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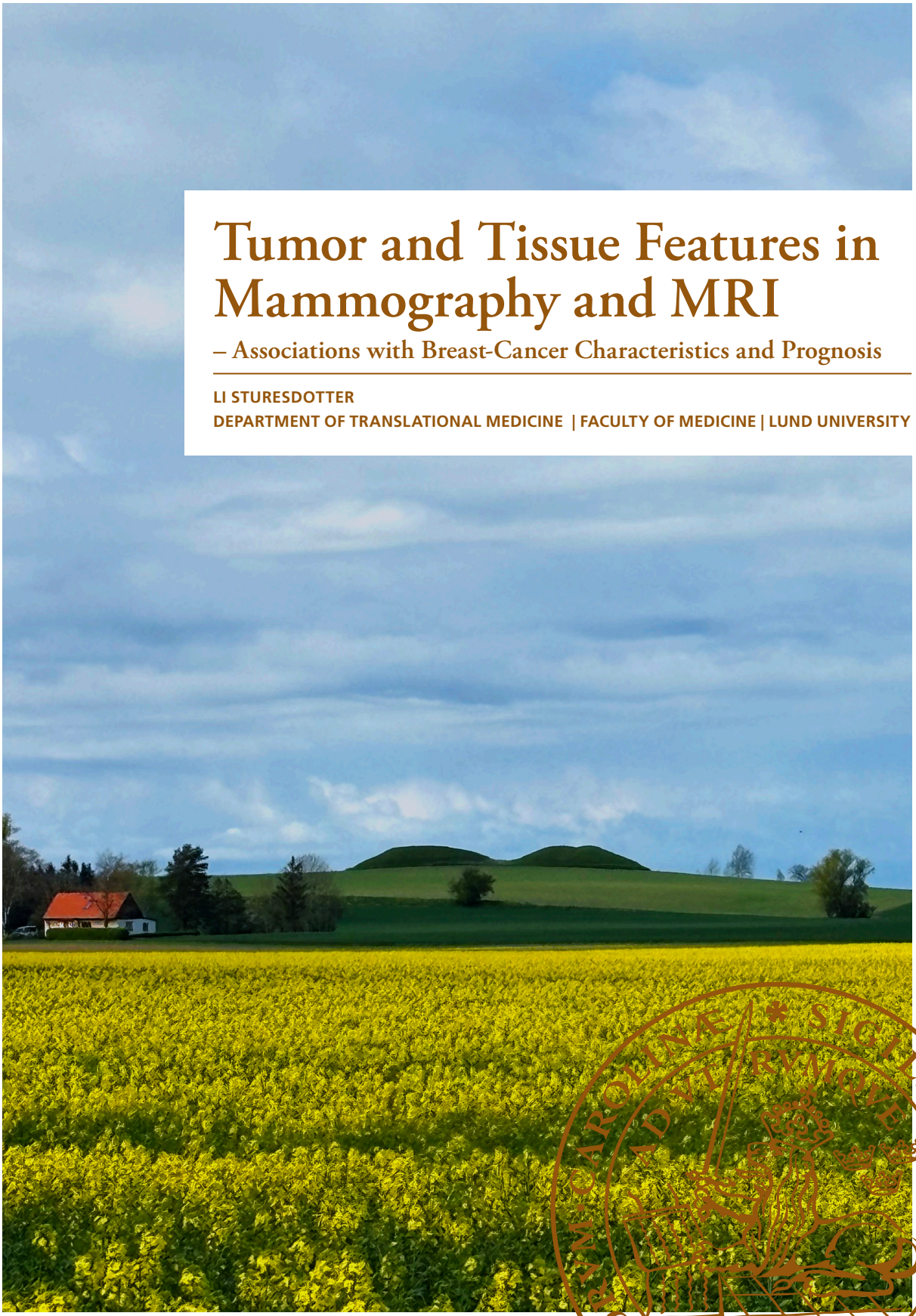

Tumor and Tissue Features in Mammography and MRI

– Associations with Breast-Cancer Characteristics and Prognosis

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LUND UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine, Lund University, to be publicly defended on 27th of March 2026 at 09.00 in Room 2005/2007, Department of Radiology and Physiology, Skåne University Hospital, Inga Marie Nilssons gata 47, 205 02 Malmö

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Abstract:

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Methods Papers I–III were observational studies involving women with invasive breast cancer in the Malmö Diet and Cancer Study cohort. Mammographic tumor appearance, breast density, and the mode of detection were linked to histopathology, surrogate molecular subtypes, and long-term breast-cancer-specific survival using regression models and Cox analyses. Paper IV evaluates a chemical-shift-encoded MRI technique to quantify fatty acid composition in breast adipose tissue. A total of 68 women underwent a dedicated multi-echo MRI sequence, and the results from the MRI examination were compared to breast density, menopausal status, tumor proximity, and gas chromatography.

Results Spiculated mammographic tumor appearance was strongly associated with favorable cancer characteristics, including hormone-receptor positivity, lower grade, lower Ki67 expression, and the luminal A-like subtype. Distinct masses were more often triple-negative breast cancer, whereas tumors with calcifications were more frequently HER2-positive. However, neither mammographic tumor appearance nor breast density was significantly associated with breast-cancer-specific survival. A novel metric quantifying the degree of spiculation, the Spic Mass Ratio, correlated with age and breast density but did not predict axillary-lymph-node involvement or survival. MRI-derived adipose content was lower in dense breasts and in premenopausal women. In women with unilateral cancer, the cancer-affected breast contained less adipose tissue than the contralateral breast. The proportion of saturated fatty acids was highest adjacent to cancer, although this finding was not statistically significant, potentially due to lack of power.

Conclusion Mammographic features at the time of breast cancer diagnosis reflect tumor biology to some extent but cannot independently predict breast-cancer survival. Chemical-shift-encoded MRI accurately depicts adipose tissue and shows potential for characterizing fatty acid composition but warrants further study to determine its potential clinical application.

Key words: Breast imaging, Breast cancer, Mammography, MRI, CSE-MRI, Tumor features, Breast density, Mammary adipose tissue, Fatty acid composition.

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Abstract

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Populärvetenskaplig sammanfattning

Bröstcancer är den vanligaste cancerformen hos kvinnor. I Sverige insjuknar varje år över 8 000 kvinnor. Trots att både behandling och överlevnad har förbättrats dramatiskt under de senaste decennierna innebär en bröstcancerdiagnos ofta mycket oro, frekventa sjukhusbesök och behandling som påverkar livet i stort. Bröstcancer delas in i distinkta subtyper som har olika allvarlighetsgrad. Dessutom är storleken på tumören och om den har spridit sig vidare från bröstet vid upptäckten viktig information vid val av behandling, och för att kunna förutspå hur det kommer gå för den drabbade kvinnan framöver.

Bilddiagnostik är en av hörnstenarna i bröstcancervården, men den involverar också alla asymtomatiska kvinnor som screenas för bröstcancer. Genom screening kan bröstcancer hittas i ett tidigt, ofta botbart stadium. Trots god bildkvalitet missar mammografi ibland tumörer, och det finns också tumörer som ger symptom mellan två screeningtillfällen, så kallad intervallcancer. En annan utmaning med screening är överdiagnostik. Det innebär att en del av tumörerna som hittas i screening aldrig skulle ha hunnit ge symtom eller utvecklas till en farlig sjukdom. Överdiagnostik leder därför till åtgärder som inte hade varit nödvändiga. Vilka tumörer som är kliniskt betydelsefulla, och vilka som inte är det, är därför angeläget att studera.

Syftet med min avhandling har varit att undersöka om information från radiologiska bilder kan ge ytterligare information om tumören, utöver att konstatera dess existens och lokalisation. Kan bilden också säga något om tumörens egenskaper, aggressivitet och prognos? Bröstcancer kan se ganska olika ut på mammografi, och mycket av denna variation verkar spegla tumörens underliggande biologi. Vissa tumörer har välavgränsade konturer och framträder tydligt mot omgivande vävnad. Andra är mer diffusa och svårare att urskilja. En särskilt intressant grupp är tumörer med så kallad ”spikulering” – tumörer med stråk som strålar ut från tumören i den omgivande vävnaden. Brösttäthet är ytterligare en bilddiagnostisk faktor som både påverkar hur lätt en tumör upptäcks och som speglar bröstets sammansättning. Kvinnor med täta bröst löper en ökad risk att utveckla bröstcancer, men om tätheten också påverkar risken att dö i bröstcancer när en tumör väl har uppstått är mindre tydligt. Dessutom ville vi undersöka om en ny typ av magnetkamerateknik kan ge tillförlitlig information om fettsammansättningen i bröstvävnaden, och då särskilt hur den är nära tumörer, då detta skulle kunna vara en ny pusselbit i förståelsen av bröstcancer.

Avhandlingen består av fyra vetenskapliga artiklar:

- Studie 1 fokuserade på sambandet mellan tumörens utseende på mammografi och tumörens biologiska egenskaper, såsom hormonreceptor-status, tumörgrad och molekylär subtyp.
- Studie 2 undersökte om tumörutseende och brösttäthet påverkar överlevnaden i bröstcancer, baserat på lång uppföljningstid i Malmö Kost Cancer-studien.
- Studie 3 undersökte om graden av spikulering i spikulerade tumörer på mammografi är relaterad tumörkaraktäristik och överlevnad i bröstcancer.
- Studie 4 utvärderade en magnetkamerateknik för att kartlägga fettsammansättningen i bröst hos kvinnor med och utan bröstcancer.

Studierna visade att tumörer med spikulering oftare hade mer gynnsamma biologiska egenskaper. Trots detta innebar spikulering inte en förbättrad överlevnad i långtidsuppföljningen. Ingen signifikant skillnad i överlevnad sågs heller beroende på hur utbredda spikuleringarna var. Brösttäthet visade sig inte påverka prognosen när en tumör väl hade upptäckts. Magnetkameratekniken för att bedöma fettsammansättning i bröstet kunde urskilja olika komponenter i fettvävnad och överensstämde någorlunda med referensmetoden (gaskromatografi) för att bestämma fettsammansättning. Fler studier behövs dock för att bekräfta dessa fynd. Sammantaget visar den här avhandlingen att information från mammografibilder och avancerad magnetkamerateknik kan säga mer om bröstcancer än vi hittills utnyttjat kliniskt.

List of papers

Papers included in thesis

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals (I–IV). Papers I–IV are appended at the end of the thesis.

I. Mammographic tumour appearance is related to clinicopathological factors and surrogate molecular breast cancer subtype.

Sturesdotter L, Sandsveden M, Johnson K, Larsson AM, Zackrisson S, Sartor H.

Scientific reports **10**, 20814 (2020).

II. Investigating the prognostic value of mammographic breast density and mammographic tumor appearance in women with invasive breast cancer: The Malmö Diet and cancer study.

Sturesdotter L, Larsson A-M, Zackrisson S, Sartor H.

The Breast **70**, 8-17 (2023).

III. The potential association between degree of mammographic spiculation and prognosis.

Sturesdotter L, Sartor H, Kristensson H, Hagberg O, Lång K.

Insights into Imaging **17**, 29 (2026).

IV. Chemical-shift-encoded MRI for estimating fatty acid composition in breast adipose tissue in women with and without breast cancer.

Sturesdotter L, Sartor H, Ohashi A, Jamtheim Gustafsson C, Peterson P, Månsson S, Zackrisson S.

Manuscript unpublished.

Papers not included in thesis

The following are co-authored, related papers that are not included in this thesis.

1. Mammographic features at primary breast cancer diagnosis in relation to recurrence-free survival.

   Lång K, **Sturesdotter L**, Bengtsson Y, Larsson AM, Sartor H.

   The Breast **75**, 103736 (2024).

2. Mammographic features differ with body composition in women with breast cancer.

   Sartor H, **Sturesdotter L**, Larsson AM, Rosendahl AH, Zackrisson S.

   European radiology (2024).

3. WHO-recommended levels of physical activity in relation to mammographic breast density, mammographic tumor appearance, and mode of detection of breast cancer.

   Boraka Ö, Sartor H, **Sturesdotter L**, Hall P, Borgquist S, Zackrisson S, Rosendahl A.

   Breast Cancer Research **26**, 136 (2024).

Abbreviations

ALNI	Axillary-lymph-node involvement
BI-RADS	Breast Imaging Reporting and Data System
CI	Confidence interval
CSE-MRI	Chemical-shift-encoded magnetic resonance imaging
DCIS	Ductal carcinoma *in situ*
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
LCIS	Lobular carcinoma *in situ*
MDCS	Malmö Diet and Cancer Study
MRI	Magnetic resonance imaging
MUFA	Monounsaturated fatty acids
OR	Odds ratio
PDFF	Proton density fat fraction
PR	Progesterone receptor
PUFA	Polyunsaturated fatty acids
ROI	Region of interest
RRR	Relative risk ratio
SFA	Saturated fatty acids
SMR	Spic Mass Ratio
TNBC	Triple-negative breast cancer
TNM	Tumor Node Metastasis system

Introduction

Breast cancer is a major health concern both in Sweden and globally.[1, 2] Incidence rates are increasing worldwide, and a substantial number of women undergo invasive diagnostic procedures followed by both surgical and medical treatment. The clinical course of breast cancer is highly variable, and depends on multiple factors, including tumor biology, clinical stage at diagnosis, and patient characteristics.[3] Mortality due to breast cancer varies considerably between continents and countries.[4] In Sweden, mortality is showing a decreasing trend, which has been attributed at least in part to early detection through breast-cancer screening, as well as continuous improvements in treatment outcomes over time.

But despite decades of advancements in screening and treatment, breast cancer is still one of the leading causes of cancer-related death among women in Sweden and globally.[1] Screening may also contribute to overdiagnosis and overtreatment of indolent tumors that would never have caused any harm.[5] Therefore, it is desirable to predict tumor behavior accurately at the time of diagnosis. Quantitative imaging biomarkers and radiomics techniques may contribute to improving precision in the prediction of tumor aggressiveness or indolence and could add information to existing tools for disease staging and prognostication.[6]

This thesis consists of four papers exploring different aspects of breast imaging in relation to the characteristics and prognosis of breast cancer. Papers I–III focus on mammographic features, and paper IV investigates a magnetic resonance imaging (MRI) technique for estimating the composition of breast adipose tissue. Breast imaging is closely linked to screening, diagnosis, treatment, morbidity, and mortality in breast cancer, and a short background is provided for these aspects to frame this thesis in a broader clinical context.

Background

Breast cancer – a major health issue

Incidence and mortality

Breast cancer is the most common malignancy among women worldwide.[1] Approximately 2.3 million new cases were diagnosed in 2022, including over 8,000 occurring in Sweden.[1, 7] Incidence rates have been rising steadily and continue to increase both in Sweden (Figure 1) and globally, which has been attributed to demographic changes in the form of both aging and growing populations, higher prevalence of modifiable risk factors, and larger diagnostic capacity.[4] A substantial part of the incidence increase could be due to improved diagnostic methods that increase the detection rates of cancer in screening,[5] but it is possible that the true incidence of both diagnosed and undiagnosed breast cancer is increasing. The incidence of breast cancer is rising among younger women,[8] which could support a true increase in incidence as these women are generally not targeted in screening programs.

Despite advances in detection and treatment, breast cancer is still one of the leading causes of cancer-related death in women and causes an estimated 670,000 deaths annually worldwide.[1] Trends in mortality differ largely between countries. Breast-cancer mortality is rising in many countries with limited access to care, but it has been stable or decreasing in most countries with strong health systems, despite similar incidence rates, which reflects inequities in detection and access to therapy.[4]

In Sweden, the age-adjusted breast-cancer mortality has declined in recent decades (Figure 1). However, the absolute number of women who die from breast cancer has been relatively stable at just under 1,500 deaths per year in the last decade. The survival rate is commonly assessed at 5 and 10 years after diagnosis, and both measures have steadily improved in Sweden over time. As of 2020, 92.8% of women with breast cancer survived at least 5 years after diagnosis, and 87.6% survived 10 years.[9]

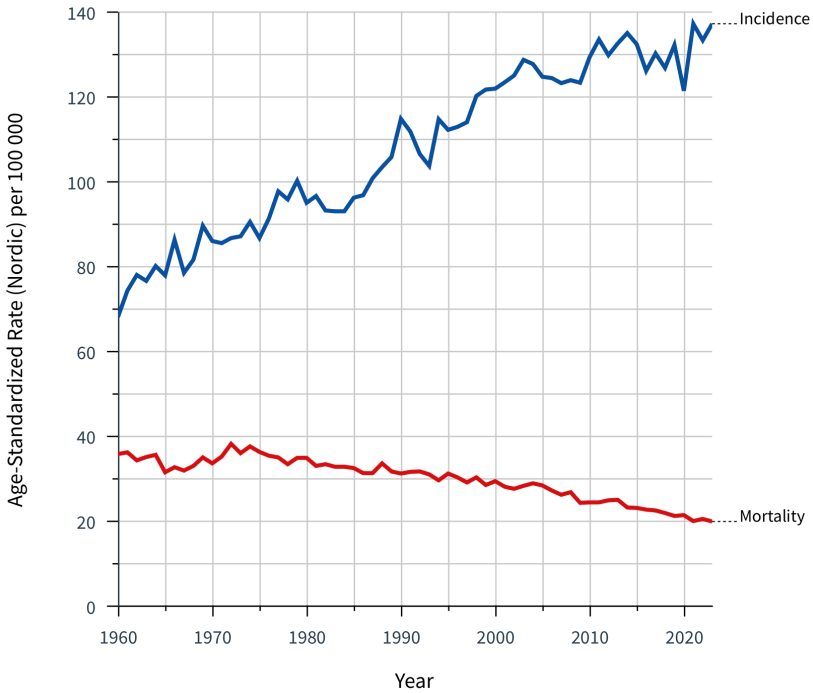

Figure 1. Incidence and mortality of breast cancer in Sweden in 1960–2023 (age standardized)
Number of new breast-cancer cases (blue line) and breast-cancer deaths (red line) per 100 000 persons per year in Sweden. Age-standardized rate according to the nordic population in year 2000.

Available from:

Diagnosis and triple assessment

Breast cancer is diagnosed through screening, symptomatic presentation, or incidentally. In Sweden, women aged 40–74 years are invited to breast-cancer screening with mammography regularly at intervals of 18–24 months.[10] The screening guidelines are stipulated by the Swedish National Board of Health and Welfare.[11] Attendance rate in Sweden is over 80% but varies considerably according to socio-demographic factors.[12] Breast cancers detected through screening generally have a more favorable prognosis than those diagnosed by other means.[13] In Sweden, slightly more than 60% of breast cancers are detected through screening in the invited population.[14]

Symptoms and work-up

Symptoms of breast cancer include a palpable lump, nipple discharge, skin changes such as dimpling (also known as *peu d'orange*) or erythema, localized swelling, and

occasionally pain.[2] The established diagnostic approach for breast complaints is triple assessment, which includes clinical examination, imaging, and tissue sampling.[2] Tissue sampling is performed by fine-needle aspiration, core needle biopsy, or vacuum-assisted biopsy. Fine needle aspiration is used for cytological assessment and can be performed on both the breast and lymph nodes in the axilla.

However, cytology is more limited than biopsy, which offers histopathological confirmation and receptor status evaluation, which is essential for treatment planning.[15] Tissue sampling is most commonly performed under ultrasound guidance, but it can also be done manually by palpation or with mammography- or MRI-guided techniques. In Sweden, breast findings in imaging and pathology are coded on a five-grade scale:[2]

1. Normal finding
2. Benign finding
3. Finding with uncertain malignant potential
4. Finding that raises the suspicion of malignancy
5. Malignant finding

The number grade is preceded by a letter that indicates the diagnostic method used: mammography (M), ultrasound (U), cytology (C), or biopsy (B). Since 2016, suspected breast cancer (code 4 and 5) is investigated according to a nationally standardized protocol in Sweden.[2] Breast lesions with uncertain malignant potential (code B3) are treated according to the presence of atypia, sampling size, lesion size, and patient preferences.[16] In Sweden, the diagnosis and treatment of breast cancer rely on recommendations in the comprehensive National Breast Cancer Care Program published by the Regional Cancer Centers.[2]

Screening – benefits, harms and challenges

The primary goal of mammography screening is to reduce mortality through the early detection and treatment of breast cancer. Major screening trials have shown that screening lowers breast-cancer-specific mortality by approximately 20%.[17, 18] However, reductions in breast-cancer-specific mortality do not account for potential increases in mortality from treatment-related side effects, such as late cardiac events following radiotherapy. Two meta-analyses have not demonstrated a reduction in all-cause mortality associated with mammography screening,[19, 20] possibly due to limited statistical power.

Advancements in mammography technology since the original screening trials have enhanced the ability to detect subtle abnormalities.[21] This has likely improved screening but has possibly also led to increased overdiagnosis – the detection of tumors that would never have caused symptoms during a woman's lifetime.

Conversely, mammography does not detect all cancers present at the time of screening. Some cancers remain undetected (false negatives),[22] and others are diagnosed between scheduled screening rounds among women who attend screening (interval cancers). There are, however, new screening tools that not only increase detection of aggressive cancers but also decrease the number of interval cancers.[23] Assessing the current benefit of screening is also complicated by the fact that breast-cancer treatment has improved since the screening trials. As a result, a benefit would likely be harder to detect if the trials were repeated today. Lastly, costs and the distress among women who are recalled from screening, of whom the majority ultimately do not have cancer,[22] must also be weighed against the benefit from screening.

This thesis investigates imaging features derived from both mammography and MRI. If imaging-based tumor and tissue characteristics can help distinguish clinically significant disease from indolent findings and accurately predict tumor behavior, screening strategies and clinical management could be individualized accordingly.

What is breast cancer?

Anatomy of the breast

The breast consists of glandular structures that include the mammary epithelium, ducts and alveoli, which are derived from the ectoderm, and support structures such as connective-tissue stroma, adipose tissue, vasculature, and smooth muscle from the mesoderm (Figure 2).[24] The glandular structures include ~15–20 lobes in each breast, which produce milk during lactation and are individually connected to the nipple via lactiferous ducts. Every lobe is made up of numerous lobules, also known as terminal duct lobular units.[25]

Both women and men have glandular breast tissue, but it is far more abundant in women.[24] Breast tissue is highly sensitive to circulating sex hormones. Estrogen promotes ductal growth, progesterone stimulates lobuloalveolar development, and prolactin drives milk secretion, while androgens have inhibitory effects. During menstrual cycles, estrogen and progesterone cause cyclical changes in epithelial structures, including ductal proliferation and alveolar budding. Pregnancy induces extensive lobuloalveolar development under the influence of estrogen, progesterone, and prolactin to prepare the breast for lactation.[26] After menopause, declining estrogen levels lead to lobular involution, where glandular tissue is replaced by fat, and the degree and rate of involution differ markedly among women.[27]

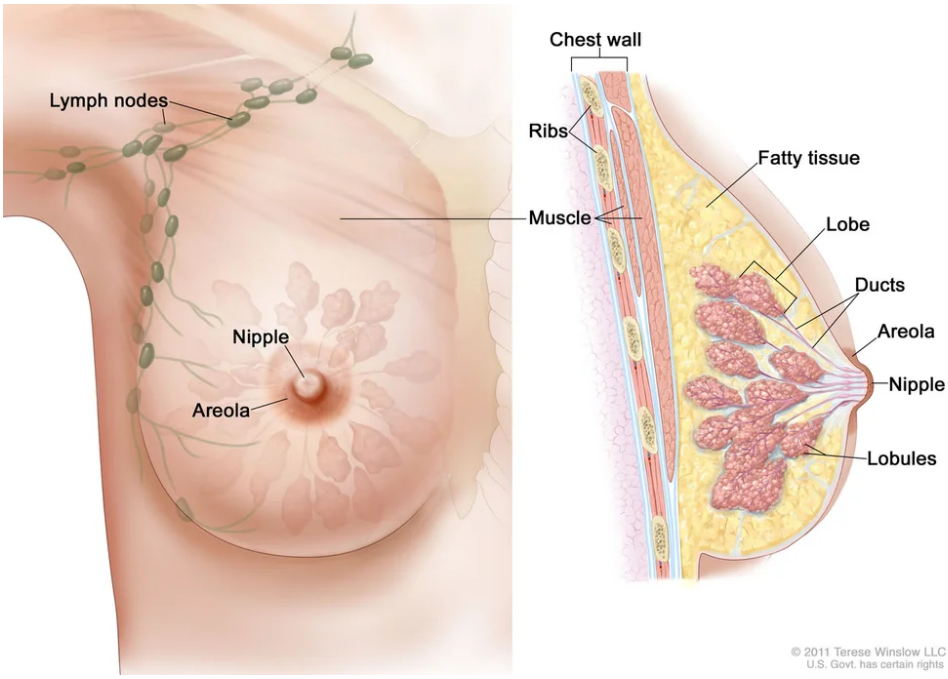

Figure 2. Anatomy of the female breast
Front view and cross-sectional side view of a normal breast of an adult female. Apart from the indicated structures in the figure, the breast also includes vessels, nerves, and lymphatic and connective tissue. Reprinted with permission: © (2011) Terese Winslow LLC, U.S. Govt. has certain rights.

Breast carcinogenesis

Breast cancer originates from epithelial cells in the terminal duct lobular units.[28] Cancer can arise from other cell types in the breast, but only tumors originating from epithelial cells are classified as 'breast cancer'.[2] For example, an angiosarcoma may occur in the breast, but as a tumor of mesenchymal origin, it is regarded as a soft-tissue sarcoma and treated accordingly. Breast cancer is either non-invasive or invasive. Non-invasive breast cancer remains confined within the duct or terminal duct lobular unit and does not penetrate the basement membrane,[2] whereas invasive breast cancer extends beyond the basement membrane into the surrounding breast tissue. Only the invasive form is considered to be capable of metastasizing.[29]

Hallmarks of cancer

A normal cell transitions to a cancer cell in a process called *carcinogenesis*, and the reason for its occurrence is not fully understood. Current evidence suggests that this transformation is driven by a combination of cellular alterations that collectively enable malignant behavior. The influential framework, "Hallmarks of Cancer," by Hanahan and Weinberg from 2000 proposes that cancer cells acquire a set of core

capabilities that are essential for cancer development, and this theory is widely accepted in cancer biology.[30] Initially, six hallmarks were defined, and subsequent updates have included new hallmarks, including tumor-promoting inflammation and deregulation of cellular metabolism,[31-33] which involves abnormal lipid metabolism.[34]

Lipid metabolism and the tumor microenvironment

The microenvironment surrounding breast cancer is frequently characterized by harsh conditions that include hypoxia, low pH, and limited availability of glucose and other nutrients, such as lipids.[35] Lipid metabolism is dysregulated during tumor development[36] and may play a critical role in the initiation and progression of cancer.[37, 38] Locally altered lipid composition has previously been reported in cancers of the breast, [39] colorectum [40], and prostate.[41]

Composition of adipose tissue

Adipose tissue consists mainly of adipocytes, fat-storing cells that contain 90–95% triglycerides.[42, 43] Triglycerides are made of three types of fatty acids that are attached to a glycerol backbone. The fatty acid molecules are built from a hydrocarbon chain (a line of carbon atoms with attached hydrogens) and a carboxyl group at one end. They vary in both saturation (number of double bonds) and chain length.[44] Saturated fatty acids (SFAs) have no double bonds between their carbon atoms, while monounsaturated fatty acids (MUFAs) have one double bond, and polyunsaturated fatty acids (PUFAs) have two or more double bonds. Fatty acids are commonly grouped according to chain length as short, medium, long, and very-long-chain fatty acids.

Fatty acid composition refers to the distribution of SFA, MUFA, and PUFA within the adipose tissue. SFA has been associated with the risk and progression of cancer, supposedly by promoting chronic inflammation and membrane rigidity.[45] For example, increased SFA levels have been reported in epithelial breast-cancer cells that were co-cultivated with mammary adipocytes.[46] The gold standard for assessing fatty acid composition is gas chromatography, which requires tissue samples.[47] MRI has previously shown promise in estimating fatty acid composition in human adipose tissue from the thigh and subcutaneous abdominal fat and has also been explored in the breast.[47-51]

Risk factors for developing breast cancer

Although the exact cause for breast carcinogenesis is unknown, several well-established risk factors have been identified. The strongest risk factors are female sex at birth and increasing age.[2]

Factors associated with hormonal exposure

Many risk factors for breast cancer are linked to lifetime exposure to sex hormones. These include early menarche (before age 12), late menopause (after age 55),[52] few or no full-term pregnancies,[53] older age at first childbirth,[54] limited or no breastfeeding,[53] use of hormone replacement therapy,[55] use of hormonal contraceptives,[56-58] and postmenopausal obesity.[2] A common feature of these risk factors is that they increase cumulative exposure to estrogen, which is considered an important hormonal driver of breast cancer.[59] However, progesterone and biosimilar agents also seem to play a significant role in breast carcinogenesis.[60, 61]

In the case of postmenopausal obesity, the increase in risk is thought to be partly due to elevated estrogen levels driven by conversion of androgens into estrogens in adipose tissue. Obesity also induces chronic low-grade inflammation, which has local and systemic tumor-promoting effects.[62] Parity and breastfeeding are associated with a protective effect,[53] particularly against aggressive forms of breast cancer. This has historically been explained by the absence of menstrual cycles for long periods of time, but new data suggest that both parity and breastfeeding can induce T-cell-mediated protection against breast cancer,[63] which implies that immunological mechanisms might be important for the protective effect.

Previous breast diagnosis

A previous breast-cancer diagnosis is associated with an increased risk of future breast cancer,[64] particularly for contralateral disease.[65] Furthermore, a previous cancer *in situ* increases the likelihood of subsequent invasive breast cancer, and even benign lesions are associated with a slight risk increase, but not at the same magnitude as a previous cancer diagnosis.[66]

Hereditary and familial predisposition

Several identified mutations that are inherited in predisposing genes are known to increase breast-cancer risk substantially. The most well-known are mutations in the *BRCA1* and *BRCA2* genes.[67] Other mutations include those in the *ATM*, *BARD1*, *CDH1*, *CHEK2*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, and *TP53* genes.[2] Women who are carriers of inherited gene mutations are considered to have a *genetic* predisposition for breast cancer, and their disease can be labelled as *hereditary* breast cancer. Such women are invited to participate in a high-risk breast-cancer surveillance program that starts at an earlier age and is more comprehensive than the regular screening program.[2]

There are also families that experience elevated incidence of breast cancer, even though a predisposing gene mutation has not been identified. Women in such families are considered to have *familial* predisposition for breast cancer, and their disease is often labelled *familial* breast cancer. The underlying reason for familial breast cancer can be a common genetic background (such as an inherited single-nucleotide-polymorphism profile or an unidentified gene mutation), shared environment and similar lifestyle choices, or just a chance clustering of sporadic cases.[67]

High breast density

Women with mammographically dense breast parenchyma (a high proportion of fibroglandular tissue in relation to adipose tissue in the breast) are at increased risk of breast cancer.[68] See "Breast density" section for more detailed information.

Behavioral risk factors

Examples of modifiable risk factors are alcohol consumption, which has been reported to have a dose-dependent risk effect, although there is conflicting evidence.[69] Physical inactivity is associated with a slight increase in relative risk. A diet high in red meat has been linked to breast cancer, as well as other types of cancer.[70] Cigarette smoking has been associated with increased risk of breast cancer, but reports are inconsistent.[71-73] Working night shifts and disruption of the circadian rhythm have also been linked to increased breast-cancer risk.[74]

Previous radiation therapy

A very rare but high-impact risk factor for breast cancer is previous radiation therapy to the chest—for example, to treat Hodgkin's lymphoma. The risk is particularly high if radiation therapy was administered during adolescence.[75] With modern mammography, radiation exposure is relatively low, and the risk of radiation-related breast cancer due to screening mammography is regarded as small.[2]

Classification and staging

Breast-cancer classification relies on multiple complementary approaches. The histopathological characteristics of the tumor are assessed using stained tissue sections and supported by immunohistochemical staining.[29] Breast cancers are categorized into distinct molecular subtypes,[76] and the extent of the disease is staged according to the TNM system, which is based on tumor (T) size, lymph node (N) involvement, and presence of metastasis (M).[77]

Histopathology

The lexicon of breast tumors of the World Health Organization (WHO) is widely regarded as the international gold standard for breast-cancer diagnosis.[29] It provides information on histopathological subcategories, standardized terminology, diagnostic criteria, and information regarding prognostic and treatment predictive markers.[29] Ductal carcinoma *in situ* (DCIS) is the only non-invasive form of breast cancer.[29] Classic lobular carcinoma *in situ* (LCIS) is no longer considered as breast cancer but rather a lesion of uncertain malignant potential (B3 lesion) and a marker of increased breast-cancer risk.[29]

The most common histological type of invasive breast cancer is invasive breast carcinoma of no special type, which was formerly known as invasive ductal carcinoma and accounts for approximately 70% of breast cancers.[29] The second most common entity is invasive lobular carcinoma (~20%).[29] The remaining 10% is made up of less frequently encountered histological types, such as tubular, cribriform, mucinous, medullary, metaplastic, micropapillary, and apocrine carcinomas, which encompass varying prognoses.[29] In addition to histology, there are also two rare clinical subtypes: inflammatory breast cancer and Paget's disease of the nipple. Inflammatory breast cancer is characterized by an aggressive clinical course and poor prognosis, while Paget's disease is usually associated with underlying *in-situ* or invasive carcinoma, and its prognosis depends on the underlying lesion.[78, 79]

Molecular subtypes

The four subtypes of breast cancer are luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, and basal-like or triple-negative breast cancer (TNBC), which were discovered by analyzing gene-expression patterns in breast cancers.[76] Surrogate definitions based on immunohistochemical staining instead of gene expression were proposed to enable use of the subtypes in a clinical setting (Table 1).[80]

Table 1. Molecular subtypes of breast cancer

Correspondence between intrinsic and surrogate molecular subtypes and definition of surrogate subtypes according to immunohistochemical staining for estrogen receptor (ER), progesterone receptor (PR), proliferation marker Ki67, and human epidermal growth factor receptor 2 (HER2).[80]

Intrinsic subtype	Surrogate molecular subtype	ER	PR	Ki67	HER2
Luminal A	Luminal A	ER and/or PR +		low	-
Luminal B	Luminal B (HER2 negative)	ER and/or PR +		high	-
	Luminal B (HER2 positive)	ER and/or PR +		any	+
HER2-enriched	HER2 positive (non-luminal)	-	-	any	+
Basal like	Triple negative	-	-	any	-

In addition to the original proposal of surrogate molecular subtypes (Table 1), histological grade[81] is also important in subtype classification, especially when distinguishing the luminal A from the luminal B subtype.[2] Tests based on gene expression define subtypes more accurately than the surrogate classifications,[82] and their use is recommended for patients whose treatment decisions can be impacted.[2]

Luminal A is the most common subtype, accounting for ~50% of breast cancers in Sweden,[14] and it has the best prognosis.[83] Luminal B has a higher grade and a worse prognosis[83] and makes up approximately ~25% of breast cancers.[14] The HER2-enriched subtype counts for ~15% of cases[14] and has seen improved survival since the introduction of HER2-targeted treatments. TNBC is the least common subtype (~10%),[14] it is often aggressive, and it has the worst prognosis.[84]

TNM staging

Anatomical staging of breast cancer is performed according to the internationally adopted TNM classification, which integrates information on tumor size (T), lymph node involvement (N), and the presence of distant metastasis (M).[77] An appropriate TNM code can be assigned by assembling clinical information, including results from imaging and tissue sampling.

The stages range from I to IV, with stage I indicating localized disease, stage II involving regional spread to nearby tissues or lymph nodes, and stage III suggesting more extensive regional involvement. At stage IV, distant metastasis has occurred.[77] In Sweden, almost 90% of breast cancers are diagnosed at stage I or II, while the remaining are diagnosed at stage III or IV.[14]

Prognostic and predictive factors

In oncology, prognostic factors are features related to the patient or tumor that can be used to estimate the probability of recurrence and survival independent of treatment.[85] In contrast, predictive factors indicate whether a patient is likely to benefit from a specific therapy.[85] In practice, many markers are important for both prognostication and treatment planning in breast-cancer management, and the terms frequently overlap.[86]

TNM status is important for prognostication,[9] as is gene-expression profiling.[87, 88] Histological grade is another central prognostic factor that is derived from the combined microscopic assessment of tubule formation, mitotic count, and nuclear pleomorphism.[81] However, TNM status, gene expression, and histological grade also influence which therapeutic regimens are offered. Additional factors that serve in both prognosis and prediction include estrogen receptor (ER), progesterone receptor (PR),[89] HER2,[90] proliferation marker Ki67,[91] and the amount of tumor-infiltrating lymphocytes.[92]

Treatment

Breast-cancer management has changed profoundly over the past century. The focus has shifted from aggressive local control through extensive surgery to therapies tailored to specific tumor characteristics,[3] which reflects the understanding that breast cancer can behave as a systemic disease. Parallel to less invasive surgery,[93] breast-cancer treatment has been revolutionized by chemotherapy, endocrine therapy, and targeted therapies. More recently, immunotherapy has emerged as an additional treatment option for women with TNBC.[94] All breast-cancer cases in Sweden are discussed at multidisciplinary conferences pre- and postoperatively, during which treatment recommendations and follow-up are decided.[2]

> *"I got the results of the test back. I definitely have breast cancer."*
>
> *"Look, don't worry about it. Everything will be fine. They're curing lots of people every day."*
>
> Dialogue from the movie "The Room" (2003), one of the worst films ever made.[95]

Surgery

The goal in breast surgery is to remove cancerous tissue. Techniques range from breast-conserving surgery to total mastectomies, in which the entire breast is resected.[2] Radical removal of the tumor is the first priority, but the functional and aesthetic outcomes are also important considerations. Breast-conserving surgery is the first choice when feasible and is often followed by (adjuvant) local radiation therapy.[96] If the tumor is large in relation to the breast volume, there are additional options to allow for breast-conserving surgery. Oncoplastic surgical techniques are increasingly used and can enable breast conservation in cases where it was previously not possible. Oncoplastic techniques are also used to achieve the best possible cosmetic result.[2]

Another option is to administer systemic therapy prior (neoadjuvant) to surgical treatment to shrink the tumor and enable less extensive surgery.[2] In 2024, almost 80% of surgeries for women with invasive disease were breast-conserving surgeries in Sweden.[14] However, total mastectomy may be the only choice for certain tumor sizes in relation to the breast. Other indications for mastectomy include recurrent disease, and strong hereditary factors. In some cases, it is performed at the woman's own request. Following mastectomy, immediate reconstruction with implants or autologous tissue may be performed,[97] which is the case for ~20% of women undergoing mastectomy in Sweden.[14] For the remaining ~80%, delayed reconstruction can be planned at a later stage if the woman wishes.

Breast surgery practically always includes axillary surgery—either removal of sentinel nodes, a targeted axillary dissection, or a full axillary dissection.[98] Axillary management is widely shifting toward less invasive procedures to minimize

morbidity. The least invasive option is sentinel node removal, which was performed in 60% of axillary surgeries in Sweden in 2008 and almost 90% in 2024.[14]

Chemotherapy

Chemotherapy is a collective term for drugs that kill cancer cells or stop them from growing and dividing, often by damaging deoxyribonucleic acid (DNA) or interrupting DNA processes.[99] Although primarily aimed at cancer cells, these agents act systemically in the body and affect all rapidly dividing cells. Inevitably, many normal physiological cells are also affected, like those in the hair follicles and the digestive tract, which causes typical side effects. However, also long-term side effects such as fatigue can occur.[100]

In breast cancer, chemotherapy can be administered both in connection with surgery (neoadjuvant or adjuvant therapy) and independently of surgery in a metastatic setting. Standard regimens typically include combinations of anthracyclines and taxanes, with the possible addition of carboplatin in TNBC.[2] Neoadjuvant chemotherapy is commonly used for TNBC and HER2-positive tumors in stages II and III; in cases of large primary tumors, lymph-node involvement, and primarily inoperable or inflammatory breast cancer; or to enable breast-conserving surgery.[2] One advantage of neoadjuvant administration is that it allows for assessment of treatment response. Adjuvant chemotherapy is offered to patients with high-risk features after surgery, while many women with small low-risk tumors can safely avoid cytotoxic therapy. Chemotherapy also plays a central role in disseminated or incurable breast cancer, where the aim shifts from cure to disease control, symptom relief, and better quality of life.[101]

Endocrine therapy

ER-positive breast cancer is routinely treated with endocrine therapy, which is also called antihormonal or hormone-blocking therapy. These therapies work by reducing the effect of estrogen on cancer cells.[102] In tumors that depend on estrogen signaling for growth, endocrine therapy significantly decreases the risk of recurrence and improves long-term survival.[103, 104] Postoperative endocrine therapy is routinely offered to all patients with hormone-receptor-positive breast cancer, provided that the tumor expresses estrogen or progesterone receptors. Preoperative endocrine therapy may also be used selectively.[2]

Two groups of drugs are available: ER modulators (which block ERs) and aromatase inhibitors (which suppress estrogen production).[2] Aromatase inhibitors can be offered to postmenopausal women because estrogen production after menopause mainly occurs in peripheral tissues, while the ER modulator tamoxifen is recommended for premenopausal women, sometimes together with ovarian suppression.[103] Estrogen suppression commonly leads to side effects such as hot flashes, joint stiffness, and vaginal dryness, and supportive measures are often needed.[105]

Radiation therapy

Radiation therapy uses beams of ionizing radiation to damage the DNA of cancer cells and diminishes their ability to divide. Although surrounding normal tissue is also exposed, modern radiation techniques have substantially reduced toxicity to nearby organs such as the heart, lungs, and skin. Despite this progress, treatment-related side effects remain an important consideration in clinical decision-making.[106] Currently, breast cancer is commonly treated with moderately hypofractionated radiation therapy, meaning that a slightly higher dose is delivered per fraction over fewer treatment sessions than with traditional fractionation. Hypofractionation provides equivalent local control and survival along with similar or lower toxicity compared with conventional fractionation.[107]

Postoperative radiation therapy is routinely recommended after breast-conserving surgery to reduce the risk of local recurrence. Depending on the tumor characteristics and nodal involvement, local breast irradiation may be complemented by regional nodal radiation to the axillary, supraclavicular, or internal mammary lymph nodes.[2, 103] After mastectomy, radiation to the chest wall is not routinely administered, but regional radiation therapy is recommended when lymph-node metastases or other high-risk features are present. In selected patients undergoing mastectomy, chest-wall irradiation may also be considered.[2]

Targeted therapies and immunotherapy

Targeted therapies are drugs that have been designed to attack cancer cells by focusing on specific molecular features that drive tumor growth and thus spare most normal cells. HER2-targeted agents are used in cases of HER2 overexpression and are the most used targeted therapy for breast cancer.[108] Other important classes include inhibitors of Cyclin-Dependent Kinases 4 and 6 (CDK4/6) and Poly ADP-Ribose polymerase inhibitors, which both act as enzyme inhibitors.[109]

Immunotherapy differs from targeted therapy since it uses the body's own immune system to recognize and destroy cancer cells. Immunotherapies include immune checkpoint inhibitors, monoclonal antibodies, tumor infiltrating lymphocytes, and CAR T-cell therapy.[110]

Image-guided minimally invasive treatment techniques

There are several emerging ultrasound-guided treatments for breast cancer that may be increasingly performed in the future.[111] Two minimally invasive techniques are cryoablation, which kills cancer by freezing it, and radiofrequency ablation, which kills cancer by heating it.[112, 113] A non-invasive technique that is under investigation is high-intensity focused ultrasound, which increases the temperature in tissues using only focused ultrasound waves, which increase temperature levels to a cytotoxic level.[114]

“BELIEVE YOUR EYES”

(Dolby Digital Cinema intro)

Breast imaging

Breast imaging has moved from a single-modality approach using mammography to a multimodality approach.[21] Advances have also moved on from purely anatomical imaging to include functional and molecular imaging.[111] This chapter introduces imaging modalities that are used in Swedish clinical practice.

Ionizing imaging modalities

Ionizing radiation is the basis of many medical imaging techniques. In X-ray-based imaging, radiation is emitted from an X-ray source, passes through the body, and is detected on the opposite side.[115] As X-rays travel through different tissues, they are attenuated to varying degrees, which is used to produce radiological images.[115] Conventional X-ray imaging produces two-dimensional projections, whereas more advanced techniques can reconstruct three-dimensional volumes.

Mammography

Mammography is a two-dimensional technique and the backbone of breast imaging.[116] Image quality has largely improved with the transition from analogue to digital mammography.[117] During a mammographic examination, the breast is compressed and imaged in different projections, which are most commonly the craniocaudal, mediolateral oblique, and lateromedial views. The different projections ensure that the whole breast is included and enable localization of lesions.

The tissues within the breast attenuate X-rays differently. Fibroglandular tissue shows stronger attenuation and appears radiopaque (white), whereas fatty tissue shows less attenuation and appears radiolucent (dark) on the subsequent mammogram. Malignant tumors also tend to attenuate X-rays and therefore appear white on mammograms. As breast density increases, fewer cancers are detected using mammography.[118] This is why supplemental imaging modalities are often recommended for women with dense breasts.[22] Nevertheless, mammography remains the primary method for breast-cancer screening and is also frequently used in the diagnosis and follow-up of breast lesions in general.[22]

Digital breast tomosynthesis

Digital breast tomosynthesis is an advanced mammographic technique in which multiple low-dose projection images are acquired from different angles and reconstructed into thin slices that can be scrolled through.[22] This technique provides a semi-three-dimensional view of the breast that improves the visibility of lesions by reducing the effect of overlapping tissue.[22] Digital breast tomosynthesis data can also be used to generate a pseudo-two-dimensional image known as a synthetic

mammogram.[119] In both screening and diagnostic settings, digital breast tomosynthesis detects more lesions than conventional mammography.[119] Two disadvantages with digital breast tomosynthesis are that it involves a slightly higher radiation dose compared to standard digital mammography, and that it requires longer reading time for the radiologist. However, the radiation dose is within recommended limits for mammography screening,[119] and reading time tends to decrease with increased experience.[119]

Contrast-enhanced mammography

Contrast-enhanced mammography is a technique in which iodinated intravenous contrast agents are used to visualize breast lesions. During tumor angiogenesis, the vessels often become permeable, which leads to accumulation of iodinated contrast material in the tissue.[120] The contrast-enhanced mammography technique can detect this accumulated iodine and visualize tumors based on their neovascularity.[121, 122] Contrast-enhanced mammography is performed after contrast administration with a dual-energy system. Low-energy images that resemble regular digital mammography are acquired, and high-energy images are used to generate a recombined or iodine image, in which areas with iodine uptake are enhanced.[121] In the recombined image, the unenhanced background tissue (the regular breast parenchyma) is subtracted, which is why interpretation of contrast-enhanced mammography is not density dependent.[121] Contrast-enhanced mammography has been proposed as an alternative to MRI,[123] since it is less expensive and has demonstrated diagnostic performance approaching that of MRI.[121]

Ductography

Ductography (also called galactography) is used to evaluate the breast ducts, primarily in patients with pathological nipple discharge.[124] The procedure involves cannulating the affected duct and injecting a small amount of contrast medium, followed by mammographic imaging. The technique can reveal intraductal lesions such as papilloma or ductal carcinoma *in situ* (DCIS).[125] Although many centers have replaced ductography with MRI, it is still in routine use at some sites, including Malmö.

Computed tomography

Computed tomography renders three-dimensional images of examined tissue. In Swedish breast-cancer management, computed tomography is used for the detection and follow-up of distant metastases in the thorax and abdomen.[2] It is routinely recommended for women who present with clinically positive lymph nodes since such patients should undergo metastatic staging.[126] It is also selectively recommended for patients with breast cancer when the risk of distant metastases is elevated. In addition, computed tomography is performed whenever clinical symptoms or findings raise suspicion of distant spread.

Ultrasound

Ultrasound uses sound waves to produce images of examined tissue[127] and is very useful both for identifying and obtaining tissue samples from breast lesions that have been detected by other modalities.[128] The method does not involve ionizing radiation and is frequently used in the work-up for both benign and malignant lesions, and is very effective in differentiating cystic from solid lesions.[128] Ultrasound is not recommended as a primary screening tool due to a high frequency of false-positive findings.[129] However, it is often used as a supplemental screening modality for women with dense breasts.[22] The fibroglandular structures that induce a dense appearance in mammography are more heterogeneous when visualized with ultrasound, and more easily interpretable for the radiologist.

Adding intravenous contrast agents can further enhance ultrasound interpretation and improve lesion detection,[130] but it is not used regularly in Sweden. Hand-held breast ultrasound is operator-dependent yet widely used in clinical practice.[131] Automated breast ultrasound systems that examine the breasts in a standardized and reproducible manner are also available. Their use has been shown to enhance cancer detection in women with dense breasts.[132] However, in Sweden, automated breast ultrasound is currently limited to a few centers and is most often confined to research settings.[133]

Magnetic resonance imaging

Brief background to MRI

Hydrogen is abundant in water and fat molecules throughout the human body. The protons in the hydrogen nuclei have magnetic properties, and MRI detects how these respond when the magnetic environment changes. When the body is placed in the magnetic field of an MRI scanner the hydrogen nuclei are slightly drawn in the direction of the field and they start to precess (rotate around the axis of the field).[134] At this stage, the summed magnetic vector from the hydrogen nuclei will be in the direction of the field.

To achieve images, the net magnetic vector must be tilted. Therefore, linear spatial variations of the magnetic field (gradients), as well as radiofrequency (RF) pulses, are required in addition to the main magnetic field. By varying the timing, angle, and combination of the RF pulses and gradients, different types of MRI sequences can be created, which each serve a specific purpose. The acquired signals are then translated into images by a Fourier transform in what is known as k-space (of which the details go far beyond the scope of this thesis).

Breast MRI

Dynamic contrast enhanced (DCE)-MRI is a well-established breast-imaging technique that has high sensitivity and is used as a complement in selected clinical situations where conventional imaging is insufficient.[22] The technique is particularly valuable for women with dense breast tissue,[22] unclear findings, or hereditary risk as it allows for better visualization of the tumor's extent, multifocality, and additional occult cancers that may potentially be present.

DCE-MRI is performed before and after administration of intravenous gadolinium-based contrast agent at several time points to capture enhancement patterns that can indicate malignancy.[135] For premenopausal women, DCE-MRI is preferably performed in the follicular phase to reduce background parenchymal enhancement, which can otherwise hinder diagnostic interpretation. The use of MRI varies depending on availability and local conventions. In Sweden, breast MRI is used for surveillance of women with high risk, for preoperative assessment in selected cases, and occasionally postoperatively when additional clarification is needed.[2]

Positron-emission tomography

Positron-emission tomography is a molecular imaging modality that is used in oncology to visualize the tumor burden throughout the body. The method uses different tracers to highlight regions with malignant tissue. The most used tracer is 18F-fluorodeoxyglucose, a glucose analogue that is accumulated in regions of increased metabolic activity, which frequently occurs in malignant tissue. In addition to fluorodeoxyglucose, other tracers relevant for breast cancer are also available.[136] Positron-emission tomography can be used for staging advanced disease,[126] detecting recurrence, and assessing treatment response.[137, 138] In Sweden, it is primarily performed for treatment evaluation.[2]

Imaging features investigated in this thesis

This thesis addresses different aspects of breast imaging characteristics. Papers I–III investigate **mammographic breast density and tumor appearance**, while paper IV involves an **MRI** technique for estimating **fatty acid composition** in adipose tissue of the breast. These imaging features are described below.

Breast density

Definition and concept

Breast density is a measure of the relative proportions of fibroglandular tissue and adipose tissue in the breasts, as seen on mammography.[139] Histopathological studies show that dense breasts contain substantially more stromal tissue than fatty breasts, while a modest difference occurs in epithelial structures (the presumed site of cancer origin).[140, 141] Although historically a mammographic feature, density can also be assessed using digital breast tomosynthesis,[142] MRI,[143] and ultrasound.[144]

Measurement and classification

Several systems for density classification exist.[139] The qualitative categorization (a–d) according to the Breast Imaging Reporting and Data System (BI-RADS)[145] (Figure 3) is widely used internationally, but not routinely in Sweden. Since visual grading is susceptible to intra- and inter-reader variability,[146] automated quantitative tools that estimate the absolute dense area/volume (cm^2 or cm^3) or percent density (dense tissue divided by total breast area/volume) have been developed.[147] No gold standard or universally accepted reference method has been established.[147]

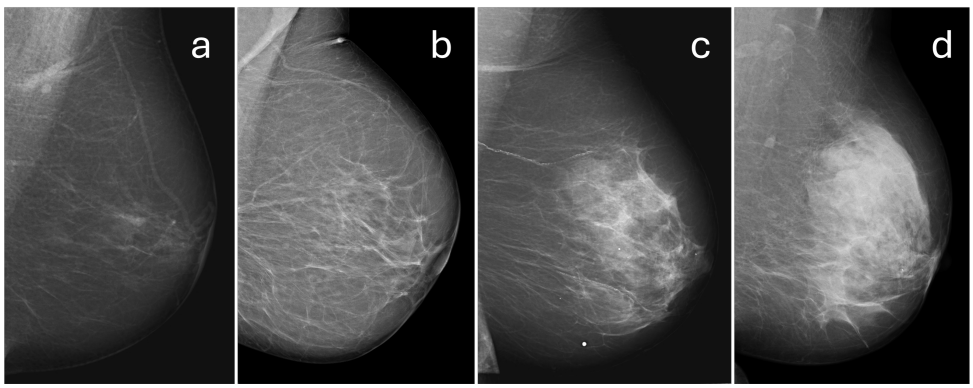

Figure 3. Mammographic breast density
From left to right, density according to BI-RADS 5th edition: **a**) almost entirely fatty, **b**) scattered areas of fibroglandular density, **c**) heterogeneously dense, and **d**) extremely dense. Image a, c, and d are previously published in paper II[148] and reprinted under a CC BY 4.0 license, b: copywright the author.

Epidemiology

Breast density is influenced by genetic and environmental factors, with heritability around 60%.[149] It is generally higher in younger women and declines with age, particularly during perimenopause and after menopause,[150] as the lobular involution of the breasts takes place[151, 152] However, persistent stromal tissue can keep some breasts dense despite involution.[153]

Density tends to decrease after each full-term pregnancy, while it is generally higher in nulliparous women[154] and in women with later age at first childbirth.[155] It is higher in women taking hormone replacement therapy,[156] and anti-hormonal agents such as tamoxifen can reduce density.[157] The effect of breastfeeding and hormonal contraceptives on breast density are less consistent.[158-161] Approximations of the density distribution among women vary, but roughly 10% of women in Western populations have the densest category of breasts (BI-RADS density category d), while around 40% have the second densest category (BI-RADS density category c).[162, 163]

Clinical significance – masking and risk

High breast density masks cancers on mammography because both dense tissue and many tumors appear radiopaque (white),[139, 164] which leads to decreased sensitivity.[165] In addition to masking, high breast density is an independent risk factor for developing breast cancer.[166] Early studies have reported four- to six-fold increases in breast-cancer risk for women with extremely dense breasts versus those with fatty breasts.[68, 166, 167] More recent studies report an approximately doubled risk of breast-cancer risk for women with BI-RADS category d compared to b.[168, 169]

Recently, additional image-based features beyond breast density, such as texture and parenchymal complexity – patterns that are not visible to the human eye – have raised interest as they may better reflect underlying biology than traditional density measurements.[170] For instance, two women with equally dense breasts can display markedly different parenchymal phenotypes, which correspond to significantly different cancer risks.[171] Nevertheless, density remains widely used because it is a simple and directly available measure.

Prognostic significance?

While high breast density is a well-established risk factor for developing breast cancer, its prognostic value once a cancer is diagnosed remains uncertain,[172] which highlights the need for further research on density as a prognostic marker. Evidence is conflicting, with some studies reporting impaired survival for women with dense breasts compared to those with less or non-dense breasts once a breast cancer is diagnosed,[173] while most studies suggest that density does not strongly influence survival.[174]

Biological basis

The biological basis linking density to breast-cancer risk is not yet completely understood. One hypothesis is that high density reflects more epithelial cells being "at risk" of carcinogenesis.[175] However, the proportion of dense tissue in a breast (percent density) predicts risk more accurately than absolute dense area,[176] which implies that the risk is driven by interactions between the epithelial structures and the microenvironmental factors rather than epithelial cell count alone.[175] Dense breast parenchyma hosts a more pro-tumorigenic microenvironment than non-dense breasts.[177, 178] However, the precise mechanisms behind the increased breast-cancer risk accompanied with high density is still unclear.

Communication

Density notification laws requiring that women be informed of their density status have been enacted in the US[179] and are being established in Australia.[180] Sweden has not adopted this practice. The goal with density notification is to enable women with dense breasts to consider supplemental imaging.[181] However, providing information on density can cause anxiety and confusion for notified women.[181] Density communication should be clear, understandable,[182] and preferably accompanied by attainable imaging alternatives along with evidence supporting their use.

Mammographic tumor appearance

Definition and classification

Malignant breast lesions can present with different mammographic appearances.[183] The most widely used classification system for tumor appearances is the BI-RADS lexicon, which provides terminology for describing masses, asymmetries, architectural distortions, calcifications, and associated features on mammography.[145] Masses can be categorized further in regard to their shape, margin, and density. Mammographic tumor appearance reflects histological architecture and can provide information on aspects of tumor morphology that relate to underlying biology and prognosis.

Tumor appearances, their biological basis, and clinical significance

A breast lesion with a **distinct** margin is a common mammographic manifestation and most often represent a benign lesion (Figure 4).[183] However, this appearance can also correspond to a malignant lesion that lacks surrounding stromal reaction.[183] TNBC often presents in this way and may therefore be mistaken for a benign lesion.[184-187] Masses with **ill-defined** or partly ill-defined margins often indicate infiltrative tumor growth (Figure 4).[183] **Spiculated** or stellate tumor appearance refers to a lesion with strands radiating from the central core (Figure 4).[188] The strands correspond to tumor infiltration, a desmoplastic stromal reaction, or

periductal fibrosis.[188] Although the spicules may contain cancer cells and reflect adipose-tissue invasion,[189] measuring the central tumor core on mammography is recommended, as it more accurately reflects the histologic tumor size.[190] Spiculated appearance is a strong predictor of malignancy.[191-193] However, despite the worrying infiltrative appearance, the spiculated tumors frequently exhibit favorable tumor traits, such as hormone receptor-positivity,[194-196] HER2 negativity,[194, 196] lower grade,[197-199] and lower expression of proliferation marker Ki67.[194, 196] Spiculation has accordingly been linked to the luminal A-like subtype[196, 200, 201] and lower mortality.[198, 202, 203]

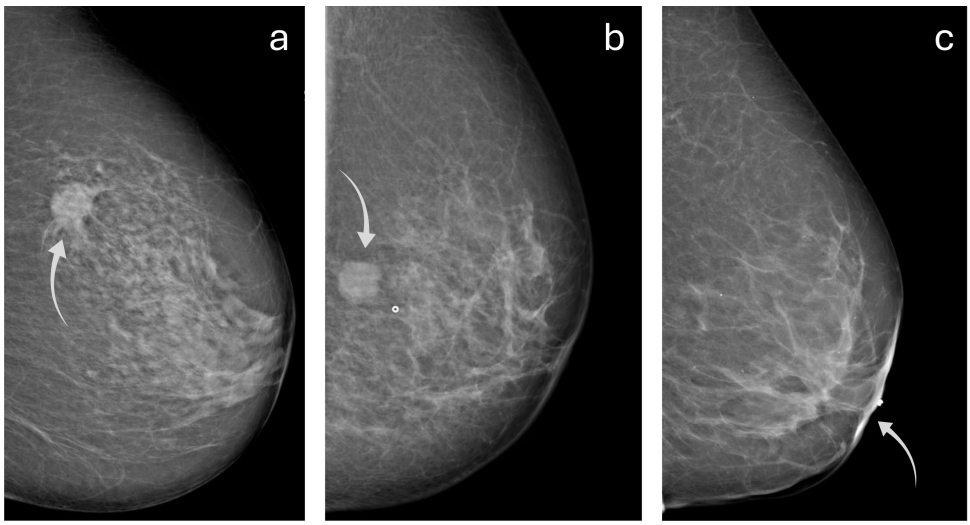

Figure 4. Examples of mammographic tumor appearences
From left to right: **a**) spiculated mass, **b**) distinct mass, and **c**) ill-defined mass (located retro-mamillary with retracted nipple). The images have previously been published in paper II (Sturesdotter *et al.* 2023)[148]. Reprinted under a CC BY 4.0 license.

Microcalcifications can be categorized based on their morphology, and some are typically benign.[204] Malignant lesions can cause microcalcifications that arise from necrosis or secretions within the ducts, with pleomorphic or linear microcalcifications being a common manifestation of DCIS.[205] The presence of microcalcifications with or without soft-tissue lesion is associated with a higher likelihood of HER2+ breast cancer.[184, 206-208] The presence of fine linear branching calcifications, which are also known as casting-type calcifications, is associated with increased mortality.[203, 209]

Asymmetry is defined as an area of focal fibroglandular tissue that lacks the well-defined margins of a true mass.[145] An asymmetry may become apparent when the area is compared with other regions of the same breast, the contralateral breast, or with prior images of the same area.[210] It is not always an obvious malignant

finding, but a difference in fibroglandular tissue signals a possible underlying abnormality, warranting further evaluation. Asymmetry is a tumor appearance that most often consists of a carcinoma, but also lymphomas and rare malignancies can present this way.[210] **Architectural distortion** is a rather common abnormality detected on mammography that can correspond to both benign and malignant underlying conditions.[211] Architectural distortion can arise due to for example stromal fibrosis, prior interventions, or invasive cancer – even in the absence of a mass.[212]

Mammographic cancer detection varies to some degree according to the tumor appearance. Some tumor appearances are more easily identified, as in the case of spiculation, while subtle asymmetries and distortions are more prone to being overlooked in screening.[213] The level of breast density also influences the perception mammographic abnormalities and tumor appearances.[214, 215] The relationship between tumor appearances and breast-cancer characteristics are well studied but not fully understood. Some tumor appearances have been linked to survival outcomes, but these associations would benefit from further investigation in large cohorts like the Malmö Diet and Cancer Study (MDCS). Moreover, investigations of the differences within the group of spiculated tumors are lacking.

MRI estimates of fatty acid composition

MRI techniques for adipose tissue

While density captures aspects of fibroglandular tissue, imaging of fatty acid composition focuses on the surrounding adipose tissue which is often overlooked. Routine clinical MRI sequences, such as T1- and T2-weighted imaging, accurately show where adipose tissue is located. However, if the goal is to determine the composition of fatty acids within adipose tissue, more specialized MRI techniques are needed. A classic method for assessing fatty acid composition is magnetic resonance spectroscopy,[216] which can detect specific resonance peaks of hydrogen atoms in triglycerides, and thereby differentiates saturated, monounsaturated, and polyunsaturated bonds.[47] Magnetic resonance spectroscopy typically provides data from a single voxel or a small region and requires long acquisition times.

Another method is chemical-shift-encoded (CSE)-MRI.[47] Instead of separating signals by their resonance peaks, this method uses a mathematical model that predicts how the MRI signal should behave at different echo times. The actual datapoints collected from multiple echoes are then compared to this model, and the model is adjusted or fitted until it matches the measured signals. This fitting process allows for estimation of the chemical properties of fat, such as the number of double bonds, without directly isolating individual frequencies.

Potential clinical importance

Expanded knowledge on peri-tumoral adipose tissue may provide valuable insights into tumor biology and could contribute to improved breast-cancer characterization, risk stratification, and treatment guidance. Imaging methods that accurately estimate fatty acid composition non-invasively, like the MRI technique investigated in paper IV, are therefore interesting to pursue. Several MRI studies have reported alterations in lipid composition in proximity to cancer. For instance, elevated levels of monounsaturated fatty acids adjacent to colorectal[40] and prostate tumors have been reported.[41] Similarly, in breast cancer, the composition of adipose tissue differs between women with and without breast cancer.[48-50] However, imaging of fatty acid composition in breast adipose tissue is an underexplored area.

Aims

The overarching aim of this thesis was to explore how tumor and tissue features on breast imaging relate to breast-cancer characteristics and prognosis. This was accomplished by the following specific aims:

Aims for the separate papers

I. To investigate how mammographic tumor appearance relates to clinical and histopathological factors, including surrogate molecular subtypes.

II. To investigate how breast density and mammographic tumor appearance relate to breast-cancer-specific survival.

III. To investigate whether the degree of spiculations relative to the tumor mass on mammography, the Spic Mass Ratio (SMR), is associated with clinical and histopathological factors and prognosis in breast cancer.

IV. To assess the feasibility of chemical-shift-encoded MRI for the evaluation of fatty acid composition in breast adipose tissue.

Methods

Scientific approach

Papers I–III are observational studies based on data from a large population-based cohort study. The three papers relate mammographic imaging features from incident breast-cancer cases to breast-cancer characteristics, and breast-cancer-specific survival. In paper III we developed a novel imaging metric for mammographically spiculated breast cancer and tested its relationship with breast-cancer characteristics and prognosis.

Paper IV is a cross-sectional single-center study that was conducted within a routine clinical breast-MRI workflow. The study evaluates an MRI technique for estimation of fatty acid composition in breast adipose tissue. We studied MRI-derived variables in relation to breast density, menopausal status, and occurrence of breast cancer.

Study populations

Papers I–III: The Malmö Diet and Cancer Study

The first three papers in this thesis are based on data from women with breast cancer in the Malmö Diet and Cancer Study (MDCS), a large population-based prospective cohort study.[217] Between 1991 and 1996, the MDCS enrolled 28,098 inhabitants in Malmö, Sweden, aged 44–74 years, of whom 17,035 were women and 11,063 were men.[218] During the first recruitment round in 1991, all inhabitants of Malmö born in 1926–1945 were eligible for inclusion. In 1995, the study was expanded to include men born in 1923–1945 and women born in 1923–1950.[219] Younger women (born in 1946–1950) were included to enable the study of premenopausal breast cancer.[219]

The primary aim of the MDCS was to study the impact of diet on cancer incidence and mortality and to serve as a resource for testing hypotheses in future studies.[217] At the study baseline, all participants went through a physical examination for collection of anthropometric variables (including height and weight). They also filled out a detailed questionnaire with information relating to topics such as heredity for various diseases, current health status, sociodemographic factors, tobacco consumption, reproductive factors, and medication, including hormone replacement therapy.[217, 218] In addition, blood samples were collected and stored in

a biobank.[217] The MDCS database is updated regularly via linkage to Swedish national registries for the identification of incident cancer cases and causes of death within the cohort. The participants of the MDCS had lower mortality compared to non-participants both during and after the study inclusion.[219]

Papers I and II included women in the MDCS who were diagnosed with invasive breast cancer between 1991 and 2014. Women with prevalent breast cancer at baseline (n = 572), bilateral breast cancer (n = 21), or carcinoma *in situ* (n = 105) were excluded, resulting in 1,116 women who were eligible for inclusion (Figure 5).[220] Paper III included women with invasive breast cancer with spiculated tumor appearance on digital mammography in the MDCS who were diagnosed in 2004–2014 (n = 161; Figure 5).[221] For women in the MDCS, the average attendance of breast-cancer screening was 92%.[222]

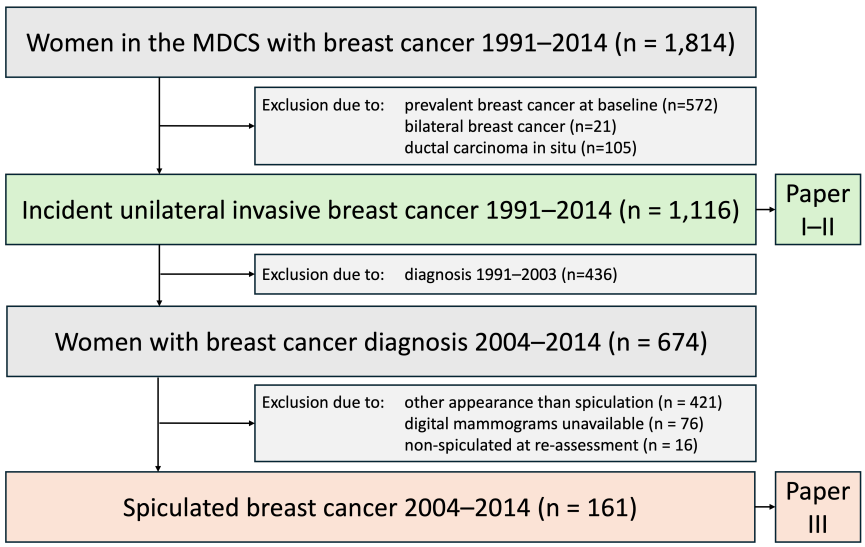

Figure 5. Derivation of study population in papers I–III
The first three papers in this thesis are based on information regarding women with breast cancer in the Malmö Diet and Cancer Study. The first two papers included 1116 women while paper III included a subset of the population (n = 161) with mammographically spiculated breast cancer.

Paper IV: A selection of women scheduled for a DCE-MRI

For paper IV, the participants comprised women scheduled for a clinical breast DCE-MRI at Skåne University Hospital in Malmö, Sweden. The cohort consisted of mostly women in the high-risk surveillance program and women diagnosed with breast cancer for whom DCE-MRI was performed pre-operatively.

A total of 73 women consented and were examined with the MRI sequence of the study between October 2022 and November 2023. There were 5 examinations that were excluded because of technical issues, leaving 68 women with complete and technically adequate MRI datasets for analysis. The enrollment process is summarized in Figure 6.

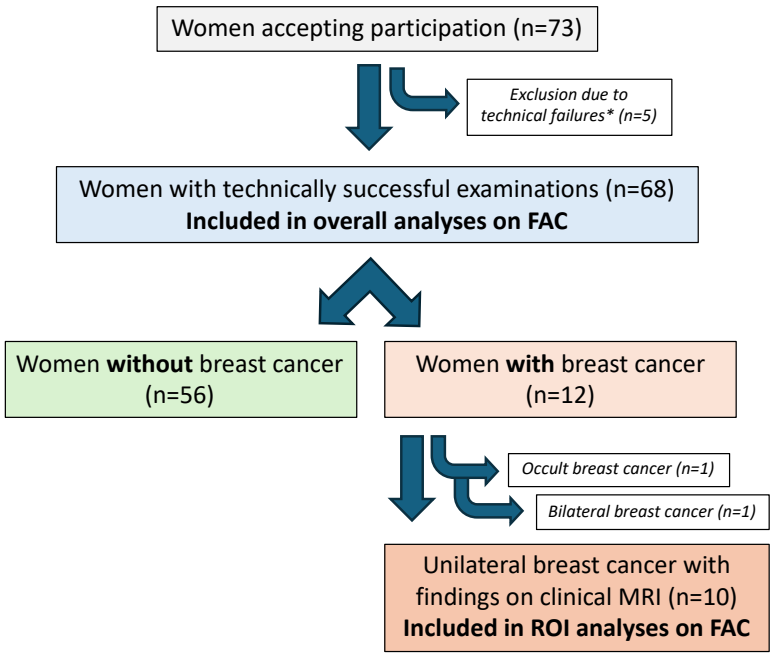

Figure 6. Derivation of study population in paper IV
Paper IV included women scheduled for a DCE-MRI at Skåne University Hospital.
*Technical failures involved either unsuccessful image transferring (n=4) or a malfunctioning algorithm (n=1). Of the 10 women with breast cancer identifiable with MRI, 7 women had invasive cancer, and 3 had DCIS. ROI = region of interest, FAC = fatty acid composition.

Study variables and techniques

Mammographic variables

Mammographic data collection

Mammography-derived variables were used in all four papers and include tumor appearance, breast density, and mode of cancer detection. **Mode of detection** was categorized as **screening-detected** or **clinically detected**. Interval cancers were included in the group of clinically detected cancers. The detection mode was missing for 7 women with breast cancer in the MDCS.[223] Screening-detected cancers were routinely imaged with bilateral mediolateral oblique and craniocaudal views,[224] and the mammograms were read by two breast radiologists.[220] These images were complemented with appropriate additional views if the woman was recalled, typically a lateromedial view of the breast containing the finding that led to recall.[224]

Occasionally, other views were obtained, such as magnification views for calcifications and axillary views for findings located in the axillary tail. The diagnostic work-up of screening-detected cancer was performed by one breast radiologist and included complementary ultrasound, and image-guided biopsies in most cases.[220] For clinically detected cases, all imaging was routinely assessed by one breast radiologist,[220] and included bilateral mediolateral oblique, craniocaudal, and lateromedial views, as well as additional views occasionally as described above.[224]

Mammographic breast density and **tumor appearance** were extracted from the original written radiology report from the diagnostic mammogram.[223] When the original report lacked data, the mammograms were re-read. This was the case in approximately one-third of cases for breast density, and in approximately one-fifth of cases for tumor appearance.[223] If the mammogram was unavailable and could not be re-read, the case was recorded as missing.[223] Density and tumor appearance were each missing in less than 10% of the population, which was mainly due to old analogous mammograms that could not be retrieved.[148]

Mammographic tumor appearance

When defining tumor appearance, only the most dominant mammographic tumor appearance was considered, even if multiple features could be present.[224] Using the scheme by Luck et al.,[225] tumors were initially classified as well-defined, partly ill-defined, ill-defined/diffuse, spiculated, comedo-type microcalcifications, non-specific calcifications, architectural distortion, or asymmetrical density.[225] The tumor appearances were consolidated into five groups to increase statistical power, these were distinct masses (well defined and partly ill-defined), ill-defined masses,

spiculated masses, calcifications (comedo-type and non-specific), and tissue abnormalities (architectural distortion and asymmetrical density).[223] This categorization was completed by H. Sartor and S. Zackrisson prior to the start of this thesis.

Mammographic breast density

In the Department of Breast Radiology in Malmö, a simplified system for breast density has long been used with three tiers: fat-involuted, moderately dense, and dense parenchyma. These can be translated to reflect the 4th edition of BI-RADS density scores as follows: fat involuted corresponds to a density score of 1, moderately dense corresponds to scores of 2–3, and dense corresponds to a score of 4. For a sub-analysis in paper II additional density assessment was performed according to the 5th edition of BI-RADS[226] (a = almost entirely fatty, b = scattered areas of fibroglandular density, c = heterogeneously dense, d = extremely dense) in a subset of women (n = 376) diagnosed in 2008–2014. In paper IV, breast density was assessed according to BI-RADS 5th edition for the full study population using the most recent mammogram prior to the MRI examination performed for the study.

In statistical analyses, the density variables were dichotomized. For the clinically used three-tier variable, women with the least dense breasts (fat-involuted) and moderately dense breasts were combined and compared to women with the densest breasts. For the BI-RADS density variable, categories were dichotomized into a+b and c+d.

Spic Mass Ratio

In cancers with spiculated appearance, we defined the Spic Mass Ratio (SMR) as the ratio of the tumor area including spiculations to the tumor's core area without spicules. Thus, higher values indicate more extensive spiculation. Spiculated cancers on diagnostic digital mammograms were first reviewed for true spiculation, and if they were assessed as truly spiculated, the SMR was annotated on the view with the greatest spiculation conspicuity. By using the area tool in Sectra PACS, the tumor core was first outlined, and then the core plus the spicules were outlined in the same session.

The boundary of the core and spicules was not set with hard criteria beforehand. Instead, the tumor core and spiculations were outlined subjectively by the readers. Margins were mostly clear with radiating spicules perpendicular to the core. Annotations were made by L. Sturesdotter, and for complex cases, they were performed together with an experienced breast radiologist, K. Lång. Figure 7 shows examples of three mammograms with and without SMR annotations. In statistical analyses the women were divided into three equally sized groups based on degree of SMR (low, moderate, and high).

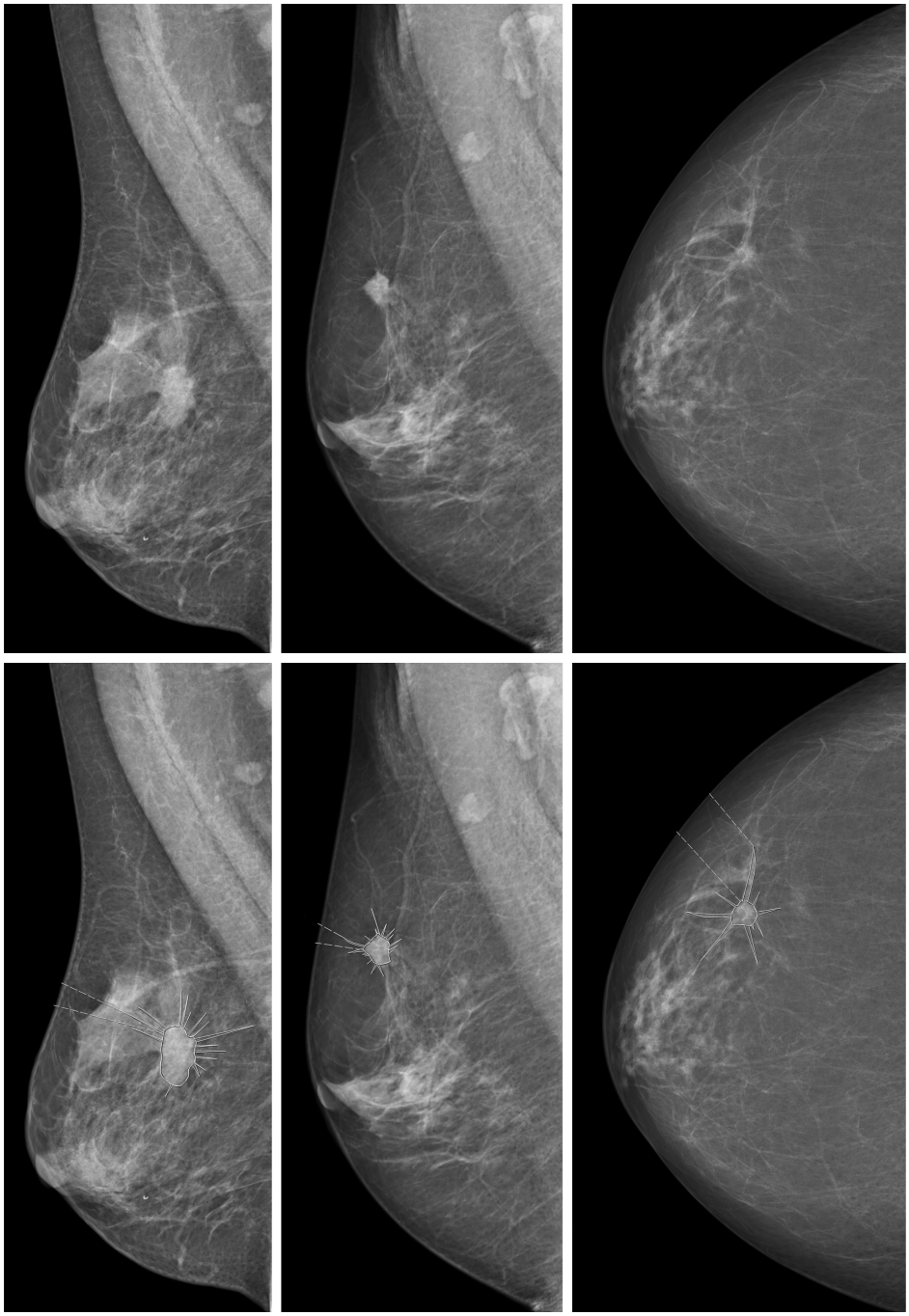

Figure 7. Three examples of SMR annotations on mammographically spiculated breast cancer
Original mammograms on the top row, and with their corresponding SMR annotations on the bottom row (the dotted lines are irrrelevant). Images previously published in paper III.[221] License: CC BY 4.0.

MRI variables

MRI technique for estimating fatty acid composition

For paper IV, a CSE-MRI technique was used to estimate the number of double bonds and methylene-interrupted double bonds in fatty acids to enable quantification of PUFA, SFA, and MUFA. A CSE-MRI sequence (GE HealthCare) had been updated in-house to increase the number of echoes, and the fatty acid composition and proton density fat fraction (PDFF) could be derived through a custom post-processing algorithm. PDFF is a map depicting the relative amount of fat in the examined tissue.

The CSE-MRI scan (3D multi-echo gradient echo with bipolar readout) was performed immediately after the clinical DCE-MRI on a 3-T scanner (GE Architect) at the Skåne University Hospital in Malmö, Sweden. The following sequence parameters were used: 256 × 256 matrix, 40 slices, TR of 26 ms, 10 echo times with inter-echo spacing of 1.54 ms, bandwidth of 781 Hz/pixel, flip angle of 10°, and acquisition time of ~4.5 min. Magnitude and phase data were acquired.

The signal intensities from the 10 echoes were fitted to a constrained signal model with phase-error correction, and voxels with non-feasible double-bond estimates were discarded. The output of the model was quantitative maps of PDFF, PUFA, and SFA. The model resulted in an effectively constant value for MUFA, which is why this parameter was excluded from further analyses. Automated segmentation was performed to remove tissue outside of the breasts, and only the central 24 slices were analyzed to limit fold-over artefacts in the slice-encoding direction.

MRI variables used in paper IV

In paper IV we defined and studied the following adipose-tissue-related variables:

- The relative adipose tissue content defined as the percentage of voxels with PDFF > 85%
- The proportions of PUFA in voxels with > 85% PDFF
- The proportions of SFA in voxels with > 85% PDFF

Values were computed for whole breasts and in regions of interest (ROIs). ROIs were drawn manually in magnitude images using ImageJ software to enable comparison of PUFA and SFA adjacent to cancer and at sites distant from cancer in both the ipsilateral and contralateral breast. ROIs were placed only for the 10 women with MRI-visible breast-cancer lesions on clinical sequences. For each participant, four ROIs were positioned in visually adipose-rich regions. ROI 1 was 1–2 cm from the cancer, and ROI 2 was distant from the cancer in the ipsilateral breast. ROIs were also placed in the mirrored locations of ROI 1 and ROI 2 in the contralateral breast (ROI 1^{contra} and ROI 2^{contra}).

MRI variables of BI-RADS 5th edition

In paper IV, images and information from both the study-specific and clinical MRI-sequences were used. For women with breast cancer (n=12), fibroglandular tissue and background parenchymal enhancement according to BI-RADS 5th edition was assessed based on the clinical MRI sequences.

Figure 8 shows examples of the fatty acid composition maps for SFA, PUFA, and PDFF from the study-specific CSE-MRI technique, clinical MRI-sequences, and digital mammography.

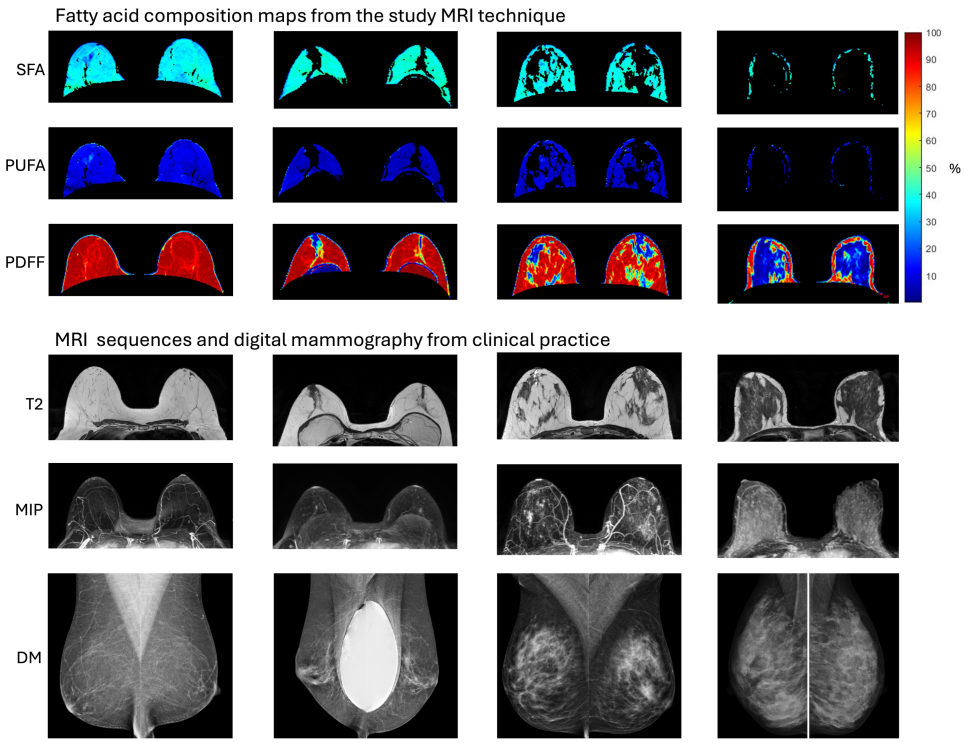

Figure 8. Fatty acid maps, clinical MRI, and mammography from four women in paper IV
From top to bottom: representative examples of SFA, PUFA, and PDFF maps; clinical T2-weighted images (T2); maximum intensity projection images (MIP); and digital mammograms (DM) from four women without breast cancer, but with varying amounts of adipose tissue in the breasts. From left to right: fat involved parenchyma (density a) to very dense parenchyma (density d) according to BI-RADS 5th edition. Note that the sharp segmentation line along the thoracic wall excludes tissue outside of the breasts on the SFA, PUFA, and PDFF images. Images from paper IV (unpublished manuscript), copyright the authors.

Gas chromatography

We compared the fatty acid composition data from MRI to gas chromatography in six surgical specimens from four women in the study who had undergone breast surgery. In January 2024, breast-tissue samples were collected at the Department of Pathology at Skåne University Hospital in Malmö. To avoid interfering with standard clinical procedures, sampling was performed after completion of routine pathological examination. This meant that the breast tissue had been sectioned and stored in formalin until sampling. As a result, the exact anatomical origin of each tissue sample within the breast could not be determined (see image for clarification; Figure 9). One piece of visually pure adipose tissue (approximately 5–10 g) was taken from each specimen. The samples were put in sterile, labeled containers and transported to a lab for gas chromatography analysis (Eurofins, Linköping, Sweden).

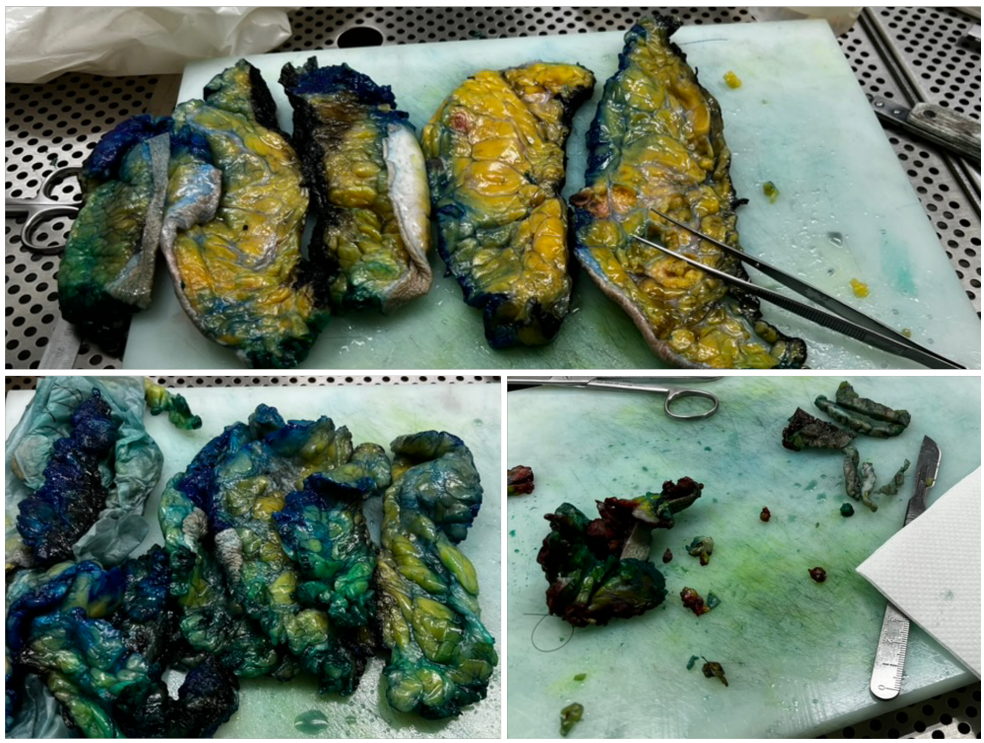

Figure 9. Surgical specimens from three of the women who had undergone a partial mastectomy
Images depicting three examples of how the specimens looked at the time for gas chromatography sampling. Prior sectioning, formalin storage, and in some cases also small specimen size (bottom right) made it difficult to appreciate where in the corresponding breast on MRI the samples were taken.

Clinical variables

Papers I–III

Clinical variables in the first three papers were collected both from the baseline inclusion in the MDCS and from the time at breast-cancer diagnosis. The use of hormone receptor therapy and body mass index were considered as confounding factors in paper II and were retrieved from baseline data. The exposures (mammographic variables) and outcomes (information from pathology reports and medical records, including axillary-lymph-node involvement (ALNI), and additional variables; see below) were based on the time of diagnosis. Follow-up information on the women in the MDCS with breast cancer diagnosed in 1991–2014, including causes of death, was available up until December 31, 2018, via linkage to the Swedish Cause of Death Register.[148] Breast-cancer-specific death was assigned when breast cancer was either the primary or a contributing cause of death.[148]

Paper IV

Breast-cancer diagnosis (prevalent or incident after inclusion), age, menopausal status at the time of MRI examination, attendance to breast-cancer screening, and risk factors for breast cancer were collected from medical records and radiology referrals in 2023–2025.

Histopathological variables

The histopathological data used in papers I–III were obtained from medical records and tissue microarray assessments. Tissue microarray is a technique in which small cylindrical cores are taken from multiple paraffin-embedded blocks (typically from different cancers), and are lined up in a single recipient block, which enables parallel assessment of many specimens on one single histological slide.[227] Separate tissue microarrays were constructed for breast cancers diagnosed in 1991–2004 and in 2005–2007. Two cores were sampled from representative regions for each tumor. The detailed tissue-microarray methodology has been reported previously.[228, 229]

Hormone receptors

ER and PR expression were determined by immunohistochemistry and obtained from the tissue-microarray assessments for cancers diagnosed in 1991–2004, and from medical records for cancers diagnosed 2005–2014. In accordance with prevailing guidelines, staining was considered negative when ≤10% of tumor cells were stained and positive with >10% staining of tumor cells.[230] This differs slightly from current guidelines, in which tumors with ≥10% stained cells are considered positive for ER and PR.[2] However, this is not important for the contents of this thesis as the material was both analyzed and studied before this change took place.

Human epidermal growth factor 2

HER2 status was retrieved from tissue-microarray evaluations for women diagnosed in 1991–2007 and from medical records in 2008–2014. From in 1991–2004, HER2 assessment relied solely on the immunohistochemistry-based HercepTest,[231] where scores of 0 and 1+ were classified as HER2– (non-amplified), 3+ indicated HER2+ (amplified), and 2+ was recorded as missing.[229] *In situ* hybridization was introduced in 2005, and from then on, cases with 2+ on the HercepTest were categorized as amplified or non-amplified if *in situ* hybridization yielded a definitive result; otherwise, they were classified as missing.[229]

Histological grade and tumor type

The tumors from women diagnosed in 1991–2004 were included in the first tissue microarray. They were re-assessed by an experienced breast pathologist who assigned a histological grade[81] and histological type according to the WHO classification.[232] For breast cancers diagnosed in 2005–2014, histological grade and type were collected from medical records.[232]

Ki-67

Ki-67 from immunohistochemistry was collected in three periods: 1991–2004, 2005–2007 (both from tissue microarray), and 2008–2014 (from medical records). Varying Ki67 distribution was noted at different time points during the follow-up period. Therefore, Ki67 was stratified into tertiles (low, intermediate, high) with roughly one-third of cases in each category during the three periods.[232] In other words, no exact cutoffs were applied for Ki-67 for the entire follow-up period.

Pathological tumor size

Tumor size was extracted from medical records for the whole follow-up period and was based on histopathological measurements.[233] The largest focus was used in cases of multifocal cancer.[220]

Surrogate molecular subtypes

Tumors were classified as surrogate molecular subtypes using an approach adopted by the Southern Swedish Breast Cancer Group: luminal A-like, luminal B-like, HER2-positive, and TNBC.[233] All ER-positive (ER+) tumors with grade 1 were considered luminal A-like, while all ER+ tumors with grade 3 were considered luminal B-like. ER+ tumors with grade 2 were also considered luminal A-like if they had low Ki67 or intermediate Ki67 *and positive* PR status. In contrast, ER+ tumors with grade 2 fell into the luminal-B-like category if they had high Ki67 or intermediate Ki67 *and negative* PR status. All tumors that expressed HER2 were considered HER2-positive, regardless of grade or hormone receptor status. Tumors that were negative for ER, PR, and HER2 were classified as TNBC.[220, 233]

Ethical considerations

Papers I–III (MDCS-based studies)

Participants in the MDCS provided written informed consent at the time of inclusion. This consent stated that the information that they provided, along with baseline data such as anthropometric measurements, could be used for future research and be published in scientific papers. Papers I–III primarily rely on data from the MDCS database, which is curated by a data manager who provides researchers with anonymized datasets. Only variables that are necessary for the specific research questions were extracted from the database. Importantly, none of the studies in this thesis required new analyses of stored biological samples (e.g., blood), nor did they involve additional tests or examinations. Therefore, the main ethical concern relates to data integrity and confidentiality. All MDCS data were handled in a pseudonymized form except in two situations: (1) identifying illustrative mammographic images for papers I–II and (2) annotating SMR on clinical mammograms for paper III. These tasks required temporary access to non-anonymized radiological images, which was performed in a secure setting. The use of imaging from individual participants is common practice in breast-imaging research and adds significant scientific value to publications by enabling visual examples and methodological transparency. Currently, identification from mammograms alone is virtually impossible, so the potential harm is considered very low, while the scientific benefit of including such images is substantial. Nevertheless, if future technologies enable identification from imaging, they will pose new ethical challenges.

Paper IV (MRI-based study)

For paper IV, participants provided written informed consent specific to the study objectives, unlike the broad consent in the MDCS. Women undergoing breast MRI may be in a more vulnerable position than the MDCS participants as they often have elevated risk for breast cancer or have already been diagnosed. This raises concerns about perceived pressure to participate. To mitigate this, the consent process emphasized the voluntary nature of participation, clarified that it would not affect clinical care, and assured participants of their right to withdraw from the study at any time without explanation. These measures are essential to uphold autonomy and prevent undue influence.

Ethics approvals

Papers I–III were approved by the Ethics Review Board in Lund, Sweden (Record Nos. 652/2005, 166/2007, and for papers II and III 2014/830), and by the Swedish Ethical Review Authority (Record No. 2022-04473-02). Paper IV was approved by the Swedish Ethical Review Authority (Record Nos. 2020-05055 and 2022-03927-02).

Statistics

Descriptive statistics were used to summarize and characterize the study populations. Mean values are reported for variables that followed an approximately normal distribution, whereas medians were used for skewed data. A *p*-value below 0.05 was considered statistically significant.

Statistical methods

Analysis of variance (paper III)

Analysis of variance compares the means of three or more groups to determine whether at least one group differs from the others. Analysis of variance is a parametric test, meaning it assumes that the data follow a specific distribution, typically a normal distribution. For example, it can be used to compare average tumor size across different breast-cancer subtypes.

Chi-squared test (paper III)

The chi-squared test is used to determine whether there is an association between two categorical variables, such as the tumor subtype and the detection method.

Cox's proportional hazards regression (papers II and III)

Cox regression is used to study how factors affect the time until an event, such as death or recurrence of disease. The method yields hazard ratios (HRs), which are the relative risks at each timepoint for one group compared to another during follow up. Cox regression allows for adjustment of confounding factors. In Cox regression, proportional hazards must be fulfilled, meaning that the relative risk between the compared groups is assumed to be constant during follow up. If the proportional hazards assumption is not fulfilled the results of Cox regression might not be reliable.

Fisher's exact test (paper III)

Fisher's exact test assesses the association between two categorical variables. This test is preferred when expected cell counts are low or sample sizes are small, for which the chi-squared approximation may be unreliable.

Kaplan–Meier estimate (papers II and III)

The Kaplan–Meier method is used to estimate survival over time. The method creates a curve that shows the proportion of patients who have not experienced an event (e.g., death) at different time points. It is often used to compare survival between groups. In contrast to Cox regression analysis, it is not possible to adjust for confounders when using Kaplan–Meier estimates.

Kruskal–Wallis test (paper IV)

The Kruskal–Wallis test is a non-parametric alternative to one-way analysis of variance, used when normality assumptions are not met. It compares the distributions of three or more independent groups using rank sums and is often interpreted as a test of median differences.

Logistic regression (paper I)

Logistic regression is used for binary outcomes when follow-up time is not of interest. The results are shown as odds ratios (ORs), which is the ratio of odds in the exposed group and the unexposed group.

Multinomial logistic regression (paper I)

Multinomial logistic regression is similar to logistic regression but is used when the outcome has three or more categories without a natural order. Such variables are called nominal variables. The method estimates the odds for each category compared to a reference category and yields relative risk ratios (RRRs) for each category compared to a reference category.

Ordinal regression (paper I)

Ordinal regression is similar to logistic regression but is used when the outcome has a natural order. Ordinal regression models the cumulative odds of being in a higher category versus all lower categories. The model therefore still yields ORs, but these are cumulative, meaning they express the likelihood of being in higher rather than lower outcome categories combined.

Wilcoxon rank-sum test (paper IV)

Also called the Mann–Whitney test, the Wilcoxon rank-sum test compares two different independent groups when data are not normally distributed (which makes it a non-parametric test).

Wilcoxon signed-rank test (paper IV)

The Wilcoxon signed-rank test compares two dependent measurements, such as measurements obtained before and after treatment, when data are not normally distributed (non-parametric).

Software for statistical analyses

Statistical analyses were performed using the following software: paper I: Stata version SE 14.2; paper II: Stata, version 16.1; paper III: R version 4.3.0; paper IV: IBM SPSS Statistics version 31.0.0.0 (IBM Corp., Armonk, New York, United States) and MATLAB (version R2024a) (MathWorks Inc., Natick, USA).

Use of artificial intelligence

This thesis was written with assistance of Copilot (Microsoft) using the version provided by Lund University. Copilot was used to for proofreading, increase readability, and aid in the creation of the list of abbreviations. AI has not been used to generate full pieces of text. All text that was altered with the assistance of AI has been thoroughly reviewed and edited by the author, who assumes full responsibility for the final content.

Results

This section summarizes the most important results from the four papers included in this thesis, along with selected tables. Complete tables and figures are available in papers I–IV in the appendices.

Paper I

The mammographic tumor appearances related significantly to many of the clinicopathological factors when studied one at the time. With the same factors combined to stratify the cohort into surrogate molecular subtypes, significant results were also found. In particular, the spiculated tumors were distinguished as frequently positive for hormone receptors, having lower Ki67 expression and histological grade, and thus more often having the luminal-A-like subtype.

Clinicopathological factors

Tumors that were mammographically ill-defined, spiculated, and presenting as tissue abnormalities were significantly more likely to be ER positive than ER negative compared to distinct masses. The adjusted odds ratio (OR_{adj}) for ER positivity was 2.0 (95% confidence interval (95% CI) 1.1–3.6) for ill-defined tumors, 6.0 (95% CI 3.2–11.2) for spiculated tumors, and 4.4 (95% CI 1.0–19.6) for tissue abnormalities (Table 2). Spiculated tumors were also more likely to be PR positive with an OR_{adj} of 1.7 (95% CI 1.2–2.5) (Table 2).

No significant association was found between mammographic tumor appearances and HER2 status (Table 2). Spiculated tumors were less likely to have histological grade 3 than grades 2 and 1 (OR_{adj} 0.5 (95% CI 0.4–0.7); Table 2), as well as high Ki67 (OR_{adj} 0.5 (95% CI 0.3–0.6); Table 2).

Table 2. Mammographic appearances in relation to ER, PR, HER2, grade, and Ki67 (paper I)

Mammographic appearance	ER-	ER+	Logistic regression	
	n (%)		OR(95% CI)	OR_{adj}*(95% CI)
Distinct mass	42 (18.4)	186 (81.6)	1.0	1.0
Ill-defined mass	25 (13.9)	155 (86.1)	1.4 (0.8 - 2.4)	2.0 (1.1 - 3.6)
Spiculated	16 (4.1)	372 (95.9)	5.2 (2.9 - 9.6)	6.0 (3.2 - 11.2)
Calcifications	17 (25.8)	49 (74.2)	0.7 (0.3 - 1.2)	0.6 (0.3 - 1.3)
Tissue abnormality	2 (6.3)	30 (93.8)	3.4 (0.8 - 14.7)	4.4 (1.0 - 19.6)
Observations (n)			894	867
***p*-value (overall)**			<0.001	<0.001
	PR-	**PR+**	**Logistic regression**	
Distinct mass	96 (43.1)	127 (56.9)	1.0	1.0
Ill-defined mass	77 (44.5)	96 (55.5)	0.9 (0.6 - 1.4)	1.1 (0.7 - 1.7)
Spiculated	115 (30.9)	257 (69.1)	1.7 (1.2 - 2.4)	1.7 (1.2 - 2.5)
Calcifications	33 (51.6)	31 (48.4)	0.7 (0.4 - 1.2)	0.8 (0.5 - 1.5)
Tissue abnormality	17 (54.8)	14 (45.2)	0.6 (0.3 - 1.3)	0.9 (0.4 - 2.1)
Observations (n)			863	839
***p*-value (overall)**			<0.001	0.007
	HER2-	**HER2+**	**Logistic regression**	
Distinct mass	199 (90.5)	21 (9.5)	1.0	1.0
Ill-defined mass	140 (84.8)	25 (15.2)	1.7 (0.9 - 3.1)	1.5 (0.8 - 3.0)
Spiculated	342 (94.5)	20 (5.5)	0.6 (0.3 - 1.0)	0.6 (0.3 - 1.1)
Calcifications	49 (84.5)	9 (15.5)	1.7 (0.8 - 4.0)	2.0 (0.8 - 5.0)
Tissue abnormality	29 (93.5)	2 (6.5)	0.7 (0.1 - 2.9)	0.7 (0.1 - 3.1)
Observations (n)			836	814
***p*-value (overall)**			0.005	0.021
	Grade 1	**Grade 2**	**Grade 3**	**Ordinal regression**	
Distinct mass	56 (24.0)	91 (39.1)	86 (36.9)	1.0	1.0
Ill-defined mass	34 (17.7)	95 (49.5)	63 (32.8)	1.0 (0.7 - 1.5)	0.8 (0.6 - 1.2)
Spiculated	127 (31.4)	210 (51.9)	68 (16.7)	0.5 (0.4 - 0.7)	0.5 (0.4 - 0.7)
Calcifications	22 (29.3)	32 (42.7)	21 (28.0)	0.7 (0.4 - 1.1)	0.9 (0.5 - 1.5)
Tissue abnormality	11 (34.4)	14 (43.8)	7 (21.8)	0.5 (0.2 - 1.0)	0.3 (0.1 - 0.6)
Observations (n)				937	912
***p*-value (overall)**				<0.001	<0.001
	Low Ki67	**Mid Ki67**	**High Ki67**	**Ordinal regression**	
Distinct mass	55 (27.9)	67 (34.0)	75 (38.1)	1.0	1.0
Ill-defined mass	49 (32.4)	45 (29.8)	57 (37.8)	0.9 (0.6 - 1.3)	0.8 (0.5 - 1.1)
Spiculated	146 (45.3)	110 (34.2)	66 (20.5)	0.5 (0.3 - 0.6)	0.5 (0.3 - 0.6)
Calcifications	21 (37.5)	16 (28.6)	19 (33.9)	0.7 (0.4 - 1.3)	0.9 (0.5 - 1.6)
Tissue abnormality	15 (50.0)	6 (20.0)	9 (30.0)	0.5 (0.2 - 1.0)	0.3 (0.2 - 0.8)
Observations (n)				756	737
***p*-value (overall)**				<0.001	<0.001

*Adjusted for age (categorical), tumor size, mode of detection, and breast density.
OR = odds ratio, OR_{adj} = adjusted odds ratio, CI= confidence interval.

Surrogate molecular subtypes

The distribution of surrogate molecular breast-cancer subtypes varied across mammographic tumor appearances (Table 3). Ill-defined masses were less likely to be the TNBC subtype than the luminal A-like subtype, as compared to distinct masses, with an adjusted relative risk ratio (RRR_{adj}) of 0.5 (95% CI 0.2–0.9) (Table 4). Spiculated tumors were less likely to be luminal B-like, HER2-positive, or TNBC than luminal A-like, as compared to distinct masses, with RRR_{adj} values of 0.6 (95% CI 0.4–1.0), 0.4 (95% CI 0.2–0.8), and 0.1 (95% CI 0.1–0.3), respectively (Table 4). In other words, spiculated tumors were associated with the luminal A-like subtype.

Table 3. Distribution of molecular subtypes across mammographic tumor appearances (paper I)
Number of tumors within each category of mammographic tumor appearance in each of the molecular subtype categories, illustrated with descriptive statistics. TNBC = triple-negative breast cancer.

Molecular subtype:	Luminal A	Luminal B	HER2+	TNBC
Mammographic appearance	n (%)	n (%)	n (%)	n (%)
Distinct mass	95 (46.8)	52 (25.6)	21 (10.3)	35 (17.3)
Ill-defined mass	67 (44.1)	43 (28.2)	25 (16.5)	17 (11.2)
Spiculated	215 (67.4)	74 (23.2)	20 (6.3)	10 (3.1)
Calcifications	23 (45.1)	12 (23.5)	9 (17.7)	7 (13.7)
Tissue abnormality	19 (63.3)	7 (23.3)	2 (6.7)	2 (6.7)
Observations (n)	419	188	77	71

Table 4. Mammographic tumor appearance in relation to surrogate molecular subtype (paper I)
Luminal A-like subtype is the reference subtype, and distinct mass is the reference mammographic tumor appearance. TNBC = triple-negative breast cancer. RRR = relative risk ratio.

Molecular subtype→	**Luminal A**	**Luminal B**	**HER2+**	**TNBC**
Mammographic appearance	**Crude**	**RRR (95% CI)**	**RRR (95% CI)**	**RRR (95% CI)**
Distinct mass	Reference	1.0	1.0	1.0
Ill-defined mass		1.2 (0.7 - 2.0)	1.7 (0.9 - 3.3)	0.7 (0.4 - 1.3)
Spiculated		0.6 (0.4 - 1.0)	0.4 (0.2 - 0.8)	0.1 (0.1 - 0.3)
Calcifications		1.0 (0.4 - 2.1)	1.8 (0.7 - 4.4)	0.8 (0.3 - 2.1)
Tissue abnormality		0.7 (0.3 - 1.7)	0.5 (0.1 - 2.2)	0.3 (0.1 - 1.3)
Observations (n)			755	
p-value (overall)			<0.001	
	Adjusted	**RRR_{adj}*(95% CI)**	**RRR_{adj}*(95% CI)**	**RRR_{adj}*(95% CI)**
Distinct mass	Reference	1.0	1.0	1.0
Ill-defined mass		0.9 (0.5 - 1.6)	1.4 (0.7 - 2.8)	0.5 (0.2 - 0.9)
Spiculated		0.6 (0.4 - 1.0)	0.4 (0.2 - 0.8)	0.1 (0.1 - 0.3)
Calcifications		1.4 (0.6 - 3.1)	2.4 (0.9 - 6.5)	0.9 (0.3 - 2.5)
Tissue abnormality		0.4 (0.1 - 1.1)	0.4 (0.1 - 1.7)	0.2 (0.0 - 0.8)
Observations (n)			737	
p-value (overall)			<0.001	

*Adjusted for age (categorical), tumor size, mode of detection, and breast density.
TNBC = triple-negative breast cancer. RRR = relative risk ratio, RRR_{adj} = adjusted relative risk ratio.

Paper II

In paper two, MDCS was used to examine breast-cancer-specific death in women diagnosed with breast cancer according to mammographic tumor appearance and breast density. During a median follow-up time of 10.7 years (range 0–27.1 years), 202 women died from breast cancer. The median follow-up time was 5.3 years among women who died from breast cancer and 11.7 years for the remaining 914 women, of which 214 women passed away due to other causes, and 4 women emigrated. Women who died from breast cancer were more often diagnosed clinically, had larger tumors with higher histological grade, and had higher prevalence of ALNI.

Breast density in relation to survival

Dense breast parenchyma did not significantly impact breast-cancer survival in comparison to fat-involuted and moderately dense parenchyma combined. The HR for breast-cancer mortality for women with dense breasts was 1.08 (95% CI 0.80–1.47), and it was similar after adjustment for confounding factors (HR_{adj} 1.15, 95% CI 0.79–1.68) (Table 5). Stratified analyses for women with screening-detected and clinically detected tumors did neither detect a statistically significant difference in survival (Table 5). Neither was breast density in a subset (n = 376) analyzed according to BI-RADS associated with breast cancer-specific survival (see Table 3 in appended paper II).

Table 5. Breast density in relation to breast-cancer-specific mortality (paper II)
a. Cox regression analysis based on the entire study population, followed by stratified analyses on **b**. women with screening-detected tumors , and **c**. women with clinically detected tumors.

a. Entire population	**Alive°**	**Deceased†**	**HR (95% CI)**	**HR_{adj}*(95% CI)**
Breast density	n (%)	n (%)		
Fat-involuted–mod. dense	581 (66.7)	109 (61.9)	1.0 (Ref.)	1.0 (Ref.)
Dense	290 (33.3)	67 (38.1)	1.08 (0.80 - 1.47)	1.15 (0.79 - 1.68)
Observations (n)			1046	864
p-value			0.609	0.466
b. Screening-detected				
Fat-involuted–mod. dense	329 (69.4)	34 (56.7)	1.0 (Ref.)	1.0 (Ref.)
Dense	145 (30.6)	26 (43.3)	1.45 (0.87 - 2.43)	1.29 (0.65 - 2.53)
Observations (n)			534	439
p-value			0.153	0.465
c. Clinically detected				
Fat-involuted–mod. dense	251 (63.4)	75 (64.7)	1.0 (Ref.)	1.0 (Ref.)
Dense	145 (36.6)	41 (35.3)	0.84 (0.57 - 1.23)	1.04 (0.65 - 1.65)
Observations (n)			512	424
p-value			0.359	0.872

° Alive or deceased from other causes. † Deceased due to breast cancer.
* Adjusted for age at diagnosis, body mass index, hormone replacement therapy, tumor size, ALNI, histological grade, and ER+.

Mammographic tumor appearance in relation to survival

Mammographically ill-defined tumors and tissue abnormalities were associated with a higher risk of death from breast cancer compared to distinct mass in the crude analysis (HR 1.64 (95% CI 1.07–2.51) and 2.37 (95% CI 1.26–4.46), respectively; Table 6). However, after adjustment the HRs were attenuated and statistically nonsignificant. Spiculated tumor appearance did not impact long-term survival in the whole population (HR_{adj} 1.24, CI 0.75–2.03) or after stratification by detection mode (Table 6). At 5 years after diagnosis, women with clinically detected spiculated tumors had significantly impaired survival compared to women with a distinct mass (HR_{adj} 2.77 (1.03–7.46); see appended A.3 in paper II).

Table 6. Tumor appearance in relation to breast-cancer-specific mortality (paper II)
a. Cox regression analysis based on the entire study population, followed by stratified analyses on **b.** women with screening-detected tumors , and **c.** women with clinically detected tumors.

a. Entire population	**Alive°**	**Deceased†**	**HR (95% CI)**	**HR_{adj}*(95% CI)**
Tumor appearance	n (%)	n (%)		
Distinct mass	228 (27.2)	38 (22.4)	1.0 (Ref.)	1.0 (Ref.)
Ill-defined mass	155 (18.5)	48 (28.2)	1.64 (1.07 - 2.51)	1.48 (0.88 - 2.49)
Spiculated	358 (42.7)	58 (34.1)	0.90 (0.60 - 1.35)	1.24 (0.75 - 2.03)
Calcifications	70 (8.3)	13 (7.6)	0.91 (0.48 - 1.70)	1.36 (0.61 - 3.03)
Tissue abnormality	28 (3.3)	13 (7.6)	2.37 (1.26 - 4.46)	2.02 (0.89 - 4.60)
Observations (n)	839	170	1009	818
p-value (overall)			0.001	0.438
b. Screening-detected				
Distinct mass	101 (21.1)	13 (23.6)	1.0 (Ref.)	1.0 (Ref.)
Ill-defined mass	79 (16.5)	9 (16.4)	0.85 (0.36 - 1.99)	0.89 (0.31 - 2.53)
Spiculated	230 (48.1)	23 (41.8)	0.76 (0.39 - 1.50)	0.89 (0.40 - 1.97)
Calcifications	56 (11.7)	6 (10.9)	0.74 (0.28 - 1.94)	0.87 (0.25 - 3.01)
Tissue abnormality	12 (2.5)	4 (7.3)	1.96 (0.64 - 6.03)	1.84 (0.38 - 8.89)
Observations (n)			533	430
p-value (overall)			0.483	0.915
c. Clinically detected				
Distinct mass	126 (35.0)	25 (21.7)	1.0 (Ref.)	1.0 (Ref.)
Ill-defined mass	76 (21.1)	39 (33.9)	2.06 (1.25 - 3.40)	1.77 (0.94 - 3.33)
Spiculated	128 (35.6)	35 (30.4)	1.24 (0.74 - 2.08)	1.57 (0.83 - 2.99)
Calcifications	14 (3.9)	7 (6.1)	1.75 (0.76 - 4.06)	1.77 (0.58 - 5.40)
Tissue abnormality	16 (4.4)	9 (7.8)	2.45 (1.14 - 5.26)	2.18 (0.79 - 6.02)
Observations (n)			475	387
p-value (overall)			0.021	0.420

° Alive or deceased from other causes. † Deceased due to breast cancer.
* Adjusted for age at diagnosis, density, tumor size, ALNI, histological grade and ER+.

Paper III

Paper III is based on a sub-cohort of women in the MDCS with radiology reports indicating a mammographically spiculated tumor appearance and diagnosis in 2004–2014. The study included a total of 161 women with a median age of 68 years (range 55–91 years) (Table 7). SMR on the diagnostic mammogram was inversely associated with breast density (p=0.030) (Table 7). SMR was associated with age at diagnosis (p=0.002) (Table 7). The mode of cancer detection was not significantly associated with the level of SMR (p=0.518) (Table 7).

In the 10% of women that exhibited the highest SMR values (>1.7), all tumors were ER-positive, most tumors showed low or intermediate Ki67 expression, and ALNI was rare compared to the rest of the population (see appended paper III).

Table 7. Baseline population characteristics according to degree of SMR (paper III)

Variable, n (%) if nothing else stated	All women (n=161)	Low SMR (n=56)	Moderate SMR (n=51)	High SMR (n=54)	*p*-value
Breast density					0.030
Fat involuted	36 (22)	10 (18)	9 (18)	17 (31)	
Moderately dense	86 (53)	26 (46)	29 (57)	31 (57)	
Dense	39 (24)	20 (36)	13 (25)	6 (11)	
Mode of cancer detection					0.518
Screening-detected	118 (73)	41 (73)	40 (78)	37 (69)	
Clinically detected	43 (27)	15 (27)	11 (22)	17 (31)	
Age in years, median (range)	68 (55–91)	66 (56–87)	67 (55–85)	71 (55–91)	0.002
Tumor size in mm, median (range)	15 (5–50)	17 (5–50)	14 (7–50)	14 (5–33)	0.165
Missing	3	0	0	3	
Estrogen receptor positivity	151 (96)	53 (95)	47 (96)	51 (98)	0.777
Missing	4	0	2	2	
Progesterone receptor positivity	122 (79)	43 (77)	39 (80)	40 (80)	0.907
Missing	6	0	2	4	
HER2 receptor positivity	8 (5)	2 (4)	3 (6)	3 (6)	0.818
Missing	6	2	1	3	
Ki67 expression					0.213
Low	54 (45)	21 (52)	18 (46)	15 (38)	
Intermediate	38 (32)	8 (20)	12 (31)	18 (45)	
High	27 (23)	11 (28)	9 (23)	7 (18)	
Missing	42	16	12	14	
Histological grade					0.051
I	49 (31)	11 (20)	22 (43)	16 (31)	
II	86 (54)	35 (62)	20 (39)	31 (60)	
III	24 (15)	10 (18)	9 (18)	5 (10)	
Missing	2	0	0	2	
Axillary-lymph-node involvement	45 (28)	17 (30)	16 (31)	12 (24)	0.631
Missing	3	0	0	3	

SMR in relation to survival

The median follow-up time in paper III was 8.45 years, during which 18 women died from breast cancer, and 33 died from other causes. Women with moderate and high SMR had non-significantly increased HRs for breast-cancer-specific death compared to women with low SMR (HR 2.01 (95% CI 0.59–6.89) and 1.88 (95% CI 0.55–6.42), respectively; Table 8). After adjustment for age and breast density, the HRs for breast-cancer death for moderate and high SMR remained nonsignificant with large CIs (HR 2.04 (95% CI 0.59–6.99) and 1.92 (95% CI 0.55–6.65), respectively; Table 8). This was also the case when the analysis was adjusted for tumor size (data not shown, see appended paper III).

Table 8. SMR status in relation to breast-cancer-specific mortality (paper III)
Cox regression analysis studying the impact of degree of SMR on breast-cancer-specific survival.

SMR	Alive	†	†BC	HR (95% CI)	HR_{adj}* (95% CI)	HR_{adj}** (95% CI)
Low	46	10	4	1	1	1
Moderate	43	8	7	2.01 (0.59–6.89)	1.89 (0.55–6.47)	2.04 (0.59–6.99)
High	39	15	7	1.88 (0.55–6.42)	1.00 (0.28–3.54)	1.92 (0.55–6.65)
Overall *p*-value				0.459	0.462	0.448
Observations	128	33	18			

† Deceased. †BC Deceased due to breast cancer.
* Adjusted for age only.
** Adjusted for breast density only.

Paper IV

The fourth paper included 68 women who were examined with a study-specific CSE-MRI sequence to estimate fatty acid composition, in addition to their clinical DCE-MRI protocol. In this group, 12 women had breast cancer. With a median age of 53 years, women who had breast cancer were older compared to those without breast cancer, who had a median age of 42 years. A larger proportion of the 12 women with breast cancer were postmenopausal than the women without breast cancer (58.3% vs. 30.4%). Women with breast cancer had a slightly higher median content of adipose tissue in their breasts (67.1%) than those without breast cancer (63.7%), likely explained by the age difference between the groups. PUFA levels were similar for women with and without breast cancer, averaging 9.5%, which was also the case for SFA, which averaged 35% both for women with and without breast cancer. For detailed baseline characteristics, see paper IV in the appendix.

Relative adipose tissue content decreased significantly with increasing breast density ($p < 3\times10^{-9}$), and relative adipose tissue content was lower in premenopausal women than in postmenopausal women (p=0.0046) (Figure 10). No significant associations were found between PUFA and breast density or menopausal status nor between SFA, breast density, and menopausal status (Figure 10).

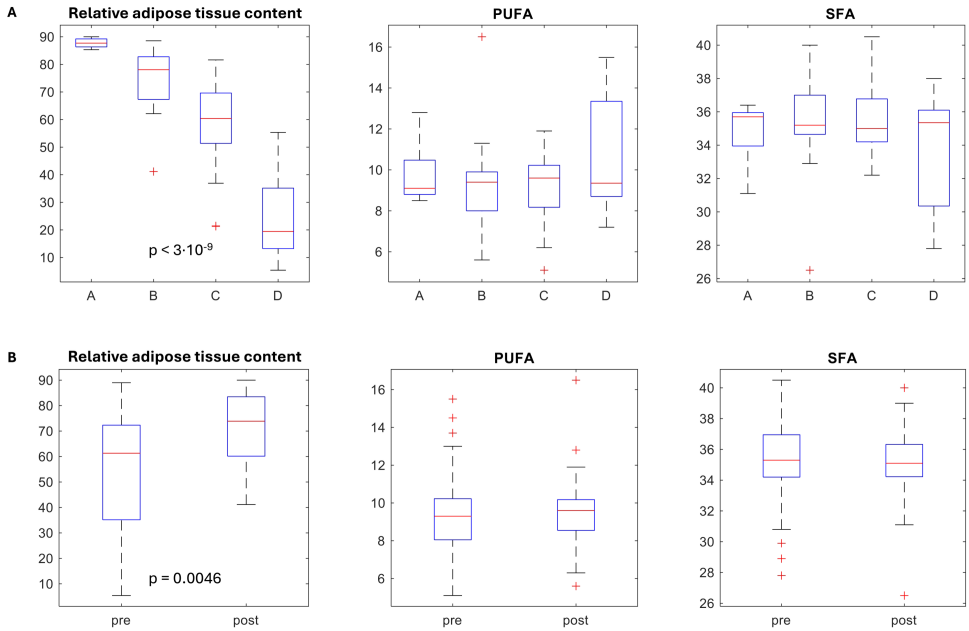

Figure 10. Fatty acid components in relation to breast density and menopausal status (paper IV)
Relative adipose tissue content, polyunsaturated fatty acids (PUFAs) and saturated fatty acids (SFAs) in the full population (n=68) stratified by **A**) breast density (a–d), according to BI-RADS 5th edition (Kruskal–Wallis test), and **B**) postmenopausal status (Wilcoxon rank-sum test). Numbers in percentages on the y axis.

Among the 12 women with breast cancer, seven had invasive carcinoma of no special type, two had invasive lobular carcinoma, and three had DCIS. Most invasive cancers occurred in postmenopausal women, whereas all women with DCIS were premenopausal.

Among women with unilateral breast cancer, the cancer-affected breast had significantly lower adipose tissue content than the contralateral breast according to paired analysis (p=0.0065). In paired analyses, the median PUFA value in the cancer-affected breast was lower than in the contralateral breast, while median SFA was higher in the cancer-affected breast compared to the contralateral breast. However, these results did not meet statistical significance (PUFA p=0.705, SFA p=0.607) (Table 9).

No significant differences in median PUFA or median SFA were observed between regions at different distance from the tumor in the cancer-affected breast as compared to the corresponding areas in the contralateral breast. Numerically, the median SFA value was highest in the ROI closest to the tumor in the cancer-affected breast, albeit non-significantly (p=0.447) (Table 10).

Table 9. Comparison of the cancer-affected breast to the contralateral breast (paper IV)

Overall relative adipose tissue content, PUFA, and SFA° in % based on the entire breast volume in the cancer-affected breast, and the contralateral breast. The right side shows results from paired tests comparing the cancer-affected breast vs. the contralateral breast.

All women with unilateral breast cancer identifiable on MR (n = 10)							
	Cancer-affected breast		Contralateral breast		Paired test: cancer-affected breast vs. contralateral*		
Parameter	median	IQR	median	IQR	median	IQR	*p*-value
rATC	53.6	30.9	68.3	29.3	−5.2	5.3	0.006
PUFA	8.8	2	9.1	1.5	0	0.8	0.705
SFA	36	2.4	35.5	1.8	0.1	0.9	0.607

°PUFA = polyunsaturated fatty acids, SFA = saturated fatty acids.
IQR = interquartile range, rATC = relative adipose tissue content.
*Wilcoxon signed-rank test.

Table 10. ROIs in the cancer-affected breast versus ROIs in contralateral breast (paper IV)

ROI values (%) of PUFA and SFA° in the cancer-affected breast and in the mirrored location in the contralateral breast. The right side shows results of paired tests comparing values in the cancer-affected breast vs. the mirrored locations in the contralateral breast.

All women with unilateral breast cancer identifiable on MR (n = 10)							
	ROI 1		**ROI 1^{contra}**		**Paired test: ROI 1 vs. ROI 1^{contra}***		
Parameter	median	IQR	median	IQR	median	IQR	*p*-value
PUFA	5.8	3.7	8.2	4.6	−1	4.1	0.334
SFA	39.8	4.4	36.7	5.6	1.2	5	0.447
	ROI 2		**ROI 2^{contra}**		**Paired test: ROI 2 vs. ROI 2^{contra}***		
Parameter	median	IQR	median	IQR	median	IQR	*p*-value
PUFA	8.5	4.5	9.7	5	−0.7	2.7	0.445
SFA	36.4	5.5	35	6.2	0.8	3.3	0.445

°PUFA = polyunsaturated fatty acids, SFA = saturated fatty acids.
ROI = region of interest, IQR = interquartile range.
*Wilcoxon signed-rank test.

Discussion

Most important findings

Mammographically spiculated tumors were more often the favorable luminal A subtype of breast cancer compared to other molecular subtypes. Variations in mammographic tumor appearance and breast density at diagnosis were, however, not significantly associated with breast-cancer mortality in long-term follow-up. Neither was the novel image-based metric SMR for mammographically spiculated tumors associated with breast-cancer mortality. SMR was associated with age and breast density.

Relative adipose tissue content from CSE-MRI correlated well with mammographic breast density, indicating that it correctly identifies adipose tissue. The CSE-MRI estimates of fatty acid composition showed similar levels of SFA and PUFA as adipose tissue analyzed with gas chromatography. The sample was however small, and further studies are needed to evaluate its accuracy.

Thesis in context

Paper I

For the first paper, we adopted a classification system with five subgroups of tumor appearance, including spiculated appearance. In comparison with mammographically distinct masses, the spiculated tumors stood out as significantly more often being ER and PR positive, more commonly having lower histological grade and lower Ki67, and more often having the luminal-A-like subtype. This pattern signals favorable tumor biology and has been consistent across multiple studies, despite methodological differences.[194-203]

The evidence for mammographically ill-defined tumors is less uniform than for spiculated tumors. Studies have reported associations between lesions with indistinct margins and TNBC, and the HER2-positive subtype.[200, 225, 234, 235] In our cohort, a larger proportion of the ill-defined tumors were of HER2-positive subtype and TNBC, compared to the spiculated tumors. But compared to distinct masses,

the ill-defined tumors in our study were less likely to be TNBC than Luminal A-like in adjusted analysis.

Subcategories of microcalcifications have long been linked to HER2 positivity,[236-238] while spiculation is linked to HER2 negativity.[194, 196] Reviews and observational studies continue to show that HER2-positive tumors often present with calcifications.[206, 239] Our frequencies pointed in the same direction, with a relatively large proportion of the tumors presenting as calcifications being HER2-positive subtype, and we found a statistically non-significantly increased relative risk ratio for being HER2-positive subtype in tumors presenting with calcifications. Specific morphologies like branching-type microcalcifications have been associated with poorer outcomes and hormone-receptor negativity.[209] By combining all types of microcalcifications, as in paper I, associations of specific calcification subtypes could have been diluted.

A distinct mass is a common finding on breast imaging. Although such masses are often benign, they can also represent malignant lesions, warranting further diagnostic investigation.[183] In paper I, we found that 17.3% of the distinct masses were TNBC, whereas only 3.1% of spiculated tumors were TNBC. This distribution aligns with previous studies showing that TNBC often presents as a distinct mass.[184, 185, 240] Overall, the results in paper I are broadly consistent with previous studies, although direct comparisons are constrained by the use of different classification systems for tumor appearance. Also, the choice of statistical method for comparing tumor appearances vary, which makes it hard to directly compare many studies. Lastly, variation in age of the studied population is also important to consider when comparing studies.

Paper II

Neither the level of mammographic breast density nor mammographic tumor appearance were significantly associated with breast-cancer-specific survival in paper II. Earlier MDCS work reported lower survival for women with dense breasts, particularly with symptomatic detection.[241] This association was not replicated in paper II, in which both the cohort size and the follow-up time were extended.[148] Also, the studies differ in how the density categories were compared. In paper II the women with the densest breasts were compared to women with the two less dense categories combined, while the earlier MDCS study compared women with dense breasts to women with fat involuted breasts.[241] A Swedish neoadjuvant cohort linked BI-RADS d density score to higher risk of recurrence and breast-cancer-specific death and suggested that extreme density may carry prognostic information in the context of neoadjuvant chemotherapy.[242] On the other hand, a contemporary study using area-based density measurements in a cohort of 224 women with breast cancer reported significantly better breast-cancer–specific survival among women with high mammographic density compared with those with low density.[243] Even if

breast density may not influence prognosis once cancer has developed, women with dense breasts have higher risk of breast-cancer death due to elevated baseline risk of developing breast cancer.[244]

Despite the favorable traits of spiculated tumors at diagnosis, as reported in paper I, the results did not translate into a survival advantage in paper II. It remains unclear which aspects of mammographic spiculation reflect favorable biology, why studies linking components of spiculation (such as spicule length, width, and number) to the molecular mammary microenvironment can be of interest. The results in paper II align with reports that neither breast density nor specific tumor appearances impact breast-cancer survival once breast cancer is established.[174, 245] Our findings support a nuanced clinical message: high density is a strong risk phenotype, and spiculation indicates favorable characteristics at diagnosis, but neither grants a survival advantage or disadvantage at the population level once the breast cancer is diagnosed.

Paper III

The degree of spiculation in mammographically spiculated tumors, assessed using the novel metric SMR, did not predict breast-cancer mortality. SMR was higher in older women and those with fat-involuted breasts, which may be due to improved conspicuity of radiating spicules in these women. Several previous studies have reported that the spiculated appearance is more common in older women.[189, 195, 198] Plausibly, this may be due to increasing fat involution and improved conspicuity of radiating spicules in older women. SMR was not significantly associated with breast-cancer-specific survival or ALNI. Although some report better survival for women with spiculated tumors versus other appearances,[198, 202, 203] we did not confirm this in our MDCS survival study (paper II).[148] The findings in paper III extend the findings from paper II, that neither the degree of spiculation was significantly associated with breast-cancer mortality.

The study sample was relatively small with few events, and it is possible that limited statistical power contributed to the non-significant correlation between SMR and breast-cancer mortality. The tumors were segmented manually, and because the visibility of spiculation is strongly influenced by breast density, this may also have affected the results. Possibly, future radiomics and AI-assisted quantification can be less sensitive for dense breast parenchyma and could be used to extract richer descriptors of spicules (e.g., length distribution, angular differences, and complexity) that might be used to assess prognosis. Beyond mammography, digital breast tomosynthesis and MRI could potentially improve spicule detection and include three-dimensional characterization, which could reduce tissue overlap and measurement bias.

Paper IV

In the last paper, the focus shifted from tumor morphology and density towards breast adipose tissue and estimations of fatty acid composition. We found that the relative adipose content in breasts using CSE-MRI decreased with higher mammographic density and was higher in postmenopausal women. These findings are consistent with a validation of this CSE-MRI technique as an imaging biomarker for density.[246]

We found no differences in PUFA or SFA levels across breast density categories or by menopausal status. This contrasts with the results reported by Freed et al.,[48] who observed significantly higher PUFA and lower SFA in postmenopausal women compared with premenopausal women. The overall proportions of PUFA and SFA in adipose tissue from both breasts were nearly identical among women with non-cancerous and cancerous findings. The reason for this might be that any local alterations in fatty-acid composition adjacent to cancerous tissue are too subtle to influence measurements derived from whole-breast volumes.

A previous study reported reasonable agreement regarding fatty acid composition with gas chromatography and the employed CSE-MRI technique, while acknowledging overestimation of SFA and underestimation of PUFA by MRI versus gas chromatography, as was also the case in paper IV.[247] Several previous studies have investigated the same CSE-MRI technique in breast adipose tissue,[49-51, 246, 248-250] but paper IV is to our knowledge the first to compare fatty acid composition from CSE-MRI with fatty acid composition from gas chromatography.

In unilateral cancers, the cancer-affected breast had lower adipose content overall than the contralateral breast, while whole-breast PUFA and SFA differences were not significant. In ROIs adjacent to cancer, SFA content was higher than in the other locations, although non-significantly. Similar peri-tumoral fatty acid composition with higher proportions of SFA have been reported in other studies.[48-51]

Methodological considerations and limitations

Confounding

TNM stage and overdiagnosis represent two important potential confounders in Paper II, as highlighted by Bell et al. in their accompanying editorial.[251] Since cancers in dense breasts tends to be diagnosed at a later stage due to the masking effect, the TNM stage might have substantially influenced the results in stratified analyses on the impact of density on survival in screening-detected cancer. The editorial pointed out that the reported increase in mortality risk for women with high density and screen-detected breast cancer could be attributable, at least in part, to this confounding.[251] In our analyses, adjustment for tumor size (a key component of TNM staging) resulted in a decrease of the mortality risk estimate, supporting the conclusion that TNM stage acts as a relevant confounder.

Overdiagnosis of indolent cancers might also have affected the results in stratified analyses on screening-detected cancers. Women with fat-involved parenchyma are more likely to be diagnosed with small and possibly over-diagnosed cancers as these cancers are more easily perceivable in fat-involuted breasts. Therefore, better breast-cancer survival for women with possibly over-diagnosed cancer might have caused an apparent increase in mortality for women with dense breasts.[251]

Selection bias and generalizability

Participants in the MDCS have higher education levels and better health than the average female population,[219] introducing selection bias that limits the generalizability of absolute risk estimates and survival outcomes. Survival outcomes are expected to be vulnerable to selection and adherence effects: healthier women are more likely to attend screening and to have independently better overall survival, which might have influenced survival estimates. Women with high education level and overall good health also have a higher risk of developing breast cancer, which complicates the interpretation of the data in the MDCS.

Internal comparisons within the cohort, such as associations between mammographic tumor appearance and histopathological features, are likely to be more robust to such selection effects. However, potential influences from selection bias cannot be completely dismissed in this case either. As a single-center study, the MDCS also might have problems with external generalizability.

Overall survival vs. breast-cancer-specific survival

Overall survival accounts for all deaths, irrespective of cause. Breast-cancer-specific survival only accounts for death attributed to breast cancer. Overall survival is the broadest outcome but is heavily influenced by competing causes of death, requiring larger sample sizes and longer follow-up to detect effects related to breast cancer. Breast-cancer-specific survival is generally more sensitive to disease-

specific factors such as screening-related differences and was therefore selected as the primary outcome in Papers II and III. Given that our main exposures relate specifically to mammographic features, this choice minimizes dilution of effect estimates by unrelated causes of death. A known limitation of breast-cancer-specific survival, however, is the potential for misclassification of cause of death in registry data.

Harmonization of breast imaging features

Comparability across studies is often complicated by heterogeneous categorizations of mammographic features, which includes both mammographic tumor appearance[184, 196, 202] and density.[174] To enhance interpretability and alignment with the international literature, Paper II employed the four-category BI-RADS density classification, despite our local clinical practice using a three-category system. Future studies aiming to integrate or compare imaging features would benefit from standardized definitions or systematic translation between local and internationally recognized classification systems.

Considerations regarding paper IV

Paper IV was designed as an exploratory study and was constrained by available data and study opportunities. The sample size was small and non-representative, which clearly restricts generalizability. In addition, manual delineation of ROIs may have introduced measurement error and reduced reproducibility. Despite these limitations, we observed numerically higher SFA values in tissue adjacent to breast cancer compared with distant tissue, although the difference did not reach statistical significance. A true biological difference may exist but could have remained undetected due to limited statistical power. Larger, prospective studies incorporating automated segmentation methods and computer-assisted quantification would help reduce measurement bias, improve reproducibility, and provide more definitive evidence.

Conclusion

Conclusions for the separate papers

I. Mammographic tumor appearance was strongly associated with clinicopathological factors, and spiculation consistently indicated favorable characteristics. This may be important complementary information during initial breast cancer assessment.

II. Neither breast density at diagnosis nor mammographic tumor appearance did significantly predict breast-cancer-specific survival in a large population-based cohort with long-term follow-up.

III. The SMR was higher in older women and those with fat-involuted breasts but showed no association with survival or axillary metastases, which limits its prognostic utility.

IV. CSE-MRI-derived adipose-tissue content decreased with increasing breast density and was lower in cancer-affected breasts compared with the contralateral breast. The MRI method shows potential for characterizing fatty acid composition in breast, but further studies are needed to determine its clinical applicability.

Future perspectives

This thesis demonstrates that human interpretation of radiological breast images reflects clinicopathological variables. However, radiological images also contain information that is not readily visible to the human eye. Manual annotation and interpretation are labor-intensive and subject to inter- and intra-reader variability. Therefore, a natural next step is to complement manual reading with objective software-based quantification, potentially involving artificial intelligence. The papers in this thesis could be used as a foundation for such studies.

Whether using manual or computed imaging variables, a practical goal is to develop tools that can be integrated into clinical workflows to support breast-cancer management. Given an aging population and rising breast-cancer incidence, such tools may also help allocate limited health care resources more efficiently. As screening evolves toward more personalized approaches,[252] image-based tools that provide information on breast tumor and tissue characteristics may help to tailor screening intervals and follow-up strategies. Identifying tumors with aggressive features may guide appropriate treatment escalation, while recognizing indolent, slow-growing lesions could support safe treatment de-escalation.

Regarding paper IV on MRI-derived fatty acid composition, additional validation is required before clinical implementation. Whole-breast averages may dilute important regional differences in fatty acid composition, making spatially resolved analyses (e.g., ROI-based approaches) important also in future work. It also remains to be determined whether potential changes in MRI-derived fatty acid composition precede cancer development, follow it, or evolve in parallel. The clinical utility of peri-tumoral fatty acid composition can be evaluated across different settings, including risk stratification in screening and surveillance, prognostication at diagnosis, and treatment monitoring.

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References

1. Bray, F.; Laversanne, M.; Sung, H., et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA Cancer J Clin*. **2024,** ***74,*** 229-263.
2. Regionala cancercentrum i samverkan *Nationellt vårdprogram för bröstcancer; version 5.4 (National Breast Cancer Care Program, in Swedish)*, https://kunskapsbanken.cancercentrum.se/diagnoser/brostcancer/vardprogram/.
3. Xiong, X.; Zheng, L. W.; Ding, Y., et al. Breast cancer: pathogenesis and treatments, *Signal Transduct Target Ther*. **2025,** ***10,*** 49.
4. Kim, J.; Harper, A.; McCormack, V., et al. Global patterns and trends in breast cancer incidence and mortality across 185 countries, *Nature Medicine*. **2025,** ***31,*** 1154-1162.
5. Jatoi, I.; Pinsky, P. F. Breast Cancer Screening Trials: Endpoints and Overdiagnosis, *JNCI: Journal of the National Cancer Institute*. **2020,** ***113,*** 1131-1135.
6. Conti, A.; Duggento, A.; Indovina, I.; Guerrisi, M.; Toschi, N. Radiomics in breast cancer classification and prediction, *Semin Cancer Biol*. **2021,** ***72,*** 238-250.
7. Socialstyrelsen (Statistics on cancer incidence 2024.). Swedish National Board of Health and Welfare, 2025.
8. Ugai, T.; Sasamoto, N.; Lee, H. Y., et al. Is early-onset cancer an emerging global epidemic? Current evidence and future implications, *Nat Rev Clin Oncol*. **2022,** ***19,*** 656-673.
9. Cancerfonden *Statistik bröstcancer (breast cancer statistics)*, https://www.cancerfonden.se/om-cancer/statistik/brostcancer, 2025.
10. Socialstyrelsen *Bröstcancer – screening med mammografi (in Swedish)*, https://www.socialstyrelsen.se/kunskapsstod-och-regler/regler-och-riktlinjer/nationella-screeningprogram/remissversioner/brostcancer/, 2023.
11. Socialstyrelsen (Swedish National Board of Health and Welfare), https://www.socialstyrelsen.se/en/about-us/.
12. Lagerlund, M.; Åkesson, A.; Zackrisson, S. Population-based mammography screening attendance in Sweden 2017-2018: A cross-sectional register study to assess the impact of sociodemographic factors, *Breast (Edinburgh, Scotland)*. **2021,** ***59,*** 16-26.
13. van der Waal, D.; Verbeek, A. L. M.; Broeders, M. J. M. Breast density and breast cancer-specific survival by detection mode, *BMC cancer*. **2018,** ***18,*** 386.
14. Swedish National Quality Register for Breast Cancer (NKBC) *Yearly report for 2024*, https://statistik.incanet.se/brostcancer/, 2025.

15. Shin, S. J.; Chen, Y.-Y.; Ginter, P. S. *A Comprehensive Guide to Core Needle Biopsies of the Breast*, 2 edn. Cham: Springer International Publishing, 2022.
16. Rubio, I. T.; Wyld, L.; Marotti, L., et al. European guidelines for the diagnosis, treatment and follow-up of breast lesions with uncertain malignant potential (B3 lesions) developed jointly by EUSOMA, EUSOBI, ESP (BWG) and ESSO, *European Journal of Surgical Oncology*. **2024, *50,*** 107292.
17. The benefits and harms of breast cancer screening: an independent review, *Lancet (London, England)*. **2012, *380,*** 1778-1786.
18. Marmot, M. G.; Altman, D. G.; Cameron, D. A., et al. The benefits and harms of breast cancer screening: an independent review, *British Journal of Cancer*. **2013, *108,*** 2205-2240.
19. Gøtzsche, P. C.; Jørgensen, K. J. Screening for breast cancer with mammography, *Cochrane Database Syst Rev*. **2013, *2013,*** Cd001877.
20. Myers, E. R.; Moorman, P.; Gierisch, J. M., et al. Benefits and Harms of Breast Cancer Screening: A Systematic Review, *Jama*. **2015, *314,*** 1615-1634.
21. Joe, B. N.; Sickles, E. A. The evolution of breast imaging: past to present, *Radiology*. **2014, *273,*** S23-44.
22. Marcon, M.; Fuchsjäger, M. H.; Clauser, P.; Mann, R. M. ESR Essentials: screening for breast cancer - general recommendations by EUSOBI, *European radiology*. **2024,** DOI 10.1007/s00330-024-10740-5.
23. Gommers, J.; Hernström, V.; Josefsson, V., et al. Interval cancer, sensitivity, and specificity comparing AI-supported mammography screening with standard double reading without AI in the MASAI study: a randomised, controlled, non-inferiority, single-blinded, population-based, screening-accuracy trial, *The Lancet*. **2026, *407,*** 505-514.
24. Jesinger, R. A. Breast Anatomy for the Interventionalist, *Techniques in Vascular and Interventional Radiology*. **2014, *17,*** 3-9.
25. Bland, K. I.; Copeland, E. M.; Klimberg, V. S.; Gradishar, W. J. *The Breast - E-Book: Comprehensive Management of Benign and Malignant Diseases*: Elsevier, 2023.
26. Alex, A.; Bhandary, E.; McGuire, K. P. Anatomy and Physiology of the Breast during Pregnancy and Lactation, *Adv Exp Med Biol*. **2020, *1252,*** 3-7.
27. Russo, J.; Russo, I. H. Development of the human breast, *Maturitas*. **2004, *49,*** 2-15.
28. Rakha, E.; Toss, M.; Quinn, C. Specific cell differentiation in breast cancer: a basis for histological classification, *J Clin Pathol*. **2022, *75,*** 76-84.
29. WHO Classification of Tumours Editorial Board *Breast Tumours*, Lyon (France): International Agency for Research on Cancer, 2019.
30. Hanahan, D.; Weinberg, R. A. The Hallmarks of Cancer, *Cell*. **2000, *100,*** 57-70.
31. Hanahan, D.; Weinberg, Robert A. Hallmarks of Cancer: The Next Generation, *Cell*. **2011, *144,*** 646-674.
32. Hanahan, D. Hallmarks of Cancer: New Dimensions, *Cancer Discov*. **2022, *12,*** 31-46.

33. Delmas, D.; Mialhe, A.; Cotte, A. K., et al. Lipid metabolism in cancer: Exploring phospholipids as potential biomarkers, *Biomedicine & Pharmacotherapy*. **2025,** ***187,*** 118095.
34. Chen, M.; Huang, J. The expanded role of fatty acid metabolism in cancer: new aspects and targets, *Precision Clinical Medicine*. **2019,** ***2,*** 183-191.
35. Ackerman, D.; Simon, M. C. Hypoxia, lipids, and cancer: surviving the harsh tumor microenvironment, *Trends in Cell Biology*. **2014,** ***24,*** 472-478.
36. Young, R. M.; Ackerman, D.; Quinn, Z. L., et al. Dysregulated mTORC1 renders cells critically dependent on desaturated lipids for survival under tumor-like stress, *Genes Dev*. **2013,** ***27,*** 1115-1131.
37. Beloribi-Djefaflia, S.; Vasseur, S.; Guillaumond, F. Lipid metabolic reprogramming in cancer cells, *Oncogenesis*. **2016,** ***5,*** e189.
38. Snaebjornsson, M. T.; Janaki-Raman, S.; Schulze, A. Greasing the Wheels of the Cancer Machine: The Role of Lipid Metabolism in Cancer, *Cell Metab*. **2020,** ***31,*** 62-76.
39. Borgquist, S.; Butt, T.; Almgren, P., et al. Apolipoproteins, lipids and risk of cancer, *International journal of cancer*. **2016,** ***138,*** 2648-2656.
40. Mosconi, E.; Minicozzi, A.; Marzola, P.; Cordiano, C.; Sbarbati, A. (1) H-MR spectroscopy characterization of the adipose tissue associated with colorectal tumor, *Journal of magnetic resonance imaging : JMRI*. **2014,** ***39,*** 469-474.
41. Iordanescu, G.; Brendler, C.; Crawford, S. E.; Wyrwicz, A. M.; Venkatasubramanian, P. N.; Doll, J. A. MRS measured fatty acid composition of periprostatic adipose tissue correlates with pathological measures of prostate cancer aggressiveness, *Journal of magnetic resonance imaging : JMRI*. **2015,** ***42,*** 651-657.
42. Hodson, L.; Skeaff, C. M.; Fielding, B. A. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake, *Progress in Lipid Research*. **2008,** ***47,*** 348-380.
43. Cinti, S. The adipose organ at a glance, *Disease Models & Mechanisms*. **2012,** ***5,*** 588-594.
44. Currie, E.; Schulze, A.; Zechner, R.; Walther, Tobias C.; Farese, Robert V., Jr. Cellular Fatty Acid Metabolism and Cancer, *Cell Metabolism*. **2013,** ***18,*** 153-161.
45. Mei, J.; Qian, M.; Hou, Y., et al. Association of saturated fatty acids with cancer risk: a systematic review and meta-analysis, *Lipids Health Dis*. **2024,** ***23,*** 32.
46. Wang, Y. Y.; Attané, C.; Milhas, D., et al. Mammary adipocytes stimulate breast cancer invasion through metabolic remodeling of tumor cells, *JCI Insight*. **2017,** ***2,*** e87489.
47. Peterson, P.; Trinh, L.; Månsson, S. Quantitative (1) H MRI and MRS of fatty acid composition, *Magn Reson Med*. **2021,** ***85,*** 49-67.
48. Freed, M.; Storey, P.; Lewin, A. A., et al. Evaluation of Breast Lipid Composition in Patients with Benign Tissue and Cancer by Using Multiple Gradient-Echo MR Imaging, *Radiology*. **2016,** ***281,*** 43-53.

49. Lewin, A. A.; Storey, P.; Moccaldi, M.; Moy, L.; Gene Kim, S. Fatty acid composition in mammary adipose tissue measured by Gradient-echo Spectroscopic MRI and its association with breast cancers, *European journal of radiology*. **2019, *116,*** 205-211.
50. Cheung, S. M.; Chan, K. S.; Zhou, W., et al. Spatial heterogeneity of peri-tumoural lipid composition in postmenopausal patients with oestrogen receptor positive breast cancer, *Scientific reports*. **2024, *14,*** 4699.
51. Chaudhary, S.; Lane, E. G.; Levy, A., et al. Estimation of fatty acid composition in mammary adipose tissue using deep neural network with unsupervised training, *Magn Reson Med*. **2025, *93,*** 2163-2175.
52. Singletary, S. E. Rating the risk factors for breast cancer, *Annals of surgery*. **2003, *237,*** 474-482.
53. 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 (London, England)*. **2002, *360,*** 187-195.
54. Hinkula, M.; Pukkala, E.; Kyyrönen, P.; Kauppila, A. Grand multiparity and the risk of breast cancer: population-based study in Finland, *Cancer causes & control : CCC*. **2001, *12,*** 491-500.
55. Narod, S. A. Hormone replacement therapy and the risk of breast cancer, *Nat Rev Clin Oncol*. **2011, *8,*** 669-676.
56. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies, *Lancet (London, England)*. **1996, *347,*** 1713-1727.
57. Cibula, D.; Gompel, A.; Mueck, A. O., et al. Hormonal contraception and risk of cancer, *Hum Reprod Update*. **2010, *16,*** 631-650.
58. Fabre, A.; Fournier, A.; Mesrine, S., et al. Oral progestagens before menopause and breast cancer risk, *Br J Cancer*. **2007, *96,*** 841-844.
59. Kim, J.; Munster, P. N. Estrogens and breast cancer, *Annals of oncology : official journal of the European Society for Medical Oncology*. **2025, *36,*** 134-148.
60. Hadizadeh, F.; Koteci, A.; Karlsson, T.; Ek, W. E.; Johansson, Å. Hormonal Contraceptive Formulations and Breast Cancer Risk in Adolescents and Premenopausal Women, *JAMA Oncology*. **2025,** DOI 10.1001/jamaoncol.2025.4480.
61. Trabert, B.; Sherman, M. E.; Kannan, N.; Stanczyk, F. Z. Progesterone and Breast Cancer, *Endocr Rev*. **2020, *41,*** 320-344.
62. Iyengar, N. M.; Gucalp, A.; Dannenberg, A. J.; Hudis, C. A. Obesity and Cancer Mechanisms: Tumor Microenvironment and Inflammation, *Journal of Clinical Oncology*. **2016, *34,*** 4270-4276.
63. Virassamy, B.; Caramia, F.; Savas, P., et al. Parity and lactation induce T cell mediated breast cancer protection, *Nature*. **2025,** DOI 10.1038/s41586-025-09713-5.

64. Schacht, D. V.; Yamaguchi, K.; Lai, J.; Kulkarni, K.; Sennett, C. A.; Abe, H. Importance of a Personal History of Breast Cancer as a Risk Factor for the Development of Subsequent Breast Cancer: Results From Screening Breast MRI, *American Journal of Roentgenology*. **2014,** ***202,*** 289-292.
65. Lizarraga, I. M.; Sugg, S. L.; Weigel, R. J.; Scott-Conner, C. E. H. Review of risk factors for the development of contralateral breast cancer, *The American Journal of Surgery*. **2013,** ***206,*** 704-708.
66. Dyrstad, S. W.; Yan, Y.; Fowler, A. M.; Colditz, G. A. Breast cancer risk associated with benign breast disease: systematic review and meta-analysis, *Breast cancer research and treatment*. **2015,** ***149,*** 569-575.
67. Azzollini, J.; Fontana, L.; Manoukian, S. Hereditary Breast CancerBreast cancer: BRCA and Other Susceptibility GenesSusceptibility genes. In *Breast MRI for High-risk Screening* (Sardanelli, F. and Podo, F. (eds.)). Cham: Springer International Publishing, 2020, 23-41.
68. Boyd, N. F.; Guo, H.; Martin, L. J., et al. Mammographic density and the risk and detection of breast cancer, *The New England journal of medicine*. **2007,** ***356,*** 227-236.
69. Larsson, S. C.; Mason, A. M.; Cronjé, H. T., et al. Alcohol consumption and risk of cancer: a Mendelian randomization analysis of four biobanks and consortium data, *BMC Med*. **2025,** ***23,*** 676.
70. Lescinsky, H.; Afshin, A.; Ashbaugh, C., et al. Health effects associated with consumption of unprocessed red meat: a Burden of Proof study, *Nat Med*. **2022,** ***28,*** 2075-2082.
71. Cui, Y.; Miller, A. B.; Rohan, T. E. Cigarette smoking and breast cancer risk: update of a prospective cohort study, *Breast cancer research and treatment*. **2006,** ***100,*** 293-299.
72. Lin, Y.; Kikuchi, S.; Tamakoshi, K., et al. Active smoking, passive smoking, and breast cancer risk: findings from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk, *J Epidemiol*. **2008,** ***18,*** 77-83.
73. White, A. J.; D'Aloisio, A. A.; Nichols, H. B.; DeRoo, L. A.; Sandler, D. P. Breast cancer and exposure to tobacco smoke during potential windows of susceptibility, *Cancer causes & control : CCC*. **2017,** ***28,*** 667-675.
74. Papantoniou, K.; Castaño-Vinyals, G.; Espinosa, A., et al. Breast cancer risk and night shift work in a case-control study in a Spanish population, *Eur J Epidemiol*. **2016,** ***31,*** 867-878.
75. Mesurolle, B.; Qanadli, S. D.; Merad, M., et al. Unusual radiologic findings in the thorax after radiation therapy, *Radiographics : a review publication of the Radiological Society of North America, Inc*. **2000,** ***20,*** 67-81.
76. Perou, C. M.; Sorlie, T.; Eisen, M. B., et al. Molecular portraits of human breast tumours, *Nature*. **2000,** ***406,*** 747-752.
77. Union for International Cancer Control (UICC) *TNM classification of malignant tumours*, 9 edn. Newark: Wiley, 2025.

78. Menta, A.; Fouad, T. M.; Lucci, A., et al. Inflammatory Breast Cancer: What to Know About This Unique, Aggressive Breast Cancer, *Surg Clin North Am*. **2018, *98,*** 787-800.

79. Kanitakis, J. Mammary and extramammary Paget's disease, *Journal of the European Academy of Dermatology and Venereology*. **2007, *21,*** 581-590.

80. Goldhirsch, A.; Wood, W. C.; Coates, A. S.; Gelber, R. D.; Thürlimann, B.; Senn, H. J. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011, *Annals of oncology : official journal of the European Society for Medical Oncology*. **2011, *22,*** 1736-1747.

81. Elston, C. W.; Ellis, I. O. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up, *Histopathology*. **1991, *19,*** 403-410.

82. Bastien, R. R.; Rodríguez-Lescure, Á.; Ebbert, M. T., et al. PAM50 breast cancer subtyping by RT-qPCR and concordance with standard clinical molecular markers, *BMC Med Genomics*. **2012, *5,*** 44.

83. Łukasiewicz, S.; Czeczelewski, M.; Forma, A.; Baj, J.; Sitarz, R.; Stanisławek, A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review, *Cancers (Basel)*. **2021, *13***.

84. Newman, L. A.; Reis-Filho, J. S.; Morrow, M.; Carey, L. A.; King, T. A. The 2014 Society of Surgical Oncology Susan G. Komen for the Cure Symposium: triple-negative breast cancer, *Annals of surgical oncology*. **2015, *22,*** 874-882.

85. Sechidis, K.; Papangelou, K.; Metcalfe, P. D.; Svensson, D.; Weatherall, J.; Brown, G. Distinguishing prognostic and predictive biomarkers: an information theoretic approach, *Bioinformatics*. **2018, *34,*** 3365-3376.

86. Markman, M. Prognostic vs Predictive Factors in Oncology Carry Differing Intent but May Have Complementary Clinical Utility, *Oncology Live®*. **2025, *26***.

87. Lundgren, C.; Tutzauer, J.; Church, S. E., et al. Tamoxifen-predictive value of gene expression signatures in premenopausal breast cancer: data from the randomized SBII:2 trial, *Breast Cancer Res*. **2023, *25,*** 110.

88. Sorlie, T.; Perou, C. M.; Tibshirani, R., et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications, *Proceedings of the National Academy of Sciences of the United States of America*. **2001, *98,*** 10869-10874.

89. Allison, K. H.; Hammond, M. E. H.; Dowsett, M., et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update, *J Clin Oncol*. **2020, *38,*** 1346-1366.

90. Bradley, R.; Braybrooke, J.; Gray, R., et al. Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials, *The Lancet Oncology*. **2021, *22,*** 1139-1150.

91. Lashen, A. G.; Toss, M. S.; Ghannam, S. F., et al. Expression, assessment and significance of Ki67 expression in breast cancer: an update, *Journal of Clinical Pathology*. **2023, *76,*** 357.

92. Ciarka, A.; Piątek, M.; Pęksa, R.; Kunc, M.; Senkus, E. Tumor-Infiltrating Lymphocytes (TILs) in Breast Cancer: Prognostic and Predictive Significance across Molecular Subtypes, *Biomedicines*. **2024,** ***12,*** 763.
93. Veronesi, U.; Cascinelli, N.; Mariani, L., et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer, *The New England journal of medicine*. **2002,** ***347,*** 1227-1232.
94. Zafar, A.; Khatoon, S.; Khan, M. J.; Abu, J.; Naeem, A. Advancements and limitations in traditional anti-cancer therapies: a comprehensive review of surgery, chemotherapy, radiation therapy, and hormonal therapy, *Discov Oncol*. **2025,** ***16,*** 607.
95. The Room See https://en.wikipedia.org/wiki/The_Room for further details.
96. Loibl, S.; André, F.; Bachelot, T., et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, *Annals of oncology : official journal of the European Society for Medical Oncology*. **2024,** ***35,*** 159-182.
97. Gilmour, A.; Cutress, R.; Gandhi, A., et al. Oncoplastic breast surgery: A guide to good practice, *Eur J Surg Oncol*. **2021,** ***47,*** 2272-2285.
98. Nijveldt, J. J.; Rajan, K. K.; Boersma, K., et al. Implementation of the Targeted Axillary Dissection Procedure in Clinically Node-Positive Breast Cancer: A Retrospective Analysis, *Annals of surgical oncology*. **2024,** ***31,*** 4477-4486.
99. Behranvand, N.; Nasri, F.; Zolfaghari Emameh, R., et al. Chemotherapy: a double-edged sword in cancer treatment, *Cancer Immunol Immunother*. **2022,** ***71,*** 507-526.
100. Di Nardo, P.; Lisanti, C.; Garutti, M., et al. Chemotherapy in patients with early breast cancer: clinical overview and management of long-term side effects, *Expert Opin Drug Saf*. **2022,** ***21,*** 1341-1355.
101. Hanna, K.; Mayden, K. Chemotherapy Treatment Considerations in Metastatic Breast Cancer, *J Adv Pract Oncol*. **2021,** ***12,*** 6-12.
102. Osborne, C. K.; Schiff, R. Mechanisms of endocrine resistance in breast cancer, *Annu Rev Med*. **2011,** ***62,*** 233-247.
103. Harbeck, N.; Gnant, M. Breast cancer, *Lancet (London, England)*. **2017,** ***389,*** 1134-1150.
104. Loibl, S.; Poortmans, P.; Morrow, M.; Denkert, C.; Curigliano, G. Breast cancer, *Lancet (London, England)*. **2021,** ***397,*** 1750-1769.
105. Cucciniello, L.; Garufi, G.; Di Rienzo, R., et al. Estrogen deprivation effects of endocrine therapy in breast cancer patients: Incidence, management and outcome, *Cancer Treat Rev*. **2023,** ***120,*** 102624.
106. Ghannam, Y.; Le Scodan, R.; Rivera, S., et al. Radiotherapy of breast cancer: 2025 update, *Cancer Radiother*. **2025,** ***29,*** 104767.
107. Lee, S. F.; Kennedy, S. K. F.; Caini, S., et al. Randomised controlled trials on radiation dose fractionation in breast cancer: systematic review and meta-analysis with emphasis on side effects and cosmesis, *BMJ (Clinical research ed)*. **2024,** ***386,*** e079089.

108. Dowling, G. P.; Keelan, S.; Toomey, S.; Daly, G. R.; Hennessy, B. T.; Hill, A. D. K. Review of the status of neoadjuvant therapy in HER2-positive breast cancer, *Front Oncol*. **2023,** ***13,*** 1066007.

109. Wang, B.; He, X.; Dutta, S., et al. New progress and challenges of targeted therapies for breast cancer, *Ann Palliat Med*. **2025,** ***14,*** 345-352.

110. Ran, R.; Chen, X.; Yang, J.; Xu, B. Immunotherapy in breast cancer: current landscape and emerging trends, *Experimental Hematology & Oncology*. **2025,** ***14,*** 77.

111. Moy, L. Change Is Good: The Evolution and Future of Breast Imaging, *Radiology*. **2023,** ***306,*** e230018.

112. Ward, R. C.; Lourenco, A. P.; Mainiero, M. B. Ultrasound-Guided Breast Cancer Cryoablation, *AJR American journal of roentgenology*. **2019,** ***213,*** 716-722.

113. Xia, L. Y.; Hu, Q. L.; Xu, W. Y. Efficacy and Safety of Radiofrequency Ablation for Breast Cancer Smaller Than 2 cm: A Systematic Review and Meta-Analysis, *Front Oncol*. **2021,** ***11,*** 651646.

114. De Maio, A.; Alfieri, G.; Mattone, M.; Ghanouni, P.; Napoli, A. High-Intensity Focused Ultrasound Surgery for Tumor Ablation: A Review of Current Applications, *Radiol Imaging Cancer*. **2024,** ***6,*** e230074.

115. Ritenour, E. R. Physics overview of screen-film radiography, *Radiographics : a review publication of the Radiological Society of North America, Inc*. **1996,** ***16,*** 903-916.

116. Galati, F.; Moffa, G.; Pediconi, F. Breast imaging: Beyond the detection, *European journal of radiology*. **2022,** ***146***.

117. Diffey, J. L. A comparison of digital mammography detectors and emerging technology, *Radiography*. **2015,** ***21,*** 315-323.

118. Weigel, S.; Heindel, W.; Heidrich, J.; Hense, H. W.; Heidinger, O. Digital mammography screening: sensitivity of the programme dependent on breast density, *European radiology*. **2017,** ***27,*** 2744-2751.

119. Kulkarni, S.; Freitas, V.; Muradali, D. Digital Breast Tomosynthesis: Potential Benefits in Routine Clinical Practice, *Canadian Association of Radiologists Journal*. **2022,** ***73,*** 107-120.

120. Kuhl, C. The current status of breast MR imaging. Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice, *Radiology*. **2007,** ***244,*** 356-378.

121. Jochelson, M. S.; Lobbes, M. B. I. Contrast-enhanced Mammography: State of the Art, *Radiology*. **2021,** ***299,*** 36-48.

122. Patel, B. K.; Lobbes, M. B. I.; Lewin, J. Contrast Enhanced Spectral Mammography: A Review, *Semin Ultrasound CT MR*. **2018,** ***39,*** 70-79.

123. Marcon, M.; Fuchsjäger, M. H.; Clauser, P.; Mann, R. M. ESR Essentials: screening for breast cancer - general recommendations by EUSOBI, *European radiology*. **2024,** ***34,*** 6348-6357.

124. Alikhassi, A.; Curpen, B. Breast ductography: to do or not to do? A pictorial essay, *Insights Imaging*. **2023,** ***14,*** 201.

125. Lee, C. I.; Lehman, C. D.; Bassett, L. W. *Breast Imaging*, 1: Oxford University Press, 2018.
126. Lother, D.; Robert, M.; Elwood, E., et al. Imaging in metastatic breast cancer, CT, PET/CT, MRI, WB-DWI, CCA: review and new perspectives, *Cancer Imaging*. **2023,** ***23,*** 53.
127. Teubner, J. Echomammography: Technique and Results. In *Radiological Diagnosis of Breast Diseases* (Friedrich, M. and Sickles, E. A. (eds.)). Berlin, Heidelberg: Springer Berlin Heidelberg, 2000, 181-220.
128. Athanasiou, A.; Tardivon, A.; Ollivier, L.; Thibault, F.; El Khoury, C.; Neuenschwander, S. How to optimize breast ultrasound, *European journal of radiology*. **2009,** ***69,*** 6-13.
129. Sprague, B. L.; Stout, N. K.; Schechter, C., et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts, *Ann Intern Med*. **2015,** ***162,*** 157-166.
130. Guo, R.; Lu, G.; Qin, B.; Fei, B. Ultrasound Imaging Technologies for Breast Cancer Detection and Management: A Review, *Ultrasound Med Biol*. **2018,** ***44,*** 37-70.
131. Sivarajah, R. T.; Brown, K.; Chetlen, A. "I can see clearly now." fundamentals of breast ultrasound optimization, *Clinical Imaging*. **2020,** ***64,*** 124-135.
132. Jassim, G.; AlZayani, F.; Dsilva, S. Adjunct Automated Breast Ultrasound in Mammographic Screening: A Systematic Review and Meta-Analysis, *J Imaging*. **2025,** ***12***.
133. Wilczek, B.; Wilczek, H. E.; Rasouliyan, L.; Leifland, K. 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, *European journal of radiology*. **2016,** ***85,*** 1554-1563.
134. Hanson, L. G. Is quantum mechanics necessary for understanding magnetic resonance?, *Concepts in Magnetic Resonance Part A*. **2008,** ***32A,*** 329-340.
135. van Nijnatten, T. J. A.; Morscheid, S.; Baltzer, P. A. T., et al. Contrast-enhanced breast imaging: Current status and future challenges, *European journal of radiology*. **2024,** ***171,*** 111312.
136. Bastidas, J. F.; Martínez de Bourio-Allona, M.; Roteta Unceta Barrenechea, A.; Rodríguez-Fraile, M.; Sancho, L. PET/CT in breast cancer, *Rev Esp Med Nucl Imagen Mol (Engl Ed)*. **2025,** ***44,*** 500139.
137. Katal, S.; McKay, M. J.; Taubman, K. PET Molecular Imaging in Breast Cancer: Current Applications and Future Perspectives, *Journal of clinical medicine*. **2024,** ***13,*** 3459.
138. Kumar, R.; Sagar, S.; Khan, D. PET/CT in Breast Cancer. In *Imaging in Management of Breast Diseases: Volume 1, Overview of Modalities* (Dhamija, E. and Deo, S. V. S. (eds.)). Singapore: Springer Nature Singapore, 2025, 157-169.
139. Freer, P. E. Mammographic breast density: impact on breast cancer risk and implications for screening, *Radiographics : a review publication of the Radiological Society of North America, Inc*. **2015,** ***35,*** 302-315.

140. Guo, Y. P.; Martin, L. J.; Hanna, W., et al. Growth factors and stromal matrix proteins associated with mammographic densities, *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. **2001,** ***10,*** 243-248.
141. Huo, C. W.; Chew, G.; Hill, P., et al. High mammographic density is associated with an increase in stromal collagen and immune cells within the mammary epithelium, *Breast Cancer Res*. **2015,** ***17,*** 79.
142. Ekpo, E. U.; McEntee, M. F. Measurement of breast density with digital breast tomosynthesis--a systematic review, *The British journal of radiology*. **2014,** ***87,*** 20140460.
143. Chen, Y.; Li, L.; Gu, H., et al. Breast density in MRI: an AI-based quantification and relationship to assessment in mammography, *npj Breast Cancer*. **2025,** ***11,*** 115.
144. Bunnell, A.; Valdez, D.; Wolfgruber, T. K., et al. Prediction of mammographic breast density based on clinical breast ultrasound images using deep learning: a retrospective analysis, *The Lancet Regional Health – Americas*. **2025,** ***46***.
145. Sickles, E., D'Orsi CJ, Bassett LW, et al. *ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System*: American College of Radiology, 2013.
146. Mesurolle, B.; El Khoury, M. Breast Cancer Risk Prediction with Radiomic Tissue Characterization on Mammograms Takes Shape, *Radiology*. **2025,** ***315,*** e250622.
147. Chalfant, J. S.; Hoyt, A. C. Breast Density: Current Knowledge, Assessment Methods, and Clinical Implications, *Journal of Breast Imaging*. **2022,** ***4,*** 357-370.
148. Sturesdotter, L.; Larsson, A.-M.; Zackrisson, S.; Sartor, H. Investigating the prognostic value of mammographic breast density and mammographic tumor appearance in women with invasive breast cancer: The Malmö Diet and cancer study, *The Breast*. **2023,** ***70,*** 8-17.
149. Boyd, N. F.; Dite, G. S.; Stone, J., et al. Heritability of mammographic density, a risk factor for breast cancer, *The New England journal of medicine*. **2002,** ***347,*** 886-894.
150. Burton, A.; Maskarinec, G.; Perez-Gomez, B., et al. Mammographic density and ageing: A collaborative pooled analysis of cross-sectional data from 22 countries worldwide, *PLoS Med*. **2017,** ***14,*** e1002335.
151. Ghosh, K.; Hartmann, L. C.; Reynolds, C., et al. Association between mammographic density and age-related lobular involution of the breast, *J Clin Oncol*. **2010,** ***28,*** 2207-2212.
152. Gierach, G. L.; Patel, D. A.; Pfeiffer, R. M., et al. Relationship of Terminal Duct Lobular Unit Involution of the Breast with Area and Volume Mammographic Densities, *Cancer Prev Res (Phila)*. **2016,** ***9,*** 149-158.
153. Ghosh, K.; Brandt, K. R.; Reynolds, C., et al. Tissue composition of mammographically dense and non-dense breast tissue, *Breast cancer research and treatment*. **2012,** ***131,*** 267-275.
154. Martin, L. J.; Boyd, N. F. Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence, *Breast Cancer Res*. **2008,** ***10,*** 201.

155. Vachon, C. M.; Kuni, C. C.; Anderson, K.; Anderson, V. E.; Sellers, T. A. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States), *Cancer causes & control : CCC*. **2000,** ***11,*** 653-662.

156. Azam, S.; Jacobsen, K. K.; Aro, A. R.; Lynge, E.; Andersen, Z. J. Hormone replacement therapy and mammographic density: a systematic literature review, *Breast cancer research and treatment*. **2020,** ***182,*** 555-579.

157. Gabrielson, M.; Hammarström, M.; Bergqvist, J., et al. Baseline breast tissue characteristics determine the effect of tamoxifen on mammographic density change, *International journal of cancer*. **2024,** ***155,*** 339-351.

158. Lope, V.; Pérez-Gómez, B.; Sánchez-Contador, C., et al. Obstetric history and mammographic density: a population-based cross-sectional study in Spain (DDM-Spain), *Breast cancer research and treatment*. **2012,** ***132,*** 1137-1146.

159. Hunt, J. T.; Kamat, R.; Yao, M.; Sharma, N.; Batur, P. Effect of contraceptive hormonal therapy on mammographic breast density: A longitudinal cohort study, *Clinical Imaging*. **2023,** ***97,*** 62-67.

160. Yaghjyan, L.; Smotherman, C.; Heine, J.; Colditz, G. A.; Rosner, B.; Tamimi, R. M. Associations of Oral Contraceptives with Mammographic Breast Density in Premenopausal Women, *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. **2022,** ***31,*** 436-442.

161. Kim, S.; Mai Tran, T. X.; Kim, M. K., et al. Associations between breast cancer risk factors and mammographic breast density in a large cross-section of Korean women, *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)*. **2024,** ***33,*** 407-413.

162. Sprague, B. L.; Gangnon, R. E.; Burt, V., et al. Prevalence of mammographically dense breasts in the United States, *Journal of the National Cancer Institute*. **2014,** ***106***.

163. Milch, H. S.; Elmore, J. G. Dense Breasts Are Common—Here Is What to Know, *JAMA Internal Medicine*. **2025,** ***185,*** 1514-1514.

164. Wanders, J. O.; Holland, K.; Veldhuis, W. B., et al. Volumetric breast density affects performance of digital screening mammography, *Breast cancer research and treatment*. **2017,** ***162,*** 95-103.

165. Brown, A. L.; Vijapura, C.; Patel, M.; De La Cruz, A.; Wahab, R. Breast Cancer in Dense Breasts: Detection Challenges and Supplemental Screening Opportunities, *Radiographics : a review publication of the Radiological Society of North America, Inc*. **2023,** ***43,*** e230024.

166. McCormack, V. A.; dos Santos Silva, I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis, *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. **2006,** ***15,*** 1159-1169.

167. Boyd, N. F.; Byng, J. W.; Jong, R. A., et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study, *Journal of the National Cancer Institute*. **1995,** ***87,*** 670-675.

168. Bodewes, F. T. H.; van Asselt, A. A.; Dorrius, M. D.; Greuter, M. J. W.; de Bock, G. H. Mammographic breast density and the risk of breast cancer: A systematic review and meta-analysis, *The Breast*. **2022,** ***66,*** 62-68.

169. Lynge, E.; Vejborg, I.; Lillholm, M.; Nielsen, M.; Napolitano, G.; von Euler-Chelpin, M. Breast density and risk of breast cancer, *International journal of cancer*. **2023,** ***152,*** 1150-1158.

170. Acciavatti, R. J.; Lee, S. H.; Reig, B., et al. Beyond Breast Density: Risk Measures for Breast Cancer in Multiple Imaging Modalities, *Radiology*. **2023,** ***306,*** e222575.

171. Winham, S. J.; McCarthy, A. M.; Scott, C. G., et al. Radiomic Parenchymal Phenotypes of Breast Texture from Mammography and Association with Risk of Breast Cancer, *Radiology*. **2025,** ***315,*** e240281.

172. Tirada, N.; Aujero, M.; Khorjekar, G., et al. Breast Cancer Tissue Markers, Genomic Profiling, and Other Prognostic Factors: A Primer for Radiologists, *Radiographics : a review publication of the Radiological Society of North America, Inc*. **2018,** ***38,*** 1902-1920.

173. Domingo, L.; Sala, M.; Louro, J., et al. Exploring the Role of Breast Density on Cancer Prognosis among Women Attending Population-Based Screening Programmes, *Journal of oncology*. **2019,** ***2019,*** 1781762.

174. Shawky, M. S.; Huo, C. W.; Henderson, M. A.; Redfern, A.; Britt, K.; Thompson, E. W. A review of the influence of mammographic density on breast cancer clinical and pathological phenotype, *Breast cancer research and treatment*. **2019,** ***177,*** 251-276.

175. Sak, M. A.; Littrup, P. J.; Duric, N.; Mullooly, M.; Sherman, M. E.; Gierach, G. L. Current and Future Methods for Measuring Breast Density: A Brief Comparative Review, *Breast cancer management*. **2015,** ***4,*** 209-221.

176. Pettersson, A.; Graff, R. E.; Ursin, G., et al. Mammographic density phenotypes and risk of breast cancer: a meta-analysis, *Journal of the National Cancer Institute*. **2014,** ***106***.

177. Lundberg, P.; Forsgren, M. F.; Tellman, J.; Kihlberg, J.; Rzepecka, A.; Dabrosin, C. Breast density is strongly associated with multiparametric magnetic resonance imaging biomarkers and pro-tumorigenic proteins in situ, *British Journal of Cancer*. **2022,** ***127,*** 2025-2033.

178. Fernández-Nogueira, P.; Mancino, M.; Fuster, G., et al. Breast Mammographic Density: Stromal Implications on Breast Cancer Detection and Therapy, *Journal of clinical medicine*. **2020,** ***9***.

179. Tanne, J. H. US women must be told breast density after mammogram, says FDA, *BMJ (Clinical research ed)*. **2024,** ***386,*** q2045.

180. Nickel, B.; Hudson, C.; Isautier, J., et al. Equity in breast density notification in Australia: A focus group study exploring the impact and needs amongst culturally and linguistically diverse (CALD) women, *Patient Education and Counseling*. **2025,** ***133,*** 108628.

181. Nickel, B.; Ormiston-Smith, N.; Cvejic, E., et al. Impact of population based breast density notification: multisite parallel arm randomised controlled trial in BreastScreen, *BMJ (Clinical research ed)*. **2025,** ***391,*** e083649.

182. Kressin, N. R.; Slanetz, P. J.; Gunn, C. M. Ensuring Clarity and Understandability of the FDA's Breast Density Notifications, *Jama*. **2023,** ***329,*** 121-122.

183. Berment, H.; Becette, V.; Mohallem, M.; Ferreira, F.; Cherel, P. Masses in mammography: what are the underlying anatomopathological lesions?, *Diagnostic and interventional imaging*. **2014,** ***95,*** 124-133.

184. Killelea, B. K.; Chagpar, A. B.; Bishop, J., et al. Is there a correlation between breast cancer molecular subtype using receptors as surrogates and mammographic appearance?, *Annals of surgical oncology*. **2013,** ***20,*** 3247-3253.

185. Boisserie-Lacroix, M.; Macgrogan, G.; Debled, M., et al. Triple-negative breast cancers: associations between imaging and pathological findings for triple-negative tumors compared with hormone receptor-positive/human epidermal growth factor receptor-2-negative breast cancers, *The oncologist*. **2013,** ***18,*** 802-811.

186. Dogan, B. E.; Turnbull, L. W. Imaging of triple-negative breast cancer, *Annals of oncology : official journal of the European Society for Medical Oncology*. **2012,** ***23 Suppl 6,*** vi23-29.

187. Gao, B.; Zhang, H.; Zhang, S. D., et al. Mammographic and clinicopathological features of triple-negative breast cancer, *The British journal of radiology*. **2014,** ***87,*** 20130496.

188. Franquet, T.; De Miguel, C.; Cozcolluela, R.; Donoso, L. Spiculated lesions of the breast: mammographic-pathologic correlation, *Radiographics : a review publication of the Radiological Society of North America, Inc*. **1993,** ***13,*** 841-852.

189. Moriuchi, H.; Yamaguchi, J.; Hayashi, H., et al. Cancer Cell Interaction with Adipose Tissue: Correlation with the Finding of Spiculation at Mammography, *Radiology*. **2016,** ***279,*** 56-64.

190. Bhatia, M.; Ahmed, R.; Nagarajakumar, A.; Alani, A.; Doddi, S.; Metafa, A. Measurement of malignant spiculated mass lesions on mammogram: Do we include the length of the spicules?, *J Cancer Res Ther*. **2023,** ***19,*** 1794-1796.

191. Burrell, H. C.; Pinder, S. E.; Wilson, A. R., et al. The positive predictive value of mammographic signs: a review of 425 non-palpable breast lesions, *Clinical radiology*. **1996,** ***51,*** 277-281.

192. Ciatto, S.; Cataliotti, L.; Distante, V. Nonpalpable lesions detected with mammography: review of 512 consecutive cases, *Radiology*. **1987,** ***165,*** 99-102.

193. Cherel, P.; Becette, V.; Hagay, C. Stellate images: anatomic and radiologic correlations, *European journal of radiology*. **2005,** ***54,*** 37-54.

194. Jiang, L.; Ma, T.; Moran, M. S., et al. Mammographic features are associated with clinicopathological characteristics in invasive breast cancer, *Anticancer research*. **2011,** ***31,*** 2327-2334.

195. Ildefonso, C.; Vazquez, J.; Guinea, O., et al. The mammographic appearance of breast carcinomas of invasive ductal type: relationship with clinicopathological parameters, biological features and prognosis, *European journal of obstetrics, gynecology, and reproductive biology*. **2008,** ***136,*** 224-231.

196. Liu, S.; Wu, X. D.; Xu, W. J.; Lin, Q.; Liu, X. J.; Li, Y. Is There a Correlation between the Presence of a Spiculated Mass on Mammogram and Luminal A Subtype Breast Cancer?, *Korean journal of radiology*. **2016,** ***17,*** 846-852.

197. De Nunzio, M. C.; Evans, A. J.; Pinder, S. E., et al. Correlations between the mammographic features of screen detected invasive breast cancer and pathological prognostic factors, *The Breast*. **1997, *6,*** 146-149.

198. Evans, A. J.; Pinder, S. E.; James, J. J.; Ellis, I. O.; Cornford, E. Is mammographic spiculation an independent, good prognostic factor in screening-detected invasive breast cancer?, *AJR American journal of roentgenology*. **2006, *187,*** 1377-1380.

199. Lamb, P. M.; Perry, N. M.; Vinnicombe, S. J.; Wells, C. A. Correlation between ultrasound characteristics, mammographic findings and histological grade in patients with invasive ductal carcinoma of the breast, *Clinical radiology*. **2000, *55,*** 40-44.

200. Taneja, S.; Evans, A. J.; Rakha, E. A.; Green, A. R.; Ball, G.; Ellis, I. O. The mammographic correlations of a new immunohistochemical classification of invasive breast cancer, *Clinical radiology*. **2008, *63,*** 1228-1235.

201. Bullier, B.; MacGrogan, G.; Bonnefoi, H., et al. Imaging features of sporadic breast cancer in women under 40 years old: 97 cases, *European radiology*. **2013, *23,*** 3237-3245.

202. Alexander, M. C.; Yankaskas, B. C.; Biesemier, K. W. Association of stellate mammographic pattern with survival in small invasive breast tumors, *AJR American journal of roentgenology*. **2006, *187,*** 29-37.

203. Tabar, L.; Tony Chen, H. H.; Amy Yen, M. F., et al. Mammographic tumor features can predict long-term outcomes reliably in women with 1-14-mm invasive breast carcinoma, *Cancer*. **2004, *101,*** 1745-1759.

204. Kufe, D. W.; Pollock, R. E.; Weichselbaum, R. R., et al. *Holland-Frei Cancer Medicine*, 6 edn.: BC Decker, 2003.

205. Tot, T.; Gere, M.; Hofmeyer, S.; Bauer, A.; Pellas, U. The clinical value of detecting microcalcifications on a mammogram, *Semin Cancer Biol*. **2021, *72,*** 165-174.

206. Elias, S. G.; Adams, A.; Wisner, D. J., et al. Imaging features of HER2 overexpression in breast cancer: a systematic review and meta-analysis, *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. **2014, *23,*** 1464-1483.

207. Bare, M.; Tora, N.; Salas, D., et al. Mammographic and clinical characteristics of different phenotypes of screen-detected and interval breast cancers in a nationwide screening program, *Breast cancer research and treatment*. **2015, *154,*** 403-415.

208. Wang, J.; Zhao, L.; Hu, X., et al. Clinicopathological characteristics and prognostic significance of casting-type calcifications in patients with invasive breast cancer presenting with microcalcification, *Scientific reports*. **2024, *14,*** 13351.

209. Li, Y.; Cao, J.; Zhou, Y.; Mao, F.; Shen, S.; Sun, Q. Mammographic casting-type calcification is an independent prognostic factor in invasive breast cancer, *Scientific reports*. **2019, *9,*** 10544.

210. Kahila, M. M. H.; Chesebro, A. L.; Giess, C. S.; Rhei, E.; Hong, X.; Lester, S. C. Pathologic Features of Malignancies Presenting as Asymmetry on Mammography, *Modern Pathology*. **2024, *37,*** 100612.

211. Goh, Y.; Quek, S. T.; Pillay, P.; Chou, C. P. Evaluation of architectural distortion with contrast-enhanced mammography, *Clinical radiology*. **2024, *79,*** 163-169.

212. Gaur, S.; Dialani, V.; Slanetz, P. J.; Eisenberg, R. L. Architectural Distortion of the Breast, *American Journal of Roentgenology*. **2013,** ***201,*** W662-W670.
213. Chotai, N.; Gadwal, A.; Buchireddy, D.; Yang, W. T. Why we still miss breast cancers: strategies for improving mammography interpretation, *Insights into Imaging*. **2026,** ***17,*** 8.
214. Andersson, I.; Ikeda, D. M.; Zackrisson, S., et al. Breast tomosynthesis and digital mammography: a comparison of breast cancer visibility and BIRADS classification in a population of cancers with subtle mammographic findings, *European radiology*. **2008,** ***18,*** 2817-2825.
215. Al Mousa, D. S.; Ryan, E. A.; Mello-Thoms, C.; Brennan, P. C. What effect does mammographic breast density have on lesion detection in digital mammography?, *Clinical radiology*. **2014,** ***69,*** 333-341.
216. Manias, K. A.; Peet, A. What is MR spectroscopy?, *Arch Dis Child Educ Pract Ed*. **2018,** ***103,*** 213-216.
217. Berglund, G.; Elmstahl, S.; Janzon, L.; Larsson, S. A. The Malmo Diet and Cancer Study. Design and feasibility, *Journal of internal medicine*. **1993,** ***233,*** 45-51.
218. Manjer, J.; Elmstahl, S.; Janzon, L.; Berglund, G. Invitation to a population-based cohort study: differences between subjects recruited using various strategies, *Scandinavian journal of public health*. **2002,** ***30,*** 103-112.
219. Manjer, J.; Carlsson, S.; Elmståhl, S., et al. The Malmö Diet and Cancer Study: representativity, cancer incidence and mortality in participants and non-participants, *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)*. **2001,** ***10,*** 489-499.
220. Sturesdotter, L.; Sandsveden, M.; Johnson, K.; Larsson, A. M.; Zackrisson, S.; Sartor, H. Mammographic tumour appearance is related to clinicopathological factors and surrogate molecular breast cancer subtype, *Scientific reports*. **2020,** ***10,*** 20814.
221. Sturesdotter, L.; Sartor, H.; Kristensson, H.; Hagberg, O.; Lång, K. The potential association between degree of mammographic spiculation and prognosis, *Insights into Imaging*. **2026,** ***17,*** 29.
222. Lagerlund, M.; Sontrop, J. M.; Zackrisson, S. Do reproductive and hormonal risk factors for breast cancer associate with attendance at mammography screening?, *Cancer causes & control : CCC*. **2013,** ***24,*** 1687-1694.
223. Sartor, H.; Borgquist, S.; Hartman, L.; Olsson, A.; Jawdat, F.; Zackrisson, S. Do mammographic tumor features in breast cancer relate to breast density and invasiveness, tumor size, and axillary lymph node involvement?, *Acta radiologica (Stockholm, Sweden : 1987)*. **2015,** ***56,*** 536-544.
224. Sartor, H. Mammographic density in relation to breast cancer Tumor characteristics, mode of detection, and density assessments. In *Faculty of Medicine*). Lund University, 2015.
225. Luck, A. A.; Evans, A. J.; James, J. J., et al. Breast carcinoma with basal phenotype: mammographic findings, *AJR American journal of roentgenology*. **2008,** ***191,*** 346-351.

226. Spak, D. A.; Plaxco, J. S.; Santiago, L.; Dryden, M. J.; Dogan, B. E. BI-RADS((R)) fifth edition: A summary of changes, *Diagnostic and interventional imaging*. **2017, *98,*** 179-190.

227. Wilkerson, M. L.; Hewitt, S. Tissue Microarray. In *Handbook of Practical Immunohistochemistry: Frequently Asked Questions* (Lin, F., Prichard, J. W., Liu, H. and Wilkerson, M. L. (eds.)). Cham: Springer International Publishing, 2022, 161-172.

228. Borgquist, S.; Anagnostaki, L.; Jirstrom, K.; Landberg, G.; Manjer, J. Breast tumours following combined hormone replacement therapy express favourable prognostic factors, *International journal of cancer*. **2007, *120,*** 2202-2207.

229. Elebro, K.; Butt, S.; Dorkhan, M.; Jernstrom, H.; Borgquist, S. Age at first childbirth and oral contraceptive use are associated with risk of androgen receptor-negative breast cancer: the Malmo Diet and Cancer Cohort, *Cancer causes & control : CCC*. **2014, *25,*** 945-957.

230. Butt, S.; Borgquist, S.; Anagnostaki, L.; Landberg, G.; Manjer, J. Breastfeeding in relation to risk of different breast cancer characteristics, *BMC research notes*. **2014, *7,*** 216.

231. Dowsett, M.; Bartlett, J.; Ellis, I. O., et al. Correlation between immunohistochemistry (HercepTest) and fluorescence in situ hybridization (FISH) for HER-2 in 426 breast carcinomas from 37 centres, *The Journal of pathology*. **2003, *199,*** 418-423.

232. Huss, L.; Butt, S. T.; Borgquist, S., et al. Vitamin D receptor expression in invasive breast tumors and breast cancer survival, *Breast Cancer Res*. **2019, *21,*** 84.

233. Sandsveden, M.; Nilsson, E.; Borgquist, S.; Rosendahl, A. H.; Manjer, J. Prediagnostic serum selenium levels in relation to breast cancer survival and tumor characteristics, *International journal of cancer*. **2020, *147,*** 2424-2436.

234. Krizmanich-Conniff, K. M.; Paramagul, C.; Patterson, S. K., et al. Triple receptor-negative breast cancer: imaging and clinical characteristics, *AJR American journal of roentgenology*. **2012, *199,*** 458-464.

235. Tamaki, K.; Ishida, T.; Miyashita, M., et al. Correlation between mammographic findings and corresponding histopathology: potential predictors for biological characteristics of breast diseases, *Cancer science*. **2011, *102,*** 2179-2185.

236. Seo, B. K.; Pisano, E. D.; Kuzimak, C. M., et al. Correlation of HER-2/neu overexpression with mammography and age distribution in primary breast carcinomas, *Academic radiology*. **2006, *13,*** 1211-1218.

237. Wang, X.; Chao, L.; Chen, L., et al. Correlation of mammographic calcifications with Her-2/neu overexpression in primary breast carcinomas, *Journal of digital imaging*. **2008, *21,*** 170-176.

238. Gajdos, C.; Tartter, P. I.; Bleiweiss, I. J., et al. Mammographic appearance of nonpalpable breast cancer reflects pathologic characteristics, *Annals of surgery*. **2002, *235,*** 246-251.

239. Boemi, S.; Pagana, A.; Bruno, M. T. Imaging Biomarkers for HER2-Positive Breast Cancer: Evidence from an Observational Study, *Journal of clinical medicine*. **2025, *14,*** 5056.

240. Wang, X.; Chao, L.; Chen, L., et al. The mammographic correlations with Basal-like phenotype of invasive breast cancer, *Academic radiology*. **2010,** ***17,*** 333-339.
241. Olsson, Å.; Sartor, H.; Borgquist, S.; Zackrisson, S.; Manjer, J. Breast density and mode of detection in relation to breast cancer specific survival: a cohort study, *BMC cancer*. **2014,** ***14,*** 229.
242. Zdanowski, A.; Sartor, H.; Feldt, M.; Skarping, I. Mammographic density in relation to breast cancer recurrence and survival in women receiving neoadjuvant chemotherapy, *Frontiers in Oncology*. **2023,** ***Volume 13 - 2023***.
243. Kanbayti, I.; Akwo, J.; Erim, A.; Ukpong, E.; Ekpo, E. Mammographic Breast Density at Breast Cancer Diagnosis and Breast Cancer-Specific Survival, *Diagnostics*. **2024,** ***14,*** 2382.
244. Chiu, S. Y.; Duffy, S.; Yen, A. M.; Tabár, L.; Smith, R. A.; Chen, H. H. Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening, *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. **2010,** ***19,*** 1219-1228.
245. Heindl, F.; Fasching, P. A.; Hein, A., et al. Mammographic density and prognosis in primary breast cancer patients, *The Breast*. **2021,** ***59,*** 51-57.
246. Borde, T.; Wu, M.; Ruschke, S., et al. Assessing breast density using the chemical-shift encoding-based proton density fat fraction in 3-T MRI, *European radiology*. **2023,** ***33,*** 3810-3818.
247. Trinh, L.; Peterson, P.; Leander, P.; Brorson, H.; Månsson, S. In vivo comparison of MRI-based and MRS-based quantification of adipose tissue fatty acid composition against gas chromatography, *Magn Reson Med*. **2020,** ***84,*** 2484-2494.
248. Ayoub, Y.; Cheung, S. M.; Maglan, B.; Senn, N.; Chan, K. S.; He, J. Differentiation of histological calcification classifications in breast cancer using ultrashort echo time and chemical shift-encoded imaging MRI, *Front Oncol*. **2024,** ***14,*** 1475090.
249. Chan, K. S.; Cheung, S. M.; Senn, N., et al. Peri-tumoural spatial distribution of lipid composition and tubule formation in breast cancer, *BMC cancer*. **2022,** ***22,*** 285.
250. Cheung, S. M.; Chan, K. S.; Senn, N., et al. Peri-Tumoural Lipid Composition and Hypoxia for Early Immune Response to Neoadjuvant Chemotherapy in Breast Cancer, *Int J Mol Sci*. **2024,** ***25***.
251. Bell, K. J. L.; Brennan, M. Does mammographic density predict survival in women with invasive breast cancer? The need to account for potential confounding from cancer stage and overdiagnosis, *The Breast*. **2023,** ***71,*** 29-30.
252. Allweis, T. M.; Hermann, N.; Berenstein-Molho, R.; Guindy, M. Personalized Screening for Breast Cancer: Rationale, Present Practices, and Future Directions, *Annals of surgical oncology*. **2021,** ***28,*** 4306-4317.