracted image that shows areas of contrast enhancement. Studies in the last few years comparing contrast-enhanced spectral mammography to CE-MRI have shown similar accuracy between the methods [227-232]. A systemic review and meta-analysis published in 2022 found higher sensitivity (97% vs 91%) and lower specificity (69% vs 74%) for CE-MRI compared to CESM [233].

In a study comparing CESM to mammography for screening of 904 women with high risk of whom 700 had dense breasts a total of 16 cancers were identified. Mammography identified 8 of 16 cancers and contrast-enhanced mammography identified 14 of 16

cancers [234]. Contrast-enhanced mammography can be performed on modern mammography devices and seems to be a cost-effective tool. As with contrast-enhanced MRI, intravenous injection may lead to adverse reactions and there are contra-indications for iodine-based contrast medium. The required dose is more nephrotoxic than MRI contrast medium.

2.10.8 Infrared imaging (thermography)

Infrared radiation can be detected by an infrared sensor that converts the energy into an image. Areas with increased temperature such as infections, inflammations and malignancies appear as hotspots on the image. The method is non-invasive and without contact with the skin and performs independent of breast density. It has been tested in several different medical areas, among them diabetic neuropathy, vascular disorder, fever scanning, rheumatologic disease and liver disease [235]. The method can detect vascular asymmetry between the breasts which can be an indirect sign of breast cancer [236-238]. For mapping of hotspots, cold stimulation is often employed. Cold stimulation causes vasoconstriction of normal blood vessels while abnormal cancer-induced blood vessels remain dilated. This enhances the contrast between normal and cancerous tissue [239].

A study published in 1998 of 63 symptomatic patients reported the sensitivity of thermography to be 25%, and specificity to be 85% [240]. Advances in spatial and thermal resolution and artificial intelligence may improve the method and its potential use in medicine [241]. In one study published in 2010 the sensitivity of the method was 0.78 among 106 biopsies [242]. In another study among 100 patients with and 100 patients without breast cancer, infrared imaging had 17% false negatives and 19% false positives [243]. In conclusion, infrared imaging seems to be a promising method and can be used as an adjunct to clinical examination and mammography, but should not replace mammography.

2.10.9 More imaging modalities

Contrast-enhanced cone beam breast computed tomography is acquired prior and after intravenous injection of iodine contrast medium. This provides high resolution three dimensional images and the derived subtracted images. In one study with 41 women with 100 breast lesions, the sensitivity was higher than for mammography but lower than that of CE-MRI [244].

Molecular imaging with technetium isotope and a dedicated gamma detector has been used as a supplementary screening modality. In one study of 1696 women, the addition

of molecular breast imaging resulted in detection of 13 mammographically occult breast malignancies giving an incremental cancer detection rate of 7.7 per 1000 [245].

Positron emission tomography (PET) uses positron emitting tracer molecules and gives functional information such as metabolism. The most common tracer is 2-[^{18}F]fluoro-2-deoxy-d-glucose ([^{18}F]FDG). PET is combined with an anatomical imaging modality such as CT or MRI. The method is useful in assessing the viability of a tumour and may be used for evaluation of response to neo-adjuvant therapy. Dedicated breast PET has higher tracer uptake and spatial resolution than whole body PET [246]. In one study including 178 women with breast cancer, dedicated breast PET had higher sensitivity than whole body PET [247]. There are also hybrid PET/MRI equipment combing the information of PET with contrast-enhanced prone-positioned breast MRI using a breast-dedicated coil. PET-MRI has higher specificity than MRI alone for evaluating lesions in the breasts, seems to have higher diagnostic accuracy in evaluation of axillary lymph nodes and provides whole-body staging [248-250].

3 Research aims

Research aims

Overall aim

To evaluate the sensitivity and specificity of supplementary modalities to mammography for detection of breast cancer and to study the association between the imaging biomarker background parenchymal enhancement at contrast-enhanced breast MRI and risk factors for breast cancer.

Specific aims

Study 1: Comparing the sensitivity and specificity of a novel breast ultrasound technique "automated breast ultrasound" with traditional handheld ultrasound in detecting breast cancer among women recalled from population-based screening due to a suspicious finding on the mammogram.

Study 2: To determine the incremental cancer detection rate when adding three-dimensional functional infrared imaging to screening mammography among women with dense breasts.

Study 3: To study the association between risk factors for breast cancer and background parenchymal enhancement of normal glandular tissue at contrast-enhanced breast MRI.

Study 4: To compare the diagnostic performance, reading time and inter-rater agreement of contrast-enhanced breast MRI full protocol with an abbreviated protocol among women with no known increased lifetime risk of breast cancer or prior biopsy.

4 Materials and methods

4.1 Study 1

Study population

Women recalled from population-based screening due to a suspicious finding on the mammogram at Södersjukhuset department of mammography were eligible (n=180). Invitation was based on convenience when trained technician was on site. A total of 113 women were included and underwent bilateral automated ultrasound in addition to handheld ultrasound of the breasts. Standard care was given on the basis of the mammographic workup and handheld ultrasound findings.

Imaging equipment

Automated breast ultrasound was performed with Acuson S2000 ABVS system (Siemens, Erlangen, Germany). Images were acquired with a special 14MHz flexible transducer with three standard acquisitions per breast (antero-posterior, medial, and lateral) and extra acquisitions when necessary. Handheld ultrasound was performed with iU22 vision 2010 system (Philips Medical Systems, Eindhoven, the Netherlands) with a L17-5 linear array or a L12-5 linear array probe.

Assessment

Image findings were scored according to the Royal College of Breast Radiologists Breast Group breast imaging classification (1=normal, 2=benign finding, 3=indeterminate finding, 4=suspicious of malignancy, 5=clearly malignant). Handheld ultrasound and ABVS were scored by two radiologists independently and after examining the screening mammography and additional workup images. Scores 1-2 constituted a negative test result, scores 3-5 constituted a positive test result. The reference standard was diagnosis of malignancy according to pathology (true positive) or two year negative follow-up (true negative).

Statistical analysis

The sensitivity and specificity of handheld ultrasound and ABVS were compared using McNemar's test.

4.2 Study 2

Study population

This study was a sub-study by the Karma research group. The Karma cohort (Karolinska Mammography Project for Risk Prediction of Breast Cancer), is a cohort of over 70 000 women with information based on self-reported questionnaires, blood samples, and mammography [251].

Women attending population-based screening (age range 40-74 years) at Södersjukhuset Division of Breast Imaging with breast density > 6% according to Volpara volumetric breast density analysis on the previous mammogram, and who could read and understand written informed consent in Swedish were prospectively recruited for this study. Invitation for study participation was posted together with the screening invitation to each woman. Women with the following conditions were excluded: epilepsy, pregnancy, breast feeding, previous breast cancer, previous breast surgery, breast biopsy throughout 6 weeks prior to the study, implanted devices in the chest area, chemotherapy and/or radiotherapy throughout 6 months prior to the study, and ongoing fever.

A total of 1804 women participated in the study. Of these 1804 women, 39 women were excluded because of equipment malfunction and 38 were excluded due to protocol deviations leaving 1727 women in the study. Of a total of 1692 women with a negative screening mammography, 222 women had a positive 3DIRI score and were referred for a CE-MRI examination for verification of breast cancer. Of these 222 women, 219 were able to undergo MRI.

Imaging equipment

Three dimensional functional infrared imaging (3DIRI) was performed using a prototype developed by Real Imaging Ltd (Airport City, Israel). The device was composed of two identical optical heads placed symmetrically in front of the subject. Each head comprised of a visible light camera, an infrared camera and a digital projector that together generated the infrared-textured bust surface. Imaging took place 15 minutes after the patient was positioned in order to achieve temperature stabilization. Continuous infrared imaging occurred for 5 minutes with stress test after 2 minutes (placing of cold gloves to induce vaso-constriction). After acquisition, three dimensional infrared image maps were generated. Multi-parametric computer analysis was carried out for differences in morphology, structure, asymmetry, and temporal changes between contralateral peripheral vascular maps.

Mammography was conducted using Philips Microdose system (Philips Healthcare) for screening and Philips Mammo Diagnost DR (Philips Medical Solutions) and Siemens MammoMat 3000 Nova (Siemens AG, Medical Solutions) for clinical workup.

Ultrasound examinations were carried out with iU22 vision 2010 US system (Philips Medical Systems) with a L17–5 linear array probe or a L12–5 linear array probe for clinical workup.

Dynamic contrast-enhanced breast MRI was performed with a 1.5-Tesla MAGNETOM Aera (Siemens Medical Solutions) with acquisition according to the European Society of Breast Imaging guidelines with a dedicated 16 channel coil.

Gadolinium contrast material (Dotarem; Gothia Medical or Clariscan: GE Healthcare) was administered intravenously 0.2 ml/kg as a bolus injection with injector followed by 15 ml saline solution.

Assessment

Three dimensional infrared imaging (3DIRI) software generated a risk score from -100 to 100. Positive values were considered test positive and negative values test negative.

Screening examinations were read by two radiologists independently according to clinical routine. Women with a mammographic suspicious finding were recalled for further workup in consensus by two radiologists. The radiologists were not aware of the 3DIRI score.

Only women with a negative screening mammogram and positive 3DIRI risk score were triaged for dynamic contrast-enhanced MRI. MRI images were read by two radiologists and scored in consensus. Women with a positive MRI examination were recalled for further workup.

Image findings at workup and MRI were scored according to the Royal College of Breast Radiologists Breast Group breast imaging classification (1=normal, 2=benign finding, 3=indeterminate finding, 4=suspicious of malignancy, 5=clearly malignant). Scores 1-2 constituted a negative test result, scores 3-5 constituted a positive test result. The reference standard for a positive test was diagnosis of malignancy according to pathology (true positive).

Statistical analysis

In this study we report the incremental cancer detection rate when adding MRI based on 3DIRI test. Estimates for diagnostic accuracy (sensitivity, specificity, positive predictive value, and negative predictive value) are reported under the assumption that if MRI was performed among women with a negative mammogram and a negative 3DIRI, it would not

yield any more cancers. We also report the positive predictive value of biopsies performed because of a positive screening mammography versus positive MRI examination.

4.3 Study 3

Study population

This retrospective study included the 214 participants of study 2 that did not have a diagnosis of breast cancer.

Variable and source of data

Three radiologists in consensus classified BPE and mammographic density by visual assessment according to BI-RADS. BPE was further dichotomized into low and high.

Data on risk factors was available from case report files and the Karma questionnaire which participants had recorded upon study entry. Medical records were examined for the use of hormones. Women were contacted by telephone when there was a discrepancy between questionnaire answer and medical records. Table 1 details the source of data for each variable. The variables were then further modelled as categorical variables.

Variable	***Source of data***
BPE	*Categorized by radiologists*
Breast density	*Categorized by radiologists*
Age	*Case report file*
Weight	*Case report file*
Height	*Case report file*
Menopausal status	*Case report file*
Menopausal treatment	*Case report file + medical records + telephone call*
Systemic progesterone	*Case report file + medical records + telephone call*
Age at menarche	*Karma database*
Age at first birth	*Karma database*
Parity	*Karma database*
Oral contraception	*Karma database*
Family history	*Karma database*
Alcohol	*Karma database*
Smoking	*Karma database*
Physical activity	*Karma database*

Table 1. Source of data for variables used in the statistical analysis.

Statistical analyses

BPE was dichotomized into low vs high. The covariates were categorized. We used logistic regression to estimate the univariable odds ratio (OR) for the association between BPE and each of the variables presented in the table. We then used a multivariable logistic regression model to evaluate the association between BPE and density, age, local estrogen treatment, systemic estrogen treatment (tablets and patches), systemic progestogen treatment (combination hormone replacement therapy as well as contraceptives), BMI, age at menarche, age at first birth, parity, oral contraceptive use, family history of breast cancer, alcohol, smoking, and physical activity.

Stata version 14.1 (StataCorp, College Station, TX, USA) was used for all statistical analysis.

4.4 Study 4

Study population

Participants from study 2 who had undergone an MRI examination were included. An additional 187 women with a suspicion of breast cancer were prospectively recruited by radiologists at the time of breast examination from the same clinic. These patients had an MRI examination BEFORE biopsy procedure to avoid telltale signs of abnormality on the MRI. These women were either recalled from screening or referred for examination based on symptoms. Exclusion criteria were the same as for study 2. Eleven examinations were excluded due to image deviations. A total of 395 MRI examinations were evaluated. The flowchart is illustrated in Figure 1.

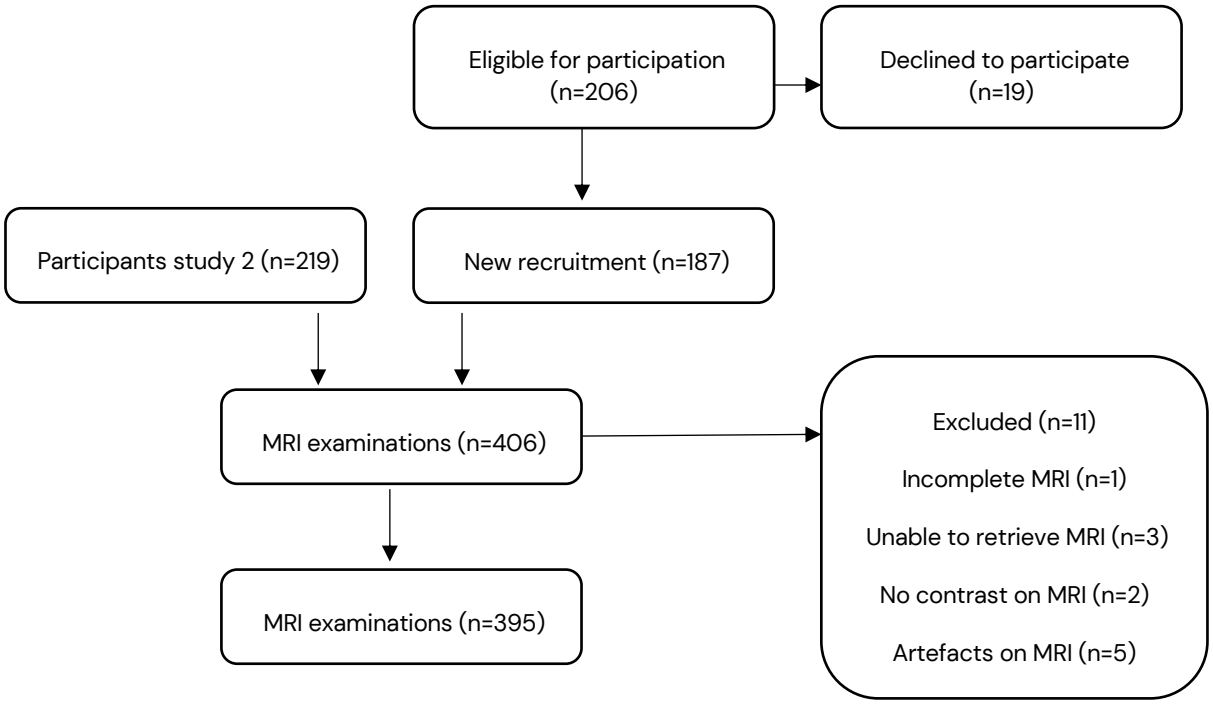

Figure 1: Flowchart of the study population

Imaging equipment

MRI examinations were performed on one 1.5 Tesla MAGNETOM Aera (Siemens Medical Solutions) using a 16-channel dedicated breast coil using a protocol based on the European Society of Breast Imaging guidelines.

Gadolinium contrast material (Dotarem; Gothia Medical or Clariscan: GE Healthcare) was administered intravenously 0.2 ml/kg as a bolus injection with injector followed by 15 ml saline solution.

Imaging protocol

The sequences for each protocol are described in Table 1. The subtracted series and derived MIP were available for reading as were the color map for the kinetics of the dynamic series and ADC map for the diffusion-weighted images.

	Pre-contrast			***Post-contrast***		
fMRI	*T1-weighted*	*T2-weighted*	*STIR*	*T1-weighted fat-saturated*	*T1-weighted fat-saturated x 5*	*Diffusion-weighted*
aMRI				*T1-weighted fat-saturated*	*First T1-weighted fat-saturated*	

Table 1. Protocol for fMRI and aMRI.

Assessment

First the abbreviated protocol (aMRI), thereafter the full protocol (fMRI) was read in random order by three radiologists independently. Patient data and date of examination were removed and substituted with study ID. Images were read in Siemens Syngovia post processing program. Each breast was scored according to the following classification (1=normal, 2=benign finding, 3=indeterminate finding, 4=suspicious of malignancy, 5=clearly malignant). Scores 1-2 constituted a negative test result, scores 3-5 constituted a positive test result.

The reference standard was diagnosis of malignancy based on pathology for positive cases, and two-year follow-up without the diagnosis of breast cancer for negative cases.

Statistical analyses

Sensitivity and specificity were calculated separately for each protocol and on a per breast basis, both separately for each reader and aggregated across all readers. A generalized estimating equations approach was used to compare sensitivity and specificity between the two protocols. The average reading time across all three readers was compared using t-tests. The Inter-reader agreement was measured using Krippendorff's alpha coefficient. Stata software version 15.1 was used for the statistical analysis.

Ethical considerations

All four studies were approved by the ethical committee and for studies 2-4 the participants had signed written informed consent. In ethical considerations, clinical research should take into account the benefit of the study for the target population against the risk of harm to an individual participant. In study 1, automated breast ultrasound may have resulted in some transient discomfort, but the method is otherwise harmless and its evaluation was an important step in implementing the method in clinical practice. As for study 2, infrared imaging is considered harmless, but verifying positive results with contrast-enhanced MRI could have led to adverse effects for individual participants. Despite a relatively large study population and much resource expenditure, the study is not able to draw any definitive conclusions on the benefit of infrared imaging because of inconsistent reference test for positive and negative cases. It is impossible to know if the incremental cancer detection rate is attributed to infrared imaging or a random selection for additional MRI examinations. This highlights the importance of good study design as a key component in ethical deliberation. Study 3 uses already available data for synthesis of a new hypothesis, without any apparent harm to participants or on a wider societal scale. In study 4, patients with a suspicion of breast cancer were recruited for an additional contrast-enhanced breast MRI, a procedure that is routine clinical practice in many hospitals and the benefits of pre-operative MRI generally outweighs the potential harm in this patient group. I hope that the encouraging results of study 4 can contribute to implementing the more cost-effective abbreviated protocol in clinical practice. With finite resources, the reduced costs in one area may be used to benefit patients in other areas of healthcare.

5 Results and discussion

5.1 Study 1

A total of 113 women recalled from screening with mean age of 55.6 years (age range 40-75) constituted the study population. Of 226 breasts, 221 were examined with both methods. We identified 26 breast cancers in 25 women.

Table 1 summarizes the statistical analysis performed on per breast basis in two categories, breasts with a suspicious finding on the mammogram and breasts with a negative mammogram. We calculated the *p* value (exact) for McNemar's test comparing the sensitivity and specificity of each method.

Finding from screening mammography	***Sensitivity***				
	Handheld		*ABVS*		
	Sensitivity	*TP/(TP+FN)*	*Sensitivity*	*TP/(TP+FN)*	*P value*
Suspicious	*88.0*	*22/25*	*88.0*	*22/25*	*1.0*
Negative	*100.0*	*1/1*	*100.0*	*1/1*	*1.0*

Finding from screening mammography	***Specificity***				
	Handheld		*ABVS*		
	Specificity	*TN/(TN+FP)*	*Specificity*	*TN/(TN+FP)*	*P value*
Suspicious	*93.5*	*87/93*	*89.2*	*83/93*	*0.29*
Negative	*100.0*	*102/102*	*94.7*	*96/102*	*0.03*

Table 1. Summary statistics on a per breast basis.

Discussion

In summary, ABVS had the same sensitivity for detection of breast cancer as handheld ultrasound. The specificity was lower when examining breasts with no suspicious finding on the mammogram and the difference was statistically significant. The lower specificity of ABVS is well established [178, 252, 253]. Certainly in many cases it is the result of reader inexperience with a new method, but is also influenced by suboptimal image quality and acoustic artefacts when the breast cannot be adequately compressed by the large transducer. ABVS failed to detect a 5 mm invasive cancer in a woman with large breasts, because the area was not covered in the ABVS examination. ABVS is however not an ideal method for scanning of large breasts because of the number of extra acquisitions that need to be done to cover the entire breast. Similar to handheld ultrasound, ABVS could not detect abnormalities in areas of mammographic malignant micro-calcifications. The detectability of microcalcifications varies among different radiologists and ultrasound equipment and not all calcifications can be detected by ultrasound [254-256].

One limitation of our study was radiologist's knowledge of the mammography prior to assessment of the handheld ultrasound or ABVS. This most likely influenced the sensitivity of both methods. It has previously been shown that ultrasound performs better when there is a known anomaly on another imaging modality, for example mammography [257]. However, since ABVS is proposed as an adjunct to mammography and a substitute for handheld examinations, the diagnostic accuracy measurements still provide an accurate comparison.

Although image acquisition is carried out by a technician, reading time is not drastically reduced for the radiologist since acoustic artefacts need to be carefully differentiated from a real finding. The greatest advantage of ABVS is documentation of the entire breast, a baseline reference for future examinations and the possibility of second reading.

5.2 Study 2

Participants

A total of 1727 women with median age of 56 (age range 43-74 years) participated in this study. Table 1 lists the investigated characteristics of study participants.

Characteristics	*Number of Participants*
Age	
40-49	*358 (21%)*
50-59	*707 (41%)*
60-69	*461 (27%)*
70-74	*201 ((12%)*
Volpara Breast Density Measurement	
<4.5%	*10 (1%)*
4.5%-7.5%	*185 (11%)*
7.5%-15.5%	*1173 (68%)*
>15%	*359 (21%)*
Menopausal Status	
Pre/peri-menopausal	*596 (35%)*
Post-menopausal	*1131 (65%)*
BMI	
<20	*157 (9%)*
20-24.9	*1150 (67%)*
25-30	*360 (21%)*
>30	*54 (3%)*
Hereditary Risk	
Known mutation for BRCA1/BRCA2	*1*
Family history of Breast Cancer	*234 (14%)*

Table 1. The characteristics of study participants. Percentages are given in parentheses.

Cancer detection rate

A total of 12 women were diagnosed with breast malignancy. One women with a negative mammogram and 3DIRI score had the diagnosis of breast cancer within one year of follow-up. The diagnostic yield of mammography was 7 of 1727 (0.41%; 95% CI 0.20–0.83%) and the diagnostic yield of mammography with additional 3DIRI to select women for further examination was 12 of 1727 (0.69%; 95% CI 0.40–1.21%). The incremental cancer detection rate among women triaged for MRI was 5 of 222 which translates to 22.5 additional cancers per 1000 (95% CI 10–52). Figure 1 illustrates number of participants in each category.

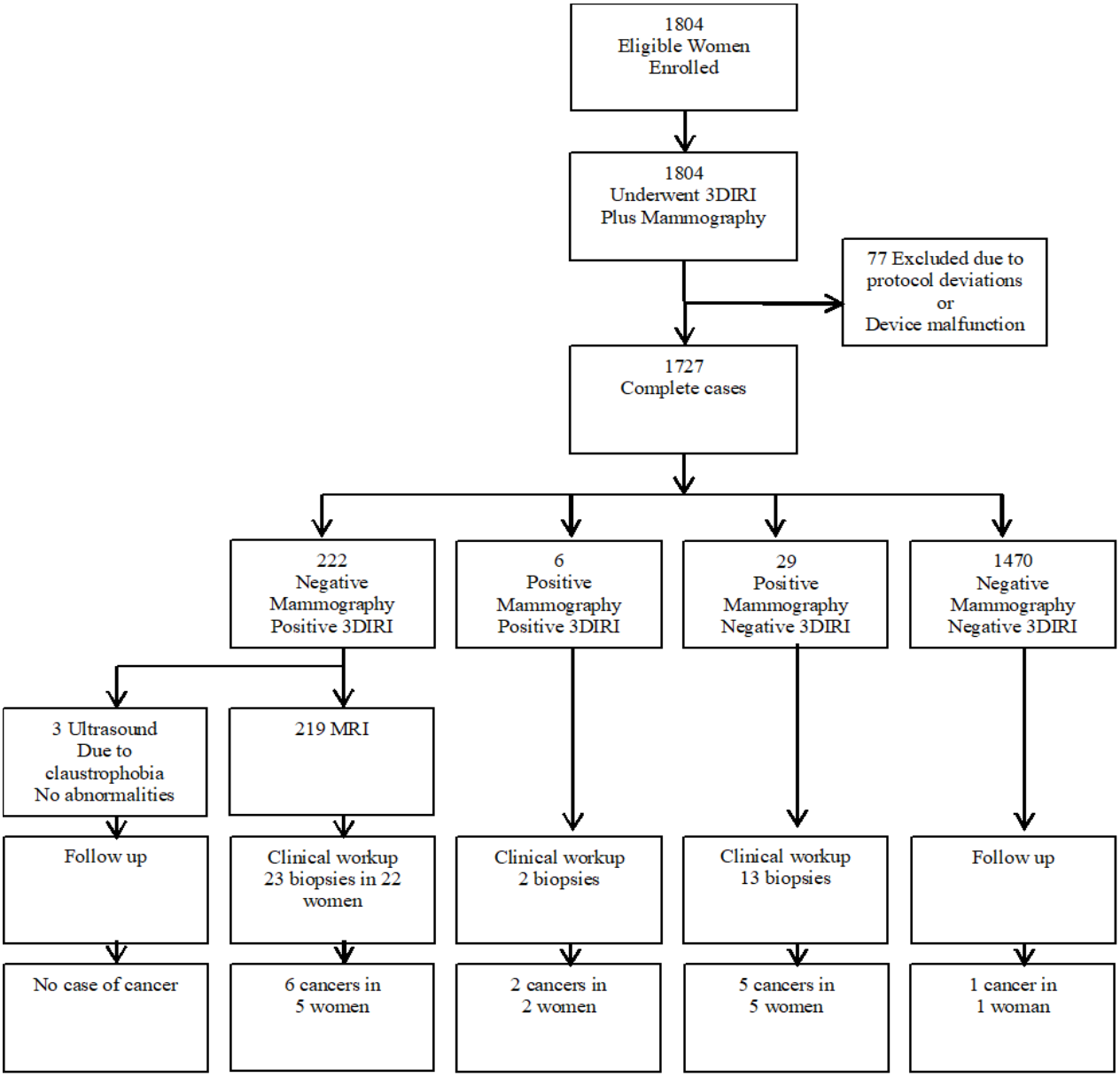

Figure 1. Number of participants in each category.

Positive predictive value of biopsy

Among women recalled from screening due to a positive mammogram and undergoing a biopsy, we identified 7 malignancies out of 15 biopsies giving a PPV_3 of 0.47 (95% CI 0.25–0.70%).

Using 3DIRI to select women for MRI, we identified 6 cancers in 23 biopsies giving a PPV_3 of 0.26 (95% CI 0.13–0.46%). Imaging and tumour characteristics are given in Table 2.

Case number	Age	Histopathological finding	Tumour size (mm)	Volpara Volumetric density	Mammography screening result	3DIRI risk score
1	*60*	*Invasive ductal carcinoma grade I*	*15*	*18.2%*	*Code 4*	*Negative (-48.5)*
2	*55*	*Carcinoma in situ grade III*	*16*	*19.0%*	*Code 3*	*Positive (4.9)*
3	*66*	*Carcinoma in situ grade III*	*43*	*44.5%*	*Code 3*	*Positive (48.6)*
4	*56*	*Invasive ductal carcinoma grade I*	*7*	*18.9%*	*Code 1*	*Positive (22.8)*
5	*72*	*Carcinoma in situ grade III*	*42*	*9.3%*	*Code 1*	*Positive (12.1)*
6	*68*	*Invasive ductal carcinoma grade I*	*11*	*11.3%*	*Code 1*	*Positive (41.9)*
7	*73*	*Carcinoma in situ grade I*	*7*	*32.3%*	*Code 1*	*Positive (3.5)*
8	*74*	*Invasive ductal carcinoma grade II*	*5*	*7.5%*	*Code 3*	*Negative (-37,2)*
9	*59*	*Invasive ductal carcinoma grade III + cancer in situ grade III*	*5 + 40 mm*	*17.7%*	*Code 5*	*Negative (-26.6)*
10	*72*	*Invasive ductal carcinoma grade III*	*35*	*43.0%*	*Code 5*	*Negative (-22.4)*
11	*73*	*Carcinoma in situ grade II*	*48*	*5.3%*	*Code 3*	*Negative (-38.6)*
12	*70*	*Left: Invasive ductal carcinoma grade II* *Right: Invasive ductal carcinoma grade III*	*Multifocal* *Multifocal*	*9.6%*	*Code 1*	*Positive (42.2)*

Table 2. Tumour characteristics and imaging findings.

Discussion

The cancer detection rates calculated in this study are given under the assumption that there were no cancers in the category of women with a negative mammogram and 3DIRI score. This is however very unlikely based on the study by Kuhl et al. where adding MRI among women of average risk and variations in breast density resulted in an increase of cancer detection rate of 22.6 per 1000 [195]. We were also able to identify one woman with a negative mammogram and 3DIRI score that had a diagnosis of breast cancer within one year. We can only conclude that when triaging women for a breast MRI examination based on 3DIRI results, more malignancies are detected. The study would have been more informative if MRI (or another reference test) was performed on all participants and the proportion of malignancies among 3DIRI positive and 3DIRI negative women were compared. It is necessary to first establish the diagnostic accuracy of 3DIRI as a

standalone method before it can be utilized as an adjunct to mammography. When designing a diagnostic accuracy study, we recommend following the STARD guidelines (Standards for Reporting of Diagnostic Accuracy Studies) [163].

5.3 Study 3

Categorical variables on 214 women with a mean age of 58 and age range 43-74 without a suspicion of breast cancer were included in the analysis. The characteristics of the study population are listed in the table 1.

Variables	*Number of individuals and percentages*
Density (BI-RADS)	
B	*94 (44%)*
C	*88 (41%)*
D	*32 (15%)*
Missing	*0*
BPE	
Low	*180 (84%)*
High	*34 (16%)*
Missing	*0*
Age	
40 - <53	*74 (34%)*
53-62	*55 (26%)*
>62 – 74	*85 (40%)*
Missing	*0*
Menopausal status	
Pre/perimenopausal	*70 (33%)*
Postmenopausal	*144 (67%)*
Missing	*0*
Local estrogen	
No	*175 (82%)*
Yes	*39 (18%)*
Missing	*0*
Systemic estrogen	
No	*209 (98%)*
Yes	*5 (2%)*
Missing	*0*
Systemic progesterone	
No	*209 (98%)*
Yes	*5 (2%)*
Missing	*0*
BMI	
<25	*155 (72%)*
25-30	*50 (23%)*
>30	*9 (4%)*
Missing	*0*
Age at menarche	
<13	*79 (37%)*
13-14	*98 (46%)*
15+	*32 (15%)*
Missing	*5 (2%)*
Age at first birth	
Nulliparous	*38 (18%)*
<26	*62 (29%)*
26-30	*37 (17%)*
>30	*73 (34%)*
Missing	*4 (2%)*
Parity	
Nulliparous	*38 (18%)*
1	*37 (17%)*
2 or more	*135 (63%)*

Missing	*4 (2%)*
Oral contraceptive use	
Never	*27 (13%)*
Ever	*179 (84%)*
Missing	*8 (4%)*
Family history of breast cancer	
No	*172 (80%)*
Yes	*34 (16%)*
Missing	*8 (4%)*
Alcohol gram/day	
<1	*49 (23%)*
1-15	*109 (51%)*
>15	*50 (23%)*
Missing	*6 (3%)*
Smoking	
Never	*108 (50%)*
Former	*80 (37%)*
Current	*20 (9%)*
Missing	*6 (3%)*
Physical activity (43+ met_hrs/day)	
Low (<43)	*113 (53%)*
High (>43)	*93 (43%)*
Missing	*8 (4%)*
Malignancy	
No	*214 (100%)*
Yes	*0*
Missing	*0*

Table 1. Characteristics of study participants. Percentages are given in parentheses.

The odds ratio for having high BPE at different categorical levels and corresponding *p*-values are summarized in table 2.

	Low BPE	High BPE	OR unadjusted (95% confidence Interval)	OR adjusted (95% confidence interval)
	N (%)	N (%)		
Density (BI-RADS)			P =0.07	P =0.23
B	84 (89)	10 (11)	1.0 (ref)	1.0 (ref)
C	73 (83)	15 (17)	1.7 (0.7-4.1)	2.1 (0.7-6.3)
D	23 (72)	9 (28)	3.3 (1.2-9.0)	3.1 (0.7-12.9)
Age at MRI			P<0.001	P=0.002
0-52	48 (65)	26 (35)	1.0 (ref)	1.0 (ref)
52-62	51 (93)	4 (7)	0.1 (0.05-0.5)	0.2 (0.04-0.6)
>62	81 (95)	4 (5)	0.1 (0.03-0.3)	0.1 (0.02-0.4)
Menopausal status			P<0.001	
Pre/perimenopausal	43 (61)	27 (39)	1.0 (ref)	
Postmenopausal	137 (95)	7 (5)	0.08 (0.03-0.2)	
Local estrogen			P=0.06	P=0.49
No	143 (82)	32 (18)	1.0 (ref)	1.0 (ref)
Yes	37 (95)	2 (5)	0.2 (0.06-1.0)	0.5 (0.09-3.2)
Systemic estrogen			P=0.80	P=0.98
No	176 (84)	33 (16)	1.0 (ref)	1.0 (ref)
Yes	4 (80)	1 (20)	1.3 (0.1-12.3)	1.0 (0.07-15.3)
Systemic progesterone			P=0.01	P=0.03
No	179 (86)	30 (14)	1.0 (ref)	1.0 (ref)
Yes	1 (20)	4 (80)	23.9 (2.6-20.9)	21.1 (1.3-46.0)
BMI			P=0.08	P=0.03
<25	133 (86)	22 (14)	1.0 (ref)	1.0 (ref)
25-29.9	42 (84)	8 (16)	1.2 (0.5-2.8)	1.4 (0.4-4.8)
30+	5 (56)	4 (44)	4.8 (1.2-19.4)	12.6 (1.9-82.7)
Age at menarche			P=0.18	P=0.82
<13	62 (78)	17 (22)	1.0 (ref)	1.0 (ref)
13-14	87 (89)	11 (11)	0.5 (0.2-1.1)	0.7 (0.2-2.2)
15+	27 (84)	5 (16)	0.7 (0.2-2.0)	1.0 (0.2-4.6)
Age at first birth			P=0.09	P=0.81
Nulliparous	32 (84)	6 (16)	1.0 (ref)	1.0 (ref)
<26	55 (89)	7 (11)	0.7 (0.2-2.2)	1.8 (0.3-10.0)
26-30	35 (95)	2 (5)	0.3 (0.1-1.6)	1.0 (0.1-8.4)
>30	56 (77)	17 (23)	1.6 (0.6-4.5)	1.8 (0.4-7.6)
Parity			P=0.95	
Nulliparous	32 (84)	6 (16)	1.0 (ref)	

1	*32 (86)*	*5 (14)*	*0.8 (0.2-3.0)*	
2+	*114 (84)*	*21 (16)*	*1.0 (0.4-2.6)*	
Oral contraceptive use			*P=0.23*	*P=0.27*
Never	*25 (93)*	*2 (7)*	*1.0 (ref)*	*1.0 (ref)*
Ever	*149 (83)*	*30 (17)*	*2.5 (0.6-11.2)*	*3.0 (0.4-20.5)*
Family history of breast cancer			*P=0.71*	*P=0.75*
No	*146 (85)*	*26 (15)*	*1.0 (ref)*	*1.0 (ref)*
Yes	*28 (82)*	*6 (18)*	*1.2 (0.5-3.2)*	*1.2 (0.4-3.9)*
Alcohol gram/day			*P=0.47*	*P=0.70*
<1	*40 (82)*	*9 (18)*	*1.0 (ref)*	*1.0 (ref)*
1-15	*91 (83)*	*18 (17)*	*0.9 (0.4-2.1)*	*1.3 (0.4-4.3)*
15+	*45 (90)*	*5 (10)*	*0.5 (0.2-1.6)*	*0.8 (0.2-3.3)*
Smoking			*P=0.90*	*P=0.95*
Never	*90 (83)*	*18 (17)*	*1.0 (ref)*	*1.0 (ref)*
Former	*69 (86)*	*11 (14)*	*0.8 (0.4-1.8)*	*1.0 (0.4-2.8)*
Current	*17 (85)*	*3 (15)*	*0.9 (0.2-3.3)*	*0.7 (0.1-4.5)*
Physical activity (met_hrs/day)			*P=0.86*	*P=0.80*
Low (<43)	*95 (84)*	*18 (16)*	*1.0 (ref)*	*1.0 (ref)*
High (>43)	*79 (85)*	*14 (15)*	*0.9 (0.4-2.0)*	*0.9 (0.3-2.4)*

Table 2. The odds ratio for having high BPE, univariable model and adjusted model.

Discussion

This study confirmed earlier findings that the proportion of women with high BPE is much lower than the proportion of women with high mammographic density [258]. One study found a strong correlation between BPE and concentration of glandular tissue in premenopausal women [259]. Accordingly, mammographic density is most likely composed of the non-enhancing fibrous tissue rather than glandular tissue. Although with a study population of 214 women, we were not able to establish a statistically significant association between BPE and mammographic density, we could establish a trend of increasing BPE with increase in density.

The study also confirmed earlier findings of a negative association between BPE and age [110, 260] as well as a positive correlation between BPE and BMI [261, 262]. The underlying mechanism for high levels of BPE among women with high BMI is proposed to be high levels of estrogen. But we could not confirm an association between estrogen intake and

BPE. We speculate that the high level of BPE may be related to a different underlying factor. With only five women with intake of systemic progesterone in our study, we were able to find a positive association with BMI. Although the result must be considered with caution, it does confirm the result of earlier studies [107, 260, 263] and why MRI should be performed day 5-12 of the menstrual cycle before the rise in endogenous progesterone [182]. We were unable to find a correlation between BPE and other investigated risk factors.

5.4 Study 4

Study participants

This study included 395 women of whom 178 had breast cancer. A total of 131 women with breast cancer were asymptomatic and the cancer was detected through the population-based mammography screening program. The main characteristics are presented in Table 1.

	Number of participants (n)
Total number of participants	*395*
Diagnosis of unilateral malignancy	*165 (41)*
Diagnosis of bilateral malignancy	*13 (3)*
Women with mammography screening detected malignancy	*131(33)*
Women with clinically detected breast malignancy	*47 (11)*
Neo-adjuvant chemotherapy	*25 (6)*

Table 1: Characteristics of study participants. Percentages are given in the parentheses.

Lesion characteristics

Table 2 gives a summary of pathology results. For invasive carcinomas, the distribution of type and grade also matches the expected distribution in the general population. There were a total of 29 biopsies with a benign outcome among these women.

Size of malignancies

For invasive tumours the median size was 16 mm with a range of 3-150 mm. For multifocal tumours, the size of the largest invasive component was reported. For ductal carcinoma in situ without invasive component, the median size was 35 mm with a range of 7-100 mm.

Lesion characteristics	*No. of findings*
Malignancy	*191*
Ductal carcinoma in situ without invasive component	*16 (8)*
Invasive tumour	*175 (92)*
Type of invasive tumour	
No special type (NST)	*141 (80)*
Lobular	*31 (18)*
Cribriform	*2 (1)*
Papillary	*1 (1)*
Grade of invasive tumour	
Grade 1	*45 (26%)*
Grade 2	*87 (50)*
Grade 3	*43 (24%)*
Non-malignant biopsy-verified findings in the breasts	*29*
Adenosis	*6*
Borderline phyllodes	*1*
Atypical ductal hyperplasia	*2*
Hyperplasia without atypia	*2*
Cystic fibroadenosis	*2*
Fibroadenoma	*7*
Columnar cell hyperplasia	*1*
Columnar cell hyperplasia with atypia	*1*
Radial scar	*3*
Papillomatosis	*1*
Fibrosis	*1*
Papilloma	*2*

Table 2: Biopsy-verified characteristics of lesions

Diagnostic accuracy

Analysis was carried out on per breast basis so that there were a total of 790 breasts in the analysis. Estimates for sensitivity and specificity for each protocol, both aggregated across all readers and separately for each of the three readers, are presented in Table 3. The overall sensitivity was 93.0% for the abbreviated protocol and 92.0% for the full protocol. The difference between the two was not statistically significantly different based on the GEE analysis (p=0.51). The overall specificity was 91.7% for the abbreviated

and 94.3% for the full protocol. The difference between the two was statistically significantly based on the GEE analysis (p=0.003).

	Sensitivity (95% confidence interval)	***Specificity (95% confidence interval)***	***ROC (95% confidence interval)***
Aggregated			
Abbreviated protocol	*93.0% (90.6% - 95.0%)*	*91.7% (90.3% - 92.9%)*	*0.92 (0.91 - 0.94)*
Full protocol	*92.0% (89.4% - 94.1%)*	*94.3% (93.2% - 95.3%)*	*0.93 (0.92 - 0.94)*
Reader 1			
Abbreviated protocol	*94.8% (90.6% - 97.5%)*	*93.8% (91.6% - 95.6%)*	*0.94 (0.92 - 0.96)*
Full protocol	*95.3% (91.2% - 97.8%)*	*94.8% (92.7% - 96.5%)*	*0.95 (0.93 - 0.97)*
Reader 2			
Abbreviated protocol	*88.5% (83.1% - 92.6%)*	*92.0% (89.5% - 94.0%)*	*0.90 (0.88 - 0.93)*
Full protocol	*86.4% (80.7% - 90.9%)*	*94.3% (92.2% - 96.0%)*	*0.90 (0.88 - 0.93)*
Reader 3			
Abbreviated protocol	*95.8% (91.9% - 98.2%)*	*89.3% (86.6% - 91.7%)*	*0.93 (0.91 - 0.94)*
Full protocol	*94.2% (89.9% - 97.1%)*	*93.8% (91.6% - 95.6%)*	*0.94 (0.92 - 0.96)*

Table 3: Sensitivity, specificity, and ROC (Receiver-operating characteristic) for each protocol aggregated across all readers and separately for each reader.

Inter-rater agreement

Krippendorff's alfa, a measure of inter-reader agreement was 0.794 for the abbreviated and 0.828 for the full protocol.

Reading time

The average aggregated reading time was 67 seconds for the abbreviated protocol and 126 seconds for the full protocol.

Discussion

Our study confirms earlier findings that the abbreviated protocol (aMRI) has similar sensitivity to the full protocol (fMRI) [200, 203, 205, 210, 212, 214-217]. Unlike most studies and similar to two studies by Chen et al, the abbreviated protocol had a lower specificity in our study [218, 219]. The average reading time of 67 seconds for aMRI is within earlier reported reading times that ranged from 28 to 179 seconds [200, 203, 204, 207, 210, 219]. We found a fairly good inter-rater agreement of 0.79 for aMRI and 0.83 for fMRI.

The study populations of earlier comparative studies have included women with increased lifetime risk of breast cancer, women with biopsy-verified breast cancer or a mix of different populations. Only one study has been carried out among unselected women with average risk of breast cancer [213]. The main aim and strength of this study was overcoming these two limitations. Women were recruited outside of surveillance programs and were biopsied AFTER the MRI examination. The study confirms the results of earlier studies, even among women who do not have increased life-time risk of breast cancer and even when there are no telltale signs of malignancy on the MRI.

Several conditions in the study differ from a real screening setting which limits the generalizability of the results. First of all, the cancer-enriched cohort with relatively few benign findings likely influenced the readers' sensitivity and specificity. The retrospective reading of the images without any real bearing on patient outcome has most certainly influenced the average reading time. Readers may theoretically have remembered images and diagnosis from earlier clinical care even though all information pertaining to the patient and date of examination had been removed.

6 Conclusions

Several complementary modalities may be added to mammography.

In study I, we found similar sensitivity but lower specificity for ABVS compared to handheld ultrasound. Its benefits include documentation of the whole breast for future comparisons, the possibility of assessment at a later date, and double reading. The drawback we found was the increase in false-positives and the method's limitation in documenting very large breasts. In deciding to implement this method in a clinical setting, the benefits and drawbacks must be carefully considered based on local conditions.

I study II, we found an incremental cancer detection rate when using a 3DIRI risk score for triaging women for additional MRI examination. Whether this selection method is superior to a selection based on established risk factors for breast cancer, such as mammographic density or family history needs further investigation.

In study III, we found that BPE is negatively associated with age and positively associated with BMI and progesterone. Our study could demonstrate a trend for increase in BPE with increasing mammographic density although the association was not statistically significant. BPE was not associated with any of the other investigated risk factors for breast cancer.

In study IV, we found that an abbreviated breast MRI protocol had similar sensitivity as a full protocol for detection of breast cancer and had a shorter reading time. The specificity and inter-rater agreement were somewhat lower. The abbreviated protocol could potentially be a more cost-effective alternative in a screening setting. This hypothesis needs to be further studied in prospective screening trials.

7 Points of perspective

A proportion of women need supplementary imaging modalities in order to benefit from screening. Automated breast ultrasound and abbreviated contrast-enhanced MRI are two highly relevant modalities that can be applied in trials exploring the benefits of personalized screening.

Contrast-enhanced spectral mammography has emerged as a tool with similar sensitivity to MRI. By upgrading the software, the examination can be performed on a pre-existing mammography device and with the same personnel. Since a mammography device has a fraction of the cost of an MRI, the method is less costly. A standard mammography and the subtracted images are acquired simultaneously which also improves workflow. It is rather likely that this method will become first choice for screening women with high risk of developing breast cancer. In the SMART trial, we plan to study the benefit of adding contrast-enhanced spectral mammography in women with high risk of developing breast cancer within two years.

Risk stratification based on mammographic density may be tweaked further. Density is comprised of various proportions of fibrous tissue and parenchyma. With the knowledge that breast cancer arises from the parenchymal tissue, it is worthwhile to study if density can be further dichotomized into mostly fibrous tissue (low risk) or mostly glandular tissue (high risk). Theoretically, women with mostly fibrous tissue will have lower risk of developing breast cancer and may require less frequent screening, although the masking effect remains the same. It could be that Background parenchymal enhancement at MRI (BPE) can make this differentiation: women with low BPE (low risk density) and high BPE (high risk density). Trials such as the ECOG-ACRIN 1141 trial and DENSE trial could test this hypothesis.

The Swedish mammography program is free of charge and easily accessible. Despite these benefits, there are considerable variations in screening participation among women of different socio-economic groups that suggests non-monetary underlying factors. Parallel to improving mammography screening for attendees, we need to focus our attention on identifying and addressing barriers among the non-attendees.

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9 References

1. Global Burden of Disease Cancer, C., et al., *Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study.* JAMA Oncol, 2019.
2. World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer.
3. Socialstyrelsen. Available from: https://www.socialstyrelsen.se/statistik-och-data/statistik/statistikamnen/cancer/
4. Global Cancer Observatory. Available from: http://gco.iarc.fr/.
5. Barlow, L., et al., *The completeness of the Swedish Cancer Register: a sample survey for year 1998.* Acta Oncol, 2009. **48**(1): p. 27-33.
6. Lynge, E., et al., *Outcome of breast cancer screening in Denmark.* BMC Cancer, 2017. **17**(1): p. 897.
7. Walters, S., et al., *Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study.* Br J Cancer, 2013. **108**(5): p. 1195-208.
8. Institute, N.C. *SEER Cancer Statistics Review*. Available from: https://seer.cancer.gov/archive/csr/1975_2012/browse_csr.php?sectionSEL=4&pageSEL=sect_04_table.13#table5.
9. Saadatmand, S., et al., *Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173,797 patients.* BMJ, 2015. **351**: p. h4901.
10. James D. Brierley (Editor), M.K.G.E., Christian Wittekind (Editor), *TNM Classification of Malignant Tumours, 8th Edition*. 2016.
11. Erbas, B., et al., *The natural history of ductal carcinoma in situ of the breast: a review.* Breast Cancer Res Treat, 2006. **97**(2): p. 135-44.
12. Brennan, M.E., et al., *Ductal carcinoma in situ at core-needle biopsy: meta-analysis of underestimation and predictors of invasive breast cancer.* Radiology, 2011. **260**(1): p. 119-28.
13. Mele, A., et al., *Breast-Conserving Surgery Alone for Ductal Carcinoma In Situ: Factors Associated with Increased Risk of Local Recurrence.* Ann Surg Oncol, 2017. **24**(5): p. 1221-1226.
14. Tabar, L., et al., *A new approach to breast cancer terminology based on the anatomic site of tumour origin: The importance of radiologic imaging biomarkers.* Eur J Radiol, 2022. **149**: p. 110189.
15. Fitzgibbons, P.L., et al., *Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999.* Arch Pathol Lab Med, 2000. **124**(7): p. 966-78.
16. Saji, S., M. Hirose, and M. Toi, *Clinical significance of estrogen receptor beta in breast cancer.* Cancer Chemother Pharmacol, 2005. **56 Suppl 1**: p. 21-6.
17. Nadji, M., *Quantitative immunohistochemistry of estrogen receptor in breast cancer: "much ado about nothing!".* Appl Immunohistochem Mol Morphol, 2008. **16**(2): p. 105-7.
18. Early Breast Cancer Trialists' Collaborative, G., *Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials.* Lancet, 2005. **365**(9472): p. 1687-717.
19. Sergina, N.V. and M.M. Moasser, *The HER family and cancer: emerging molecular mechanisms and therapeutic targets.* Trends Mol Med, 2007. **13**(12): p. 527-34.

20. Gonzalez-Angulo, A.M., et al., *High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller.* J Clin Oncol, 2009. **27**(34): p. 5700-6.
21. Slamon, D.J., et al., *Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene.* Science, 1987. **235**(4785): p. 177-82.
22. Davey, M.G., et al., *Ki-67 as a Prognostic Biomarker in Invasive Breast Cancer.* Cancers (Basel), 2021. **13**(17).
23. Nielsen, T.O., et al., *Assessment of Ki67 in Breast Cancer: Updated Recommendations From the International Ki67 in Breast Cancer Working Group.* J Natl Cancer Inst, 2021. **113**(7): p. 808-819.
24. Parker, J.S., et al., *Supervised risk predictor of breast cancer based on intrinsic subtypes.* J Clin Oncol, 2009. **27**(8): p. 1160-7.
25. Perou, C.M., et al., *Molecular portraits of human breast tumours.* Nature, 2000. **406**(6797): p. 747-52.
26. Sorlie, T., et al., *Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications.* Proc Natl Acad Sci U S A, 2001. **98**(19): p. 10869-74.
27. Cardoso, F., et al., *European Breast Cancer Conference manifesto on breast centres/units.* Eur J Cancer, 2017. **72**: p. 244-250.
28. Freeman, M.D., J.M. Gopman, and C.A. Salzberg, *The evolution of mastectomy surgical technique: from mutilation to medicine.* Gland Surg, 2018. **7**(3): p. 308-315.
29. Moran, M.S., et al., *Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer.* J Clin Oncol, 2014. **32**(14): p. 1507-15.
30. Morrow, M., et al., *Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma in Situ.* Pract Radiat Oncol, 2016. **6**(5): p. 287-295.
31. Pilewskie, M. and M. Morrow, *Margins in breast cancer: How much is enough?* Cancer, 2018. **124**(7): p. 1335-1341.
32. Lynch, S.P., et al., *Breast cancer multifocality and multicentricity and locoregional recurrence.* Oncologist, 2013. **18**(11): p. 1167-73.
33. Nijenhuis, M.V. and E.J. Rutgers, *Conservative surgery for multifocal/multicentric breast cancer.* Breast, 2015. **24 Suppl 2**: p. S96-9.
34. Yerushalmi, R., et al., *Is breast-conserving therapy a safe option for patients with tumor multicentricity and multifocality?* Ann Oncol, 2012. **23**(4): p. 876-81.
35. Houssami, N., et al., *The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis.* Ann Surg Oncol, 2014. **21**(3): p. 717-30.
36. Agarwal, S., et al., *Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer.* JAMA Surg, 2014. **149**(3): p. 267-74.
37. Bagaria, S.P., et al., *Is mastectomy undertreatment for low-risk breast cancers eligible for breast-conserving therapy?* Cancer, 2015. **121**(16): p. 2705-12.
38. Hwang, E.S., et al., *Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status.* Cancer, 2013. **119**(7): p. 1402-11.
39. Lagendijk, M., et al., *Breast conserving therapy and mastectomy revisited: Breast cancer-specific survival and the influence of prognostic factors in 129,692 patients.* Int J Cancer, 2018. **142**(1): p. 165-175.

40. Tan, M.P. and E. Silva, *Addressing the paradox of increasing mastectomy rates in an era of de-escalation of therapy: Communication strategies.* Breast, 2018. **38**: p. 136-143.
41. Kummel, S., J. Holtschmidt, and S. Loibl, *Surgical treatment of primary breast cancer in the neoadjuvant setting.* Br J Surg, 2014. **101**(8): p. 912-24.
42. Fisher, B., et al., *Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer.* N Engl J Med, 2002. **347**(16): p. 1233-41.
43. Litiere, S., et al., *Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial.* Lancet Oncol, 2012. **13**(4): p. 412-9.
44. Veronesi, U., et al., *Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer.* N Engl J Med, 2002. **347**(16): p. 1227-32.
45. Early Breast Cancer Trialists' Collaborative, G., et al., *Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials.* Lancet, 2011. **378**(9804): p. 1707-16.
46. Ebctcg, et al., *Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials.* Lancet, 2014. **383**(9935): p. 2127-35.
47. Ivens, D., et al., *Assessment of morbidity from complete axillary dissection.* Br J Cancer, 1992. **66**(1): p. 136-8.
48. Sacre, R.A., *Clinical evaluation of axillar lymph nodes compared to surgical and pathological findings.* Eur J Surg Oncol, 1986. **12**(2): p. 169-73.
49. Houssami, N., et al., *Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla.* Ann Surg, 2011. **254**(2): p. 243-51.
50. Bergkvist, L., et al., *Multicentre study of detection and false-negative rates in sentinel node biopsy for breast cancer.* Br J Surg, 2001. **88**(12): p. 1644-8.
51. Bergkvist, L., et al., *Multicentre validation study of sentinel node biopsy for staging in breast cancer.* Br J Surg, 2005. **92**(10): p. 1221-4.
52. Kuehn, T., et al., *Sentinel-node biopsy for axillary staging in breast cancer: results from a large prospective German multi-institutional trial.* Eur J Surg Oncol, 2004. **30**(3): p. 252-9.
53. Mansel, R.E., et al., *Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial.* J Natl Cancer Inst, 2006. **98**(9): p. 599-609.
54. Veronesi, U., et al., *Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series.* J Natl Cancer Inst, 1999. **91**(4): p. 368-73.
55. Zavagno, G., et al., *A Randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial.* Ann Surg, 2008. **247**(2): p. 207-13.
56. Krag, D.N., et al., *Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial.* Lancet Oncol, 2010. **11**(10): p. 927-33.
57. Del Bianco, P., et al., *Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the sentinella-GIVOM Italian randomised clinical trial.* Eur J Surg Oncol, 2008. **34**(5): p. 508-13.

58. Galimberti, V., et al., *Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial.* Lancet Oncol, 2018. **19**(10): p. 1385-1393.
59. Sola, M., et al., *Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multicenter clinical trial AATRM 048/13/2000.* Ann Surg Oncol, 2013. **20**(1): p. 120-7.
60. Swarnkar, P.K., et al., *The Evolving Role of Marked Lymph Node Biopsy (MLNB) and Targeted Axillary Dissection (TAD) after Neoadjuvant Chemotherapy (NACT) for Node-Positive Breast Cancer: Systematic Review and Pooled Analysis.* Cancers (Basel), 2021. **13**(7).
61. Krop, I., et al., *Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update.* J Clin Oncol, 2017. **35**(24): p. 2838-2847.
62. Yi, M., et al., *Which threshold for ER positivity? a retrospective study based on 9639 patients.* Ann Oncol, 2014. **25**(5): p. 1004-11.
63. Moja, L., et al., *Trastuzumab containing regimens for early breast cancer.* Cochrane Database Syst Rev, 2012(4): p. CD006243.
64. Geyer, C.E., Jr., et al., *Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer.* Ann Oncol, 2022. **33**(12): p. 1250-1268.
65. Early Breast Cancer Trialists' Collaborative, G., et al., *Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials.* Lancet, 2012. **379**(9814): p. 432-44.
66. Cortazar, P., et al., *Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis.* Lancet, 2014. **384**(9938): p. 164-72.
67. Ogston, K.N., et al., *A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival.* Breast, 2003. **12**(5): p. 320-7.
68. Symmans, W.F., et al., *Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy.* J Clin Oncol, 2007. **25**(28): p. 4414-22.
69. Yau, C., et al., *Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients.* Lancet Oncol, 2022. **23**(1): p. 149-160.
70. Ofri, A. and K. Moore, *Occult breast cancer: Where are we at?* Breast, 2020. **54**: p. 211-215.
71. Javed, A. and A. Lteif, *Development of the human breast.* Semin Plast Surg, 2013. **27**(1): p. 5-12.
72. Macias, H. and L. Hinck, *Mammary gland development.* Wiley Interdiscip Rev Dev Biol, 2012. **1**(4): p. 533-57.
73. Watson, C.J., *Involution: apoptosis and tissue remodelling that convert the mammary gland from milk factory to a quiescent organ.* Breast Cancer Res, 2006. **8**(2): p. 203.
74. Cancerfonden. Available from: https://www.cancerfonden.se/om-cancer/statistik/cancersjukdomar-som-drabbar-flest.
75. McCormack, V.A. and I. dos Santos Silva, *Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis.* Cancer Epidemiol Biomarkers Prev, 2006. **15**(6): p. 1159-69.

76. Boyd, N.F., et al., *Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study.* J Natl Cancer Inst, 1995. **87**(9): p. 670-5.
77. Azam, S., et al., *Determinants of Mammographic Density Change.* JNCI Cancer Spectr, 2019. **3**(1): p. pkz004.
78. Brand, J.S., et al., *Common genetic variation and novel loci associated with volumetric mammographic density.* Breast Cancer Res, 2018. **20**(1): p. 30.
79. American College of Radiology. Available from: https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Bi-Rads.
80. Wolfe, J.N. and R.C. Wilkie, *Breast pattern classification and observer error.* Radiology, 1978. **127**(2): p. 343-4.
81. Gram, I.T., E. Funkhouser, and L. Tabar, *The Tabar classification of mammographic parenchymal patterns.* Eur J Radiol, 1997. **24**(2): p. 131-6.
82. Eriksson, M., et al., *A comprehensive tool for measuring mammographic density changes over time.* Breast Cancer Res Treat, 2018.
83. Lee, H.N., Y.M. Sohn, and K.H. Han, *Comparison of mammographic density estimation by Volpara software with radiologists' visual assessment: analysis of clinical-radiologic factors affecting discrepancy between them.* Acta Radiol, 2015. **56**(9): p. 1061-8.
84. van der Waal, D., et al., *Comparing Visually Assessed BI-RADS Breast Density and Automated Volumetric Breast Density Software: A Cross-Sectional Study in a Breast Cancer Screening Setting.* PLoS One, 2015. **10**(9): p. e0136667.
85. McPherson, K., C.M. Steel, and J.M. Dixon, *ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics.* BMJ, 2000. **321**(7261): p. 624-8.
86. Singletary, S.E., *Rating the risk factors for breast cancer.* Ann Surg, 2003. **237**(4): p. 474-82.
87. Pharoah, P.D., et al., *Family history and the risk of breast cancer: a systematic review and meta-analysis.* Int J Cancer, 1997. **71**(5): p. 800-9.
88. Wendt, C. and S. Margolin, *Identifying breast cancer susceptibility genes - a review of the genetic background in familial breast cancer.* Acta Oncol, 2019. **58**(2): p. 135-146.
89. Chen, S. and G. Parmigiani, *Meta-analysis of BRCA1 and BRCA2 penetrance.* J Clin Oncol, 2007. **25**(11): p. 1329-33.
90. Ferreira, M.A., et al., *Genome-wide association and transcriptome studies identify target genes and risk loci for breast cancer.* Nat Commun, 2019. **10**(1): p. 1741.
91. Evans, D.G.R., et al., *Breast cancer pathology and stage are better predicted by risk stratification models that include mammographic density and common genetic variants.* Breast Cancer Res Treat, 2019. **176**(1): p. 141-148.
92. Kohler, B.A., et al., *Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State.* J Natl Cancer Inst, 2015. **107**(6): p. djv048.
93. Collaborative Group on Hormonal Factors in Breast, C., *Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease.* Lancet, 2002. **360**(9328): p. 187-95.
94. Ewertz, M., et al., *Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries.* Int J Cancer, 1990. **46**(4): p. 597-603.
95. Key, T.J., *Endogenous oestrogens and breast cancer risk in premenopausal and postmenopausal women.* Steroids, 2011. **76**(8): p. 812-5.
96. Cleary, M.P. and M.E. Grossmann, *Minireview: Obesity and breast cancer: the estrogen connection.* Endocrinology, 2009. **150**(6): p. 2537-42.

97. Narod, S.A., *Hormone replacement therapy and the risk of breast cancer.* Nat Rev Clin Oncol, 2011. **8**(11): p. 669-76.
98. Clavel-Chapelon, F. and C. Hill, *[Hormone replacement therapy in menopause and risk of breast cancer]*. Presse Med, 2000. **29**(31): p. 1688-93.
99. Jiang, Y., Q. Xie, and R. Chen, *Breast Cancer Incidence and Mortality in Relation to Hormone Replacement Therapy Use Among Postmenopausal Women: Results From a Prospective Cohort Study.* Clin Breast Cancer, 2022. **22**(2): p. e206-e213.
100. Hodis, H.N. and W.J. Mack, *Menopausal Hormone Replacement Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease: It Is About Time and Timing.* Cancer J, 2022. **28**(3): p. 208-223.
101. van den Brandt, P.A., et al., *Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk.* Am J Epidemiol, 2000. **152**(6): p. 514-27.
102. Continuous Update Project Report: Diet, N., Physical Activity and Breast Cancer: World Cancer Research Fund International/American Institute for Cancer Research. Available from: https://www.wcrf.org/dietandcancer/breast-cancer/.
103. Catsburg, C., A.B. Miller, and T.E. Rohan, *Active cigarette smoking and risk of breast cancer.* Int J Cancer, 2015. **136**(9): p. 2204-9.
104. Giess, C.S., et al., *Background parenchymal enhancement at breast MR imaging: normal patterns, diagnostic challenges, and potential for false-positive and false-negative interpretation.* Radiographics, 2014. **34**(1): p. 234-47.
105. Price, E.R., et al., *The impact of bilateral salpingo-oophorectomy on breast MRI background parenchymal enhancement and fibroglandular tissue.* Eur Radiol, 2014. **24**(1): p. 162-8.
106. Kang, S.S., et al., *Background parenchymal enhancement on breast MRI: influence of menstrual cycle and breast composition.* J Magn Reson Imaging, 2014. **39**(3): p. 526-34.
107. Kajihara, M., et al., *Effect of the menstrual cycle on background parenchymal enhancement in breast MR imaging.* Magn Reson Med Sci, 2013. **12**(1): p. 39-45.
108. Amarosa, A.R., et al., *Evaluation of the kinetic properties of background parenchymal enhancement throughout the phases of the menstrual cycle.* Radiology, 2013. **268**(2): p. 356-65.
109. King, V., et al., *Impact of tamoxifen on amount of fibroglandular tissue, background parenchymal enhancement, and cysts on breast magnetic resonance imaging.* Breast J, 2012. **18**(6): p. 527-34.
110. King, V., et al., *Impact of menopausal status on background parenchymal enhancement and fibroglandular tissue on breast MRI.* Eur Radiol, 2012. **22**(12): p. 2641-7.
111. King, V., et al., *Effect of aromatase inhibitors on background parenchymal enhancement and amount of fibroglandular tissue at breast MR imaging.* Radiology, 2012. **264**(3): p. 670-8.
112. Thompson, C.M., et al., *The Association of Background Parenchymal Enhancement at Breast MRI with Breast Cancer: A Systematic Review and Meta-Analysis.* Radiology, 2019: p. 182441.
113. Vårdprogram. 2020; Available from: https://kunskapsbanken.cancercentrum.se/globalassets/cancerdiagnoser/brost/vardprogram/nationellt-vardprogram-brostcancer.pdf.
114. Glynn, R.J., et al., *Comparison of Questionnaire-Based Breast Cancer Prediction Models in the Nurses' Health Study.* Cancer Epidemiol Biomarkers Prev, 2019. **28**(7): p. 1187-1194.
115. Yang, X., et al., *Prospective validation of the BOADICEA multifactorial breast cancer risk prediction model in a large prospective cohort study.* J Med Genet, 2022. **59**(12): p. 1196-1205.

116. Eerola, H., et al., *Familial breast cancer in southern Finland: how prevalent are breast cancer families and can we trust the family history reported by patients?* Eur J Cancer, 2000. **36**(9): p. 1143-8.
117. Hartmann, L.C., et al., *Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer.* N Engl J Med, 1999. **340**(2): p. 77-84.
118. Hartmann, L.C., et al., *Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers.* J Natl Cancer Inst, 2001. **93**(21): p. 1633-7.
119. De Felice, F., et al., *Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis.* Ann Surg Oncol, 2015. **22**(9): p. 2876-80.
120. Nelson, H.D., et al., *Medication Use for the Risk Reduction of Primary Breast Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force.* JAMA, 2019. **322**(9): p. 868-886.
121. Mocellin, S., A. Goodwin, and S. Pasquali, *Risk-reducing medications for primary breast cancer: a network meta-analysis.* Cochrane Database Syst Rev, 2019. **4**(4): p. CD012191.
122. Cuzick, J., et al., *Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial.* Lancet Oncol, 2015. **16**(1): p. 67-75.
123. Land, S.R., et al., *Symptoms and QOL as Predictors of Chemoprevention Adherence in NRG Oncology/NSABP Trial P-1.* J Natl Cancer Inst, 2016. **108**(4).
124. Eriksson, M., et al., *Low-Dose Tamoxifen for Mammographic Density Reduction: A Randomized Controlled Trial.* J Clin Oncol, 2021. **39**(17): p. 1899-1908.
125. Picard, J.D., *[History of mammography]*. Bull Acad Natl Med, 1998. **182**(8): p. 1613-20.
126. Wilson, J.M. and Y.G. Jungner, *[Principles and practice of mass screening for disease]*. Bol Oficina Sanit Panam, 1968. **65**(4): p. 281-393.
127. Shapiro, S., P. Strax, and L. Venet, *Evaluation of periodic breast cancer screening with mammography. Methodology and early observations.* JAMA, 1966. **195**(9): p. 731-8.
128. Bjurstam, N.G., L.M. Bjorneld, and S.W. Duffy, *Updated results of the Gothenburg Trial of Mammographic Screening.* Cancer, 2016. **122**(12): p. 1832-5.
129. Moss, S.M., et al., *Effect of mammographic screening from age 40 years on breast cancer mortality in the UK Age trial at 17 years' follow-up: a randomised controlled trial.* Lancet Oncol, 2015. **16**(9): p. 1123-1132.
130. Tabar, L., et al., *Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades.* Radiology, 2011. **260**(3): p. 658-63.
131. Moss, S.M., et al., *Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial.* Lancet, 2006. **368**(9552): p. 2053-60.
132. Bjurstam, N., et al., *The Gothenburg Breast Screening Trial.* Cancer, 2003. **97**(10): p. 2387-96.
133. Frisell, J., et al., *Followup after 11 years--update of mortality results in the Stockholm mammographic screening trial.* Breast Cancer Res Treat, 1997. **45**(3): p. 263-70.
134. Tabar, L., et al., *Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial.* Cancer, 1995. **75**(10): p. 2507-17.
135. Andersson, I., et al., *Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial.* BMJ, 1988. **297**(6654): p. 943-8.
136. Shapiro, S., et al., *Ten- to fourteen-year effect of screening on breast cancer mortality.* J Natl Cancer Inst, 1982. **69**(2): p. 349-55.

137. Harris, R., et al., *Reconsidering the criteria for evaluating proposed screening programs: reflections from 4 current and former members of the U.S. Preventive services task force.* Epidemiol Rev, 2011. **33**: p. 20-35.
138. Gotzsche, P.C. and K.J. Jorgensen, *Screening for breast cancer with mammography.* Cochrane Database Syst Rev, 2013(6): p. CD001877.
139. Nelson, H.D., et al., *Effectiveness of Breast Cancer Screening: Systematic Review and Meta-analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation.* Ann Intern Med, 2016. **164**(4): p. 244-55.
140. Njor, S.H., et al., *Decline in breast cancer mortality: how much is attributable to screening?* J Med Screen, 2015. **22**(1): p. 20-7.
141. Broeders, M., et al., *The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies.* J Med Screen, 2012. **19 Suppl 1**: p. 14-25.
142. Li, T., et al., *A systematic review of the impact of the COVID-19 pandemic on breast cancer screening and diagnosis.* Breast, 2023. **67**: p. 78-88.
143. Elewonibi, B.R., A.D. Thierry, and P.Y. Miranda, *Examining Mammography Use by Breast Cancer Risk, Race, Nativity, and Socioeconomic Status.* J Immigr Minor Health, 2018. **20**(1): p. 59-65.
144. Renna Junior, N.L., et al., *Ethnic, racial and socioeconomic disparities in breast cancer survival in two Brazilian capitals between 1996 and 2012.* Cancer Epidemiol, 2021. **75**: p. 102048.
145. Stuart, G.W., J.A. Chamberlain, and R.L. Milne, *Socio-economic and ethnocultural influences on geographical disparities in breast cancer screening participation in Victoria, Australia.* Front Oncol, 2022. **12**: p. 980879.
146. Teran, L., et al., *On-time mammography screening with a focus on Latinas with low income: a proposed cultural model.* Anticancer Res, 2007. **27**(6C): p. 4325-38.
147. Akinyemiju, T., et al., *Life-course socioeconomic status and breast and cervical cancer screening: analysis of the WHO's Study on Global Ageing and Adult Health (SAGE).* BMJ Open, 2016. **6**(11): p. e012753.
148. Bozhar, H., et al., *Socio-economic inequality of utilization of cancer testing in Europe: A cross-sectional study.* Prev Med Rep, 2022. **26**: p. 101733.
149. Belkic, K., et al., *Imaging surveillance programs for women at high breast cancer risk in Europe: Are women from ethnic minority groups adequately included? (Review).* Int J Oncol, 2015. **47**(3): p. 817-39.
150. Feig, S., *Cost-effectiveness of mammography, MRI, and ultrasonography for breast cancer screening.* Radiol Clin North Am, 2010. **48**(5): p. 879-91.
151. Eriksson, L., et al., *Mammographic density and survival in interval breast cancers.* Breast Cancer Res, 2013. **15**(3): p. R48.
152. Eriksson, M., et al., *A clinical model for identifying the short-term risk of breast cancer.* Breast Cancer Res, 2017. **19**(1): p. 29.
153. Mandelson, M.T., et al., *Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers.* J Natl Cancer Inst, 2000. **92**(13): p. 1081-7.
154. Tornberg, S., et al., *A pooled analysis of interval cancer rates in six European countries.* Eur J Cancer Prev, 2010. **19**(2): p. 87-93.
155. Bakker, M.F., et al., *Supplemental MRI Screening for Women with Extremely Dense Breast Tissue.* N Engl J Med, 2019. **381**(22): p. 2091-2102.
156. Allweis, T.M., et al., *Personalized Screening for Breast Cancer: Rationale, Present Practices, and Future Directions.* Ann Surg Oncol, 2021. **28**(8): p. 4306-4317.
157. *Breast Screening – Risk Adaptive Imaging for Density*. Available from: https://radiology.medschl.cam.ac.uk/research/research-themes/breast-imaging/braid-trial/.

158. Dembrower, K., et al., *Comparison of a Deep Learning Risk Score and Standard Mammographic Density Score for Breast Cancer Risk Prediction.* Radiology, 2020. **294**(2): p. 265-272.
159. Eriksson, M., et al., *Identification of Women at High Risk of Breast Cancer Who Need Supplemental Screening.* Radiology, 2020. **297**(2): p. 327-333.
160. Hickman, S.E., G.C. Baxter, and F.J. Gilbert, *Adoption of artificial intelligence in breast imaging: evaluation, ethical constraints and limitations.* Br J Cancer, 2021. **125**(1): p. 15-22.
161. Salim, M., et al., *External Evaluation of 3 Commercial Artificial Intelligence Algorithms for Independent Assessment of Screening Mammograms.* JAMA Oncol, 2020. **6**(10): p. 1581-1588.
162. Eusebi, P., *Diagnostic accuracy measures.* Cerebrovasc Dis, 2013. **36**(4): p. 267-72.
163. Bossuyt, P.M., et al., *STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies.* Radiology, 2015. **277**(3): p. 826-32.
164. Alabousi, M., et al., *Digital breast tomosynthesis for breast cancer detection: a diagnostic test accuracy systematic review and meta-analysis.* Eur Radiol, 2020.
165. Kolb, T.M., J. Lichy, and J.H. Newhouse, *Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations.* Radiology, 2002. **225**(1): p. 165-75.
166. Hwang, J.Y., et al., *Screening Ultrasound in Women with Negative Mammography: Outcome Analysis.* Yonsei Med J, 2015. **56**(5): p. 1352-8.
167. Corsetti, V., et al., *Breast screening with ultrasound in women with mammography-negative dense breasts: evidence on incremental cancer detection and false positives, and associated cost.* Eur J Cancer, 2008. **44**(4): p. 539-44.
168. Berg, W.A., et al., *Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer.* JAMA, 2008. **299**(18): p. 2151-63.
169. Nothacker, M., et al., *Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue. A systematic review.* BMC Cancer, 2009. **9**: p. 335.
170. Choi, E.J., et al., *Evaluation of an automated breast volume scanner according to the fifth edition of BI-RADS for breast ultrasound compared with hand-held ultrasound.* Eur J Radiol, 2018. **99**: p. 138-145.
171. Girometti, R., et al., *Automated breast volume scanner (ABVS) in assessing breast cancer size: A comparison with conventional ultrasound and magnetic resonance imaging.* Eur Radiol, 2018. **28**(3): p. 1000-1008.
172. Hellgren, R., et al., *Comparison of handheld ultrasound and automated breast ultrasound in women recalled after mammography screening.* Acta Radiol, 2017. **58**(5): p. 515-520.
173. Jeh, S.K., et al., *Comparison of automated breast ultrasonography to handheld ultrasonography in detecting and diagnosing breast lesions.* Acta Radiol, 2016. **57**(2): p. 162-9.
174. Schmachtenberg, C., et al., *Diagnostic Performance of Automated Breast Volume Scanning (ABVS) Compared to Handheld Ultrasonography With Breast MRI as the Gold Standard.* Acad Radiol, 2017. **24**(8): p. 954-961.
175. Xiao, Y.M., et al., *The efficacy of automated breast volume scanning over conventional ultrasonography among patients with breast lesions.* Int J Gynaecol Obstet, 2015. **131**(3): p. 293-6.
176. Zhang, L., et al., *Diagnostic Performance Using Automated Breast Ultrasound System for Breast Cancer in Chinese Women Aged 40 Years or Older: A Comparative Study.* Ultrasound Med Biol, 2019. **45**(12): p. 3137-3144.

177. Zhang, X., et al., *Diagnostic value of an automated breast volume scanner compared with a hand-held ultrasound: a meta-analysis.* Gland Surg, 2019. **8**(6): p. 698-711.
178. Brem, R.F., et al., *Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SomoInsight Study.* Radiology, 2015. **274**(3): p. 663-73.
179. Wilczek, B., et al., *Adding 3D automated breast ultrasound to mammography screening in women with heterogeneously and extremely dense breasts: Report from a hospital-based, high-volume, single-center breast cancer screening program.* Eur J Radiol, 2016. **85**(9): p. 1554-63.
180. van Zelst, J.C., et al., *Validation of radiologists' findings by computer-aided detection (CAD) software in breast cancer detection with automated 3D breast ultrasound: a concept study in implementation of artificial intelligence software.* Acta Radiol, 2019: p. 284185119858051.
181. Knopp, M.V., et al., *Pathophysiologic basis of contrast enhancement in breast tumors.* J Magn Reson Imaging, 1999. **10**(3): p. 260-6.
182. Mann, R.M., et al., *Breast MRI: guidelines from the European Society of Breast Imaging.* Eur Radiol, 2008. **18**(7): p. 1307-18.
183. Chiarelli, A.M., et al., *Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the ontario high risk breast screening program.* J Clin Oncol, 2014. **32**(21): p. 2224-30.
184. Kuhl, C., et al., *Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial.* J Clin Oncol, 2010. **28**(9): p. 1450-7.
185. Kuhl, C.K., et al., *Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer.* J Clin Oncol, 2005. **23**(33): p. 8469-76.
186. Riedl, C.C., et al., *Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density.* J Clin Oncol, 2015. **33**(10): p. 1128-35.
187. Sardanelli, F., et al., *Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk italian 1 study): final results.* Invest Radiol, 2011. **46**(2): p. 94-105.
188. Sung, J.S., et al., *Breast Cancers Detected at Screening MR Imaging and Mammography in Patients at High Risk: Method of Detection Reflects Tumor Histopathologic Results.* Radiology, 2016. **280**(3): p. 716-22.
189. Vreemann, S., et al., *Influence of Risk Category and Screening Round on the Performance of an MR Imaging and Mammography Screening Program in Carriers of the BRCA Mutation and Other Women at Increased Risk.* Radiology, 2018. **286**(2): p. 443-451.
190. Leach, M.O., et al., *Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS).* Lancet, 2005. **365**(9473): p. 1769-78.
191. Sardanelli, F., et al., *Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results.* Radiology, 2007. **242**(3): p. 698-715.
192. Warner, E., et al., *Prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging.* J Clin Oncol, 2011. **29**(13): p. 1664-9.

193. Warner, E., et al., *Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination.* JAMA, 2004. **292**(11): p. 1317-25.
194. Warner, E., et al., *Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer.* Ann Intern Med, 2008. **148**(9): p. 671-9.
195. Kuhl, C.K., et al., *Supplemental Breast MR Imaging Screening of Women with Average Risk of Breast Cancer.* Radiology, 2017: p. 161444.
196. Veenhuizen, S.G.A., et al., *Supplemental Breast MRI for Women with Extremely Dense Breasts: Results of the Second Screening Round of the DENSE Trial.* Radiology, 2021. **299**(2): p. 278-286.
197. Tedeschi, E., et al., *Gadolinium retention in the body: what we know and what we can do.* Radiol Med, 2017. **122**(8): p. 589-600.
198. Geuzinge, H.A., et al., *Cost-Effectiveness of Magnetic Resonance Imaging Screening for Women With Extremely Dense Breast Tissue.* J Natl Cancer Inst, 2021. **113**(11): p. 1476-1483.
199. Warren, R.M., et al., *Reading protocol for dynamic contrast-enhanced MR images of the breast: sensitivity and specificity analysis.* Radiology, 2005. **236**(3): p. 779-88.
200. Kuhl, C.K., et al., *Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection-a novel approach to breast cancer screening with MRI.* J Clin Oncol, 2014. **32**(22): p. 2304-10.
201. Leithner, D., et al., *Abbreviated MRI of the Breast: Does It Provide Value?* J Magn Reson Imaging, 2019. **49**(7): p. e85-e100.
202. Dogan, B.E., et al., *American College of Radiology-Compliant Short Protocol Breast MRI for High-Risk Breast Cancer Screening: A Prospective Feasibility Study.* AJR Am J Roentgenol, 2018. **210**(1): p. 214-221.
203. Grimm, L.J., et al., *Abbreviated screening protocol for breast MRI: a feasibility study.* Acad Radiol, 2015. **22**(9): p. 1157-62.
204. Harvey, S.C., et al., *An Abbreviated Protocol for High-Risk Screening Breast MRI Saves Time and Resources.* J Am Coll Radiol, 2016. **13**(11S): p. R74-R80.
205. Panigrahi, B., et al., *An Abbreviated Protocol for High-risk Screening Breast Magnetic Resonance Imaging: Impact on Performance Metrics and BI-RADS Assessment.* Acad Radiol, 2017. **24**(9): p. 1132-1138.
206. Heacock, L., et al., *Evaluation of a known breast cancer using an abbreviated breast MRI protocol: Correlation of imaging characteristics and pathology with lesion detection and conspicuity.* Eur J Radiol, 2016. **85**(4): p. 815-23.
207. Mango, V.L., et al., *Abbreviated protocol for breast MRI: are multiple sequences needed for cancer detection?* Eur J Radiol, 2015. **84**(1): p. 65-70.
208. Choi, B.H., et al., *Usefulness of abbreviated breast MRI screening for women with a history of breast cancer surgery.* Breast Cancer Res Treat, 2018. **167**(2): p. 495-502.
209. Jain, M., et al., *FAST MRI breast screening revisited.* J Med Imaging Radiat Oncol, 2017. **61**(1): p. 24-28.
210. Moschetta, M., et al., *Abbreviated Combined MR Protocol: A New Faster Strategy for Characterizing Breast Lesions.* Clin Breast Cancer, 2016. **16**(3): p. 207-11.
211. Oldrini, G., et al., *Abbreviated breast magnetic resonance protocol: Value of high-resolution temporal dynamic sequence to improve lesion characterization.* Eur J Radiol, 2017. **95**: p. 177-185.
212. Romeo, V., et al., *Preliminary Results of a Simplified Breast MRI Protocol to Characterize Breast Lesions: Comparison with a Full Diagnostic Protocol and a Review of the Current Literature.* Acad Radiol, 2017. **24**(11): p. 1387-1394.

213. Strahle, D.A., et al., *Systematic development of an abbreviated protocol for screening breast magnetic resonance imaging.* Breast Cancer Res Treat, 2017. **162**(2): p. 283-295.
214. Machida, Y., et al., *Feasibility and potential limitations of abbreviated breast MRI: an observer study using an enriched cohort.* Breast Cancer, 2017. **24**(3): p. 411-419.
215. Oldrini, G., et al., *Impact of an abbreviated protocol for breast MRI in diagnostic accuracy.* Diagn Interv Radiol, 2018. **24**(1): p. 12-16.
216. Park, K.W., et al., *MRI surveillance for women with a personal history of breast cancer: comparison between abbreviated and full diagnostic protocol.* Br J Radiol, 2020. **93**(1106): p. 20190733.
217. Petrillo, A., et al., *Abbreviated breast dynamic contrast-enhanced MR imaging for lesion detection and characterization: the experience of an Italian oncologic center.* Breast Cancer Res Treat, 2017. **164**(2): p. 401-410.
218. Chen, S.Q., et al., *Application of Abbreviated Protocol of Magnetic Resonance Imaging for Breast Cancer Screening in Dense Breast Tissue.* Acad Radiol, 2016.
219. Chen, S.Q., et al., *Abbreviated MRI Protocols for Detecting Breast Cancer in Women with Dense Breasts.* Korean J Radiol, 2017. **18**(3): p. 470-475.
220. Weinstein, S.P., et al., *Abbreviated Breast Magnetic Resonance Imaging for Supplemental Screening of Women With Dense Breasts and Average Risk.* J Clin Oncol, 2020. **38**(33): p. 3874-3882.
221. Baltzer, P.A., M. Dietzel, and W.A. Kaiser, *MR-spectroscopy at 1.5 tesla and 3 tesla. Useful? A systematic review and meta-analysis.* Eur J Radiol, 2012. **81 Suppl 1**: p. S6-9.
222. Bitencourt, A.G.V., et al., *Clinical applications of breast cancer metabolomics using high-resolution magic angle spinning proton magnetic resonance spectroscopy (HRMAS 1H MRS): systematic scoping review.* Metabolomics, 2019. **15**(11): p. 148.
223. Baltzer, P., et al., *Diffusion-weighted imaging of the breast-a consensus and mission statement from the EUSOBI International Breast Diffusion-Weighted Imaging working group.* Eur Radiol, 2020. **30**(3): p. 1436-1450.
224. Baxter, G.C., et al., *A Meta-analysis of the Diagnostic Performance of Diffusion MRI for Breast Lesion Characterization.* Radiology, 2019. **291**(3): p. 632-641.
225. Begley, J.K., et al., *In vivo proton magnetic resonance spectroscopy of breast cancer: a review of the literature.* Breast Cancer Res, 2012. **14**(2): p. 207.
226. Belkic, D. and K. Belkic, *Proof-of-the-Concept Study on Mathematically Optimized Magnetic Resonance Spectroscopy for Breast Cancer Diagnostics.* Technol Cancer Res Treat, 2015. **14**(3): p. 277-97.
227. Cheung, Y.C., et al., *Preoperative assessment of contrast-enhanced spectral mammography of diagnosed breast cancers after sonographic biopsy: Correlation to contrast-enhanced magnetic resonance imaging and 5-year postoperative follow-up.* Medicine (Baltimore), 2020. **99**(5): p. e19024.
228. Clauser, P., et al., *Low-Dose, Contrast-Enhanced Mammography Compared to Contrast-Enhanced Breast MRI: A Feasibility Study.* J Magn Reson Imaging, 2020.
229. Fallenberg, E.M., et al., *Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multi-reader evaluation.* Eur Radiol, 2017. **27**(7): p. 2752-2764.
230. Kim, E.Y., et al., *Diagnostic Value of Contrast-Enhanced Digital Mammography versus Contrast-Enhanced Magnetic Resonance Imaging for the Preoperative Evaluation of Breast Cancer.* J Breast Cancer, 2018. **21**(4): p. 453-462.
231. Sumkin, J.H., et al., *Diagnostic Performance of MRI, Molecular Breast Imaging, and Contrast-enhanced Mammography in Women with Newly Diagnosed Breast Cancer.* Radiology, 2019. **293**(3): p. 531-540.

232. Xing, D., et al., *Diagnostic Value of Contrast-Enhanced Spectral Mammography in Comparison to Magnetic Resonance Imaging in Breast Lesions.* J Comput Assist Tomogr, 2018.
233. Potsch, N., et al., *Contrast-enhanced Mammography versus Contrast-enhanced Breast MRI: A Systematic Review and Meta-Analysis.* Radiology, 2022. **305**(1): p. 94-103.
234. Sung, J.S., et al., *Performance of Dual-Energy Contrast-enhanced Digital Mammography for Screening Women at Increased Risk of Breast Cancer.* Radiology, 2019. **293**(1): p. 81-88.
235. Lahiri, B.B., et al., *Medical applications of infrared thermography: A review.* Infrared Phys Technol, 2012. **55**(4): p. 221-235.
236. Mahfouz, A.E., et al., *Gadolinium-enhanced MR angiography of the breast: is breast cancer associated with ipsilateral higher vascularity?* Eur Radiol, 2001. **11**(6): p. 965-9.
237. Sardanelli, F., et al., *Breast vascular mapping obtained with contrast-enhanced MR imaging: implications for cancer diagnosis, treatment, and risk stratification.* Eur Radiol, 2007. **17 Suppl 6**: p. F48-51.
238. Verardi, N., et al., *Contrast-enhanced MR imaging of the breast: association between asymmetric increased breast vascularity and ipsilateral cancer in a consecutive series of 197 patients.* Radiol Med, 2013. **118**(2): p. 239-50.
239. Deng, Z.S. and J. Liu, *Enhancement of thermal diagnostics on tumors underneath the skin by induced evaporation.* Conf Proc IEEE Eng Med Biol Soc, 2005. **2005**: p. 7525-8.
240. Kontos, M., R. Wilson, and I. Fentiman, *Digital infrared thermal imaging (DITI) of breast lesions: sensitivity and specificity of detection of primary breast cancers.* Clin Radiol, 2011. **66**(6): p. 536-9.
241. Jones, B.F., *A reappraisal of the use of infrared thermal image analysis in medicine.* IEEE Trans Med Imaging, 1998. **17**(6): p. 1019-27.
242. Wishart, G.C., et al., *The accuracy of digital infrared imaging for breast cancer detection in women undergoing breast biopsy.* Eur J Surg Oncol, 2010. **36**(6): p. 535-40.
243. Keyserlingk, J.R., et al., *Infrared Imaging of the Breast: Initial Reappraisal Using High-Resolution Digital Technology in 100 Successive Cases of Stage I and II Breast Cancer.* Breast J, 1998. **4**(4): p. 245-51.
244. Wienbeck, S., et al., *Contrast-enhanced cone-beam breast-CT (CBBCT): clinical performance compared to mammography and MRI.* Eur Radiol, 2018. **28**(9): p. 3731-3741.
245. Shermis, R.B., et al., *Supplemental Breast Cancer Screening With Molecular Breast Imaging for Women With Dense Breast Tissue.* AJR Am J Roentgenol, 2016. **207**(2): p. 450-7.
246. Hathi, D.K., et al., *Evaluation of primary breast cancers using dedicated breast PET and whole-body PET.* Sci Rep, 2020. **10**(1): p. 21930.
247. Kalinyak, J.E., et al., *Breast cancer detection using high-resolution breast PET compared to whole-body PET or PET/CT.* Eur J Nucl Med Mol Imaging, 2014. **41**(2): p. 260-75.
248. Fowler, A.M. and R.M. Strigel, *Clinical advances in PET-MRI for breast cancer.* Lancet Oncol, 2022. **23**(1): p. e32-e43.
249. Romeo, V., T.H. Helbich, and K. Pinker, *Breast PET/MRI Hybrid Imaging and Targeted Tracers.* J Magn Reson Imaging, 2023. **57**(2): p. 370-386.
250. Ruan, D. and L. Sun, *Diagnostic Performance of PET/MRI in Breast Cancer: A Systematic Review and Bayesian Bivariate Meta-analysis.* Clin Breast Cancer, 2022.

251. Gabrielson, M., et al., *Cohort profile: The Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA).* Int J Epidemiol, 2017.
252. Arleo, E.K., et al., *Recall rate of screening ultrasound with automated breast volumetric scanning (ABVS) in women with dense breasts: a first quarter experience.* Clin Imaging, 2014. **38**(4): p. 439-444.
253. Kelly, K.M., et al., *Breast cancer detection using automated whole breast ultrasound and mammography in radiographically dense breasts.* Eur Radiol, 2010. **20**(3): p. 734-42.
254. Nagashima, T., et al., *Ultrasound Demonstration of Mammographically Detected Microcalcifications in Patients with Ductal Carcinoma in situ of the Breast.* Breast Cancer, 2005. **12**(3): p. 216-20.
255. Soo, M.S., J.A. Baker, and E.L. Rosen, *Sonographic detection and sonographically guided biopsy of breast microcalcifications.* AJR Am J Roentgenol, 2003. **180**(4): p. 941-8.
256. Stoblen, F., et al., *High-frequency breast ultrasound for the detection of microcalcifications and associated masses in BI-RADS 4a patients.* Anticancer Res, 2011. **31**(8): p. 2575-81.
257. Skaane, P., et al., *Interpretation of automated breast ultrasound (ABUS) with and without knowledge of mammography: a reader performance study.* Acta Radiol, 2015. **56**(4): p. 404-12.
258. Hansen, N.L., et al., *Does MRI breast "density" (degree of background enhancement) correlate with mammographic breast density?* J Magn Reson Imaging, 2014. **40**(2): p. 483-9.
259. Sung, J.S., et al., *Histopathologic characteristics of background parenchymal enhancement (BPE) on breast MRI.* Breast Cancer Res Treat, 2018. **172**(2): p. 487-496.
260. Muller-Schimpfle, M., et al., *Menstrual cycle and age: influence on parenchymal contrast medium enhancement in MR imaging of the breast.* Radiology, 1997. **203**(1): p. 145-9.
261. Brown, J.C., et al., *The Dose-Response Effects of Aerobic Exercise on Body Composition and Breast Tissue among Women at High Risk for Breast Cancer: A Randomized Trial.* Cancer Prev Res (Phila), 2016. **9**(7): p. 581-8.
262. Gillman, J., et al., *The relationship of obesity, mammographic breast density, and magnetic resonance imaging in patients with breast cancer.* Clin Imaging, 2016. **40**(6): p. 1167-1172.
263. Kuhl, C.K., et al., *Healthy premenopausal breast parenchyma in dynamic contrast-enhanced MR imaging of the breast: normal contrast medium enhancement and cyclical-phase dependency.* Radiology, 1997. **203**(1): p. 137-44.