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Mammographic density—a review on the current understanding of its association with breast cancer

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Abstract

Purpose

There has been considerable recent interest in the genetic, biological and epidemiological basis of mammographic density (MD), and the search for causative links between MD and breast cancer (BC) risk. This report will critically review the current literature on MD and summarize the current evidence for its association with breast cancer.

Methods

Keywords “mammographic dens*”, “dense mammary tissue” or “percent dens*” were used to search the existing literature in English on PubMed and Medline. All reports were critically analyzed. The data was assigned to one of the following aspects of MD: general association with BC, its relationship with the breast hormonal milieu, the cellular basis of MD, the generic variations of MD, and its significance in the clinical setting.

Results

MD adjusted for age and BMI is associated with increased risk of BC diagnosis, advanced tumour stage at diagnosis, and increased risk of both local recurrence and second primary cancers. The MD measures that predict BC risk have high heritability, and to date several genetic markers associated with BC risk have been found to also be associated with these MD risk-predictors. Change in MD could be a predictor of the extent of chemoprevention with tamoxifen.

Conclusions

Although the biological and genetic pathways that determine and perhaps modulate MD remain largely unresolved, significant inroads are being made into the understanding of MD, which may lead to benefits in clinical screening, assessment, and treatment strategies. This review provides a timely update on the current understanding of MD’s association with breast cancer risk.

Keywords

Mammographic density; breast cancer risk; stroma; adipose tissue; tamoxifen; biochamber; extracellular matrix; breast cancer screening.

Mammographic density (MD) and its association with breast cancer risk

On a mammogram, stromal and epithelial tissues are thought to attenuate x-rays more than adipose tissues. Mammographic density (MD) describes the extent of white or radio-opaque tissue (dense area) on a mammogram, and the term percent MD (PMD) is used to represent this dense area as a proportion of the total tissue area of the breast on a mammogram [1]. Published literature on MD since 2007 have been provided in Tables 1 to 9, using a format adapted from McCormack *et al.* [2] who provided a comprehensive review at that time.

Historically, the concept that certain aspects of the appearance of a mammogram were associated with breast cancer (BC) risk was first proposed by Wolfe *et al.* in 1976, who described four different breast parenchymal patterns [3]. Since then, many case-control studies, usually nested within a screening cohort, have consistently confirmed that after adjusting for age and BMI, MD as measured by Wolfe patterns and other methods- are risk factors for BC [4,2]. Conventional classification methods include the Breast Imaging-Reporting and Data system (BIRADS) [5], Wolfe [3] and Tabár [6] systems, and the novel Cumulus technique [7]. The specifics of which are detailed in Table 10. The increased risk associated with age- and BMI- adjusted MD as measured by Cumulus is about 40% per standard deviation, whether it be the dense area or the PMD [8].

The adjustment for age and BMI is necessary because MD decreases with age, and more strongly with body mass index (BMI). BC risk, however, increases with age and, for women of population screening age, with BMI, and this is more critical for PMD than for dense area [9]. Therefore the case-control studies have adjusted for this ‘negative confounding’, a point that needs to be remembered when interpreting the analyses. Not only is high BMI associated with increased non-dense area in the breast, which is a fat storage site [10-13], it has been found to negatively correlate with absolute dense area in many [14-17], but not all studies [12,18,11]. The reason for this possible inverse relationship is unclear. It is hypothesized that androgens derived from increased adiposity

may play a role in reducing fibroglandular components [19] or high BMI stimulates the differentiation of stromal preadipocytes into fat rather than collagen [20,21].

Studies have shown that BC arising within areas of high MD are more commonly associated with factors indicative of a poor prognosis, including large tumor size, high histological grade, lympho-vascular invasion (LVI) and advanced stage, compared to those arising within low MD tissue [22,23] [22-24]. Although this would suggest that high MD is associated with poor BC survival, two large retrospective studies using BIRADS found no association between MD and BC-specific survival [25,26]. The reason that high MD tumours have more aggressive features compared with low MD tumors remains elusive, although it is plausible that factors influencing the initiation of BC differ from those that affect prognosis once cancer progresses, or that MD influences on BC survival are nullified by current treatment approaches.

MD appears also to be associated with increased local recurrence and the risk of a second primary BC. Using the Wolfe classification of MD adjusted for age at diagnosis but not BMI, women with higher MD have a greater risk of local recurrence, particularly those who did not receive adjuvant radiotherapy following breast-conserving surgery (BCS) [27]. In addition, a recent study of 607 cases with almost 13 years of follow-up [25] found that higher MD, corrected for age and BMI and measured by Cumulus, was associated with a worse outcome for women who did not receive radiotherapy post-BCS. Moreover, higher MD was also found to be associated with an increased risk of a second BC. In another study with 5 years of follow-up, Buist *et al.* [28] found that BCS without radiation was associated with an increased risk of recurrence, and women with higher MD, measured by BIRADS, had a greater risk of a second primary, but not of a local recurrence. However, an interaction between radiation therapy and MD was not examined, and only 353 women had MD measured, so the sample size might have been too small to detect an association between MD and local recurrence. It is worthwhile noting that although BC arising from high MD areas has been found to demonstrate more aggressive features, most studies did not adjust for tumour size, LVI, nuclear grade and

stage when examining the relationship between MD and local recurrences [29,28,30,27] (see Table 3).

MD and the breast hormonal milieu

The use of HRT appears to increase MD. A Norwegian study of 2,424 post-menopausal women found that MD was higher for women currently using combined progestogen and oestrogen therapy (E+P HRT) than for former or non-users [31], and the use of high-dose norethisterone acetate (NETA) was particularly associated with higher MD. These findings are consistent with other published studies [32-34], in which Greendale *et al.* and Persson *et al.* observed higher MD for E+P HRT users in large Caucasian population studies [32,33]. A smaller decline in MD with aging was found for E+P HRT users compared with non-users by a combined Dutch and British study [34]. Furthermore, the association between E+P HRT use and PMD was stronger for women who later developed BC [35]. In a review of 80,867 mammograms from 39,296 postmenopausal women, oestrogen-alone HRT was found to be associated with higher MD, although the association was not as strong as that seen with combined HRT and MD [36].

Parity is inversely associated with MD, with a decrease of about 10% of the standard deviation of MD measures adjusted for age and BMI, per live-birth [9]. This is equivalent to about a 4% decrease in risk per birth that could be attributed to a decrease in MD, should the association be causal. Studies of the association between lactation and MD have to date produced conflicting results [37,38]. A longitudinal study of 2,000 women found that breastfeeding was inversely associated with PMD [37]. Using a xenograft model of human mammary tissue, Chew *et al.* observed that high MD human tissues have less stromal and more adipose components after murine postpartum involution or lactation [39]. However, the biological rationale behind these observations remains unclear.

Since MD might be reduced by the cessation of HRT and parity, and increases with HRT use, it is possible that MD is modulated by endogenous and exogenous hormonal exposures. For this reason, it has been proposed that tumours occurring in women with high MD are more likely to be oestrogen receptor (ER) or progesterone receptor (PR)-positive than those diagnosed in non-dense tissue [40,41]. However, Antoni *et al.* performed a meta-analysis of 7 cohort and 12 case-control studies and found that the magnitude of the association between MD and BC of differing subtypes was similar [42]. This finding is consistent with that of a Spanish study of 1,172 women, in which the strength of association between MD was not found to differ by BC subtypes based on their hormonal receptor status [43]. The reason for this observation, as hypothesized by some authors, could be that MD occurs secondary to long-term tissue-specific inflammation as a result of cumulative exposure to environmental factors such as androgen and estrogen, which are associated with an increased risk of both ER-positive and ER-negative tumors [44-47]. Refuting this hypothesis, a case-only study of 2,410 women reported an inverse association between MD and ER expression [48]. This was surprising considering MD has been associated with both extrinsic and intrinsic hormonal exposures such as HRT and parity. Despite the lack of an association between MD and ER-positive BC, MD was found to be positively associated with PR expression by the same study [48]. Research using mouse models [49,50] has shown that proliferation of mammary stem cells was under the influence of progesterone, which could underpin the MD associations. In addition, the association between MD and BC risk is not found to differ by human epidermal growth factor receptor (HER2) status in published population studies [23,43] [51].

The cellular basis of MD

Mammographically dense breast tissues have a higher composition of stroma, higher relative gland counts, and a lower proportion of fat than low MD counterparts [52,53]. Because high MD tissues have been positively associated with stromal and epithelial proliferation [54-57], investigations of cell proliferation markers such as Ki-67 have been

performed, but most studies did not find any association between Ki-67 expression and MD [58,22,59]. The only positive association was reported by Harvey *et al.*, who examined the benign breast tissue of 56 postmenopausal women and found that higher MD was associated with increased Ki-67 activity [60]. In another study of 783 premenopausal and 436 post-menopausal women [61], mitogenic factors implicated in tumor development and progression, such as insulin-like growth factor-1 (IGF-1), insulin-like growth factor-binding protein-3 and growth hormone (GH), were examined from blood samples using ELISA assays, and were not found to be associated with MD.

The breast tissue stroma is composed of ECM proteins, adipocytes, fibroblasts and immune cells. CD-36, a transmembrane receptor that modulates many stromal processes including adipocyte differentiation, apoptosis, and cell-ECM interactions, was reduced in multiple cellular compartments within the stroma of high MD tissues compared with low MD tissues [62]. DeFilippis *et al.* found the level of CD-36 expression to be minimal in many cell types of mammary tumour stroma compared with non-malignant tissues in the same breast [62]. It would be valuable for future studies to examine the association between CD-36 and MD, and to assess its potential as a possible target for MD-associated BC prevention.

Higher MD has often been associated with increased collagen content and ECM stiffness [38,63,64]. This is potentially driven by macrophages, which promote collagen fibrillogenesis in the mouse mammary gland [65], and by tissue metalloproteinase-3 (TIMP3)-mediated inhibition of matrix degradation [66], however there are likely to be many other environmental and genetic regulators, some of which are discussed in the following section. Increased ECM stiffness has been shown to promote the focal adhesion kinase-Rho-extracellular signal-related kinase (FAK-Rho-ERK) signaling network to stimulate cell proliferation, and consequently results in a malignant phenotype of mouse mammary epithelial cells [67]. The authors have proposed a causal relationship between higher MD and BC tumourigenesis. Supporting this, dense matrix associated with MD has been found to raise Rho associated coiled-coil containing protein kinase 1 (ROCK1) activity, which plays a role in cell migration [68]. In addition, our collaborators

have shown that dense matrices of collagen (20 mg/cm^3), similar in concentration to that found in dense connective tissue associated with high MD, stimulated ameboid-like cell migration of human BC cells [69]. The presence of such ameboid-like cells in dense connective tissue surrounding invasive ductal carcinomas has been tentatively associated with local recurrence [69]. The dense collagen network could also serve to increase migration of tumour-associated macrophages [70], which promote tumour progression and metastasis [71].

Given the complex interplay between the epithelial, stromal and ECM compartments in the breast microenvironment, as summarized in Figure 1, a robust animal model could help clarify the molecular mechanisms of MD associated malignancy risk. Indeed, mammary glands from genetically altered mice have been used to examine MD-like phenotypes *in vivo* [72], and we recently developed a novel model where high and low MD human breast tissues implanted in separate murine biochambers supported by the inferior epigastric pedicles maintained their viability and MD phenotype [73].

Genetic factors and variation in MD measures that predict BC

In 1987, a small within-pair twin study using BIRADs measures showed that MD measurements were correlated in twin pairs, but was not powered to address the hypothesis that this was due to genetic factors by testing if monozygotic (MZ) pairs were more highly correlated than dizygotic (DZ) pairs [74]. MD risk-associated measures based on CUMULUS were found to be correlated in sister and mother-daughter pairs [75], but a nuclear family design alone cannot differentiate genetic from shared environmental factors as causes of familial correlation.

The breakthrough publication in this regard came in 2002 when two large twin studies, one conducted in Australia and the other in North America, demonstrated that MZ pairs were about twice as correlated as DZ pairs, consistent with genetic factors explaining about 60% of the variance in the CUMULUS measures that predict BC risk [76,77]. The

study was also remarkable in finding highly consistent results in terms of variances and MZ and DZ pair co-variances across Caucasian women from the two continents.

While studies of common variants (polymorphisms) in candidate genes based on biological arguments identified some putative associations, these were not conclusive. The next major advance came from studies of single nucleotide polymorphisms (SNPs) found to be associated with BC risk by genome-wide association studies (GWAS) [78]. The findings of the twin study above were consistent with a small overlap in BC and MD genes, and this was borne out by a nested case-control study which predicted that there would be about a 14% overlap (95% CI 4-39%) [79].

Early attempts to examine if these BC associated SNPs were also associated with the MD measures that predict BC risk failed to find convincing evidence. A larger Australian study of twins and sisters showed that, taken as a group, the 12 BC susceptibility SNPs studied were more strongly associated with MD than would be expected by chance [80]. In particular, the SNP rs3817198 in the region of the *LSP1* gene was significantly associated with dense and percent dense area.

A pooled cross-sectional study by the DENSNP consortium confirmed the association described above with the *LSP1* region SNP, and also found evidence that a SNP in the region of *RAD51L1* was implicated in MD [81]. A meta-analysis of five GWAS of MD measures by the MODE consortium found that the SNP rs10995 in the region of *ZNF365*, which had been shown to be associated with BC risk [82], was also associated with MD. Another GWAS implicated SNPs in a region on chromosome 12q24 [83]. Further studies by the MODE and DENSP consortiums are being conducted.

In summary, around 10% of common SNPs associated with BC risk are also associated with the MD measures that predict BC risk, but to date these explain only a few percent of the variance. MD is likely to be affected by a number of genes that are largely unknown at the present time. With regards to gene expression profiles, Sun and colleagues found that high MD was associated with the inactive subtype of the

extratumoral gene expression signature. The inactive phenotype had a higher expression of adhesion genes than the active subtype; and similar to high MD, was associated with increased stromal composition, increased estrogen response and reduced TGF- β signaling. The authors highlighted the importance of studying the stromal microenvironment of high MD tissue, despite breast cancer being of epithelial origin [84]. Furthermore, novel molecular multigene tests such as Mammaprint® and Oncotype DX® are increasingly utilized as decision aids. It would be of clinical interest to examine whether there is any association between MD specific gene expression profiles and these predictive tests. To date, there is no published report in this regard.

Translation of MD into the clinical setting

To date, MD has not been reported systematically in the clinical setting due to the lack of an automated tool. Conventionally, assessments of MD are based on subjective reporting of mammographic parenchymal patterns, which can be time consuming and examiner dependent. Since these measures were not specifically designed for the purpose of selecting women at increased risk of developing BC, they may not be appropriate for incorporation into population screening programs. The current trend of moving from film-based screening mammograms to digital ones has enabled alternative approaches to be developed, such as calibrated planar and volumetric measures, and automated variation measure [85-87], in the hope of achieving efficient and standardized reporting that is comparable across studies. The aforementioned Cumulus has been validated by epidemiological studies and is currently considered to be the gold standard for measuring MD and predicting BC risk [88], with greater intra-observer reliability than BIRADS [89]. An automated version of Cumulus, *AutoDensity*, that could be suitable for digital mammography has recently been developed [90]. Despite the need for more studies to validate the novel MD assessment techniques, these automated approaches may hold the key to risk stratification in future screening, while reducing the time and cost of acquiring MD data.

MD can represent a preventative and therapeutic target. In the primary prevention IBIS-1 trial, women who received tamoxifen prophylaxis - and had a minimum of 10% reduction in MD in the first 1.5 years of taking tamoxifen - were found to have a 63% reduction in BC risk; whereas no effect on BC risk was observed for those women who had a less than 10% decrease in MD [91]. In addition, a recent retrospective study of 974 postmenopausal BC patients with a 15-year follow-up found a relative reduction of 20% in MD for women who received adjuvant tamoxifen, and this MD reduction was associated with a 50% risk reduction of BC-specific mortality [92]. Furthermore, Kim *et al.* found that changes in MD predicted recurrences in 1,065 women with ER-positive BC who were treated with tamoxifen for at least 5 years, with recurrence more than doubled in women with no change in MD compared with those who had at least a 10% decrease in MD [93]. However, MD was not adjusted for BMI, which is inversely associated with MD but directly associated with BC risk in this age group. Paradoxically, 18% of these women had increased MD post-endocrine therapy for reasons that are unclear. Overall, reduction in MD as a host response could be an effective and non-invasive biomarker to assess or predict the efficacy of tamoxifen for prevention and treatment. Women with dense breasts may benefit from a trial of tamoxifen for 12-18 months to help reduce MD, and therefore their BC risk. However, the current evidence is insufficient to make this recommendation at a population level, given potential side effects of endometrial cancer and thromboembolic events.

The recent mandating of MD reporting in several states in the USA [94] is raising awareness of the role of MD in increasing BC risk. The introduction of this legislation is largely in response to the high-profile campaign by the Density Education National Survivors' Effort (Are you dense?) [95], which encourages women to ask for an ultrasound (US) or magnetic resonance imaging (MRI) if their breast tissues are reported as heterogenous or dense on mammogram. However, whether this move will improve clinical outcome and be cost-effective without unnecessarily increasing women's anxiety remains to be examined. Breast-screening programs are designed to reduce mortality by detecting BC at an early stage when treatment options may be more effective. Imaging additional to mammography demands a higher level of resources and can produce

increased false-positive results, hence high MD can play a role in helping select women who need it most. Since the implementation of Connecticut Public Act 09, there have been two recent studies conducted to assess the role of US in detecting BC for women with dense breasts [96,97]. Both found that US contributed to increased cancer detection yield (an additional cancer detection rate of 3.2 per 1000 women screened) in women who have dense breasts and normal mammograms, with no additional risk factors. However, manual US is labour-intensive and subjective, being radiographer-operated. A newer modality, automated whole breast ultrasound (AWUS), may warrant further investigation as the automation reduces labour and time costs [96,98].

While breast MRI has high sensitivity in women with increased benign parenchyma enhancement, the high false positive rate and cost may render it a less attractive modality for screening in women with high MD [96]. The ACRIN 6666 study confirmed that use of a single screening MRI or addition of annual screening breast US in women with heterogeneously or extremely dense parenchyma in at least one quadrant on mammogram resulted in an increased BC detection yield (additional 14.7 cancers with MRI and 3.7 cancers with ultrasound per 1000 screens) but also increased false-positive findings and higher biopsy rates [99]. Breast tomosynthesis is also available as a diagnostic tool, but its role in screening of high MD women is unclear. There is no evidence to suggest that tomosynthesis is superior to mammogram; on the contrary, digital tomosynthesis has been found to significantly underestimate MD compared to digital mammogram [100].

A large prospective cohort study of 11,474 women with BC also found that annual mammography screening among women aged 40 to 49 years who had extremely dense breasts was associated with decreased risk of advanced-stage cancer or large tumour, compared to biennial screening in this age group. However, the probability of a false-positive result was high (65.5%). In addition, annual screening mammography for women aged 50 to 74 years did not reduce the risk of detecting advanced BC compared to biennial screening, regardless of their MD status [101].

We propose that women aged 40 to 74 at the initial screening mammogram with MD in the BIRADS category 4 (extremely dense) or in the $\geq 50\%$ PMD category measured by Cumulus should be considered for additional imaging such as US to help detect early small BC. Consideration should be given as to whether a woman with extremely dense parenchyma $\geq 75\%$ would be recommended for a single screening breast MRI at commencement. These considerations should also take into account the inverse relationship between MD and age/BMI, and the overall risk profile for BC, including family history and exogenous endocrine exposure. Nevertheless, we acknowledge this is currently a contentious topic and more studies are warranted to evaluate how MD can be best incorporated into clinical practice.

Conclusion

Research to date has confirmed the importance of MD in BC risk prediction and outcomes, as well as its association with changes in the breast tissue hormonal milieu and heritable factors. However, the evidence suggests that the underlying biological and genetic basis of MD is likely to be complex. Key areas for further investigation include how endogenous steroids affect MD, which could up- or down-regulate cellular signaling pathways that are related to altered BC risk. Although tamoxifen appears to modify MD, this finding needs to be externally validated by further studies and the mechanisms behind this relationship explored. Further clinical and epidemiological studies are also needed to try to determine how to effectively employ MD in a clinical environment. In the future, measurement of MD – especially if it is automated as part of digital mammography for the purpose of personalized medicine - might be used to improve BC screening and treatment strategies.

Competing interests

The authors declare that they have no conflict of interests.

Fig.

1. The current understanding of possible biological mechanisms behind MD associated BC risk.

HRT= hormonal replacement therapy; TGF- β = transforming growth factor beta; ECM= extracellular matrix; BC= breast cancer; MD= mammographic density; ROCK1= Rho associated coiled-coil containing protein kinase 1; FAK-Rho-ERK= focal adhesion kinase-Rho-extracellular signal-related kinase; TAM= tumour associated macrophage.

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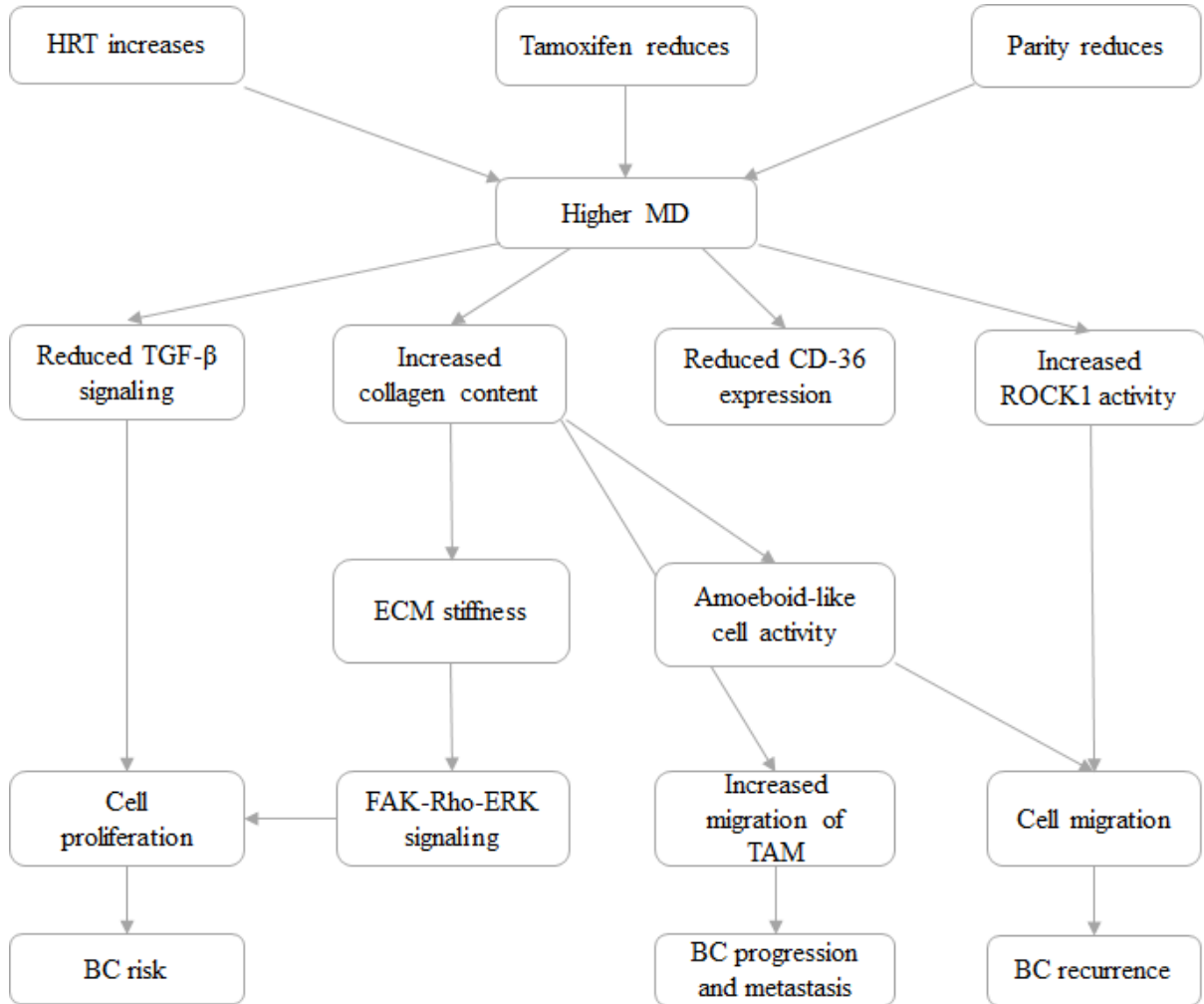


Fig.1 The current understanding of possible biological mechanisms behind MD associated BC risk.

Table 1: Published literature on mammographic density as a risk factor for breast cancer

First author, y [ref.]	Study design. Study population characteristics. Matching variables if applicable (Match). Variables adjusted for in analysis (Adj)	No. cases: noncases	Age (y)	Mammo-graphic feature	Key Finding
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Tice, 2013 [102]	Cohort: BCSC, USA, 1994-2009. Adj: A, race, HRT, BMI.	1,359: 41,459	30+	BIRADS	Combination of atypical hyperplasia and HD was A/W high risk of BC (HR=5.34, 95% CI= 3.52-8.09, $p<.001$).
Linton, 2013 [101]	CC. Sisters from BCFR, USA; WEBC, Canada; and Canadian twin study. Match: AAM. Adj: A, BMI, MS, parity, HRT	687: NK	Mean 50	Cumulus	PD was A/W an increased risk of BC when comparing cases to sister controls (IQOR=2.19) and to unrelated controls.
Yaghjian, 2013 [103]	NCC. NHS prospective cohort, USA. Match: ATC, MS, HRT, FUT. Adj: AAD, BMI, AAM, parity, AAFB, MS, HRT, Fhx, AC, S.	1,045: 567	30-55	Cumulus	The magnitude of the association between PD and BC remains similar for up to 10 years after the first mammogram.
Pollán, 2013 [43]	CC. NBCSP, Spain. 1990-2004. Match: SR, SYB, POR. Adj: A, AAFB, MS, AAM, Fhx, HOPB.	1,172: 1,831	45-65	Boyd semiquantitative scale	OR for MD >75% compared to MD <10% was 3.47 for DCIS, and 2.95 for invasive tumours.
Cecchini, 2012 [104]	Cohort: NSABP, USA, 1999-2004. Adj: A, TR, BMI, S, D.	13,409: 6,338	NK	BIRADS	High BI-RADS density was A/W increased BC risk.
Razzaghi, 2012 [105]	CC: CBCS, USA, 1993-2001. Match: A, BMI, HRT, P. Adj: A, R, BMI, MS, Fhx, AM, HRT.	1,019: 1,292	20-74	BIRADS	MD is A/W increased BC risk, and the effect measure modification by R (White vs. AA) was not significant.
Lokate, 2011 [106]	Cohort: EPIC-NL, the Netherlands, 2001-06. Adj: ATM, AM, AAFB, P, HRT, OCP, Fhx, BMI.	358:859	49-70	Cumulus	HD tissue and fat tissue were independently A/W higher BC risk (OR 2.8 and 2.4 respectively)
Petterson, 2011 [107]	NCC. NHS (1976-1990) and NHS II (1989-1999), USA. Adj: BMI, AM, Fhx, P, AAFB, HRT, AAM.	1,424: 2,660	Mean 47	Cumulus	HD tissue was A/W a greater risk of BC (OR=2.01 for premenopausal and OR = 2.19 for postmenopausal women) whereas non dense area was A/W decreased risk of BC.
Shepherd, 2011 [86]	CC. SPCPMC, USA, 2004-06. Match: A, R. Adj: Fhx, BMI, HOPB, AAFB.	275:825	18+	CAM	Fibroglandular volume and PD were A/W BC risk (highest vs. lowest quintile: OR 2.5 and 2.9 respectively)
Stone, 2010 [108]	CC. CNBSP, UK, 1995-2003. Match: A.	634:1,880	50-75	CAM	Dense area was a better predictor on BC risk than PD.
Chiu, 2010 [109]	Cohort: KRCT, Sweden. Adj: A, BMI, TS, G, NS.	15,658: 1,045	45-59	Tabár	Dense tissue was A/W BC incidence (RR=1.58) and BC mortality (RR=1.91)
Martin,	NCC. NBSS (1984-1990),	1,164:1,1	Mean	CAM	MD was A/W increased BC risk.

2010 [79]	SMPBC (1988-1999), OBSP (1992-98). Match: YESP, SS; AEP, Adj: A, Fhx, AAFB, AAM, AM.	58	56		(OR 1.37 for having one affected relative, 2.45 for having ≥ 2 affected relatives)
Stone, 2009 [12]	XS. IBCIS-I, 1992-2001. Adj: A, BMI, MS, SS.	799:11	35-70	Cumulus	PD was negatively A/W A, BMI, MS, predicted BC risk and SS; however, dense area was negatively A/W only A and BMI.
Olsen, 2009 [110]	Cohort: MSP, Denmark, 1991-2001. Adj: A.	989: 133,651	50-69	BIRADS	The OR of an interval cancer for women with dense breasts was 1.62 and AARR was 2.45 for BC incidence.
Kavanagh, 2008 [111]	CC. MSP, Australia, 1994- 96. Adj: A, HRT, Fhx.	1,706:56 37	50-69	CAM	The risk of large screen-detected cancers was almost 3-fold for the second quintile, and about 4-fold for the third and fourth quintiles compared with low quintiles of MD.
Tamimi, 2007 [112]	NCC. NHS, USA. 1989- 1990. Match: A, FSBC. Adj: BMI, P, AAFB, AAM, AM HRT.	253:520	30-55	Cumulus	The relative risk of BC A/W MD (RR for highest quartile compared with lowest quartile = 3.8.
Boyd, 2007 [1]	NCC. NBSS (1984-1990), SMPBC (1988-1999), OBSP (1992-98). Match: A, AEP,SS. Adj: A, BMI, AM, AAM, P, MS, HRT, Fhx.	1,112: 97	40-80	CAM	Women with density $\geq 75\%$ had an increased risk of BC (OR 4.7) than women with density $< 10\%$. The increased risk persisted for ≥ 8 years after study entry and was greater in younger than in older women.
Vachon, 2007 [113]	CC: MSP, the Mayo Clinic, USA, 1997-2001. Match: A, FSED, MS, TBFM, PSM. Adj: BMI, MS, Fhx, AAFB, P HRT.	372:713	50+	Cumulus	MD represented a general marker of BC risk that is not specific to breast side or location of the eventual cancer.

Abbreviations: A, age; A/W, associated with; AAM, Age at menopause; ATC, age at the time of blood collection; AAD, age at diagnosis; AAFB, age at first birth; AC, alcohol consumption; AM, age at menarche; AA, African American; AEP, age at entry to the program; AARR, age-adjusted rate ratio; BCSC, breast cancer surveillance consortium; BC, breast cancer; BMI, body mass index; BIRADS, Breast Imaging Reporting and Data Systems; BCFR, Breast Cancer Family Registry; CC, case-control; CBCS, Carolina Breast Cancer study; CAM, computer-assisted method; CNBSP, Cambridge and Norwich breast screening programs; DCIS, ductal carcinoma *in situ*; D, diabetes; EPIC-NL, the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition; FUT, follow-up time; Fhx, family history of breast cancer; FSBC, fasting status at the time of blood collection; FSED, final screening exam date; G, grade; HD, high density;

HRT, hormonal replacement therapy; HOPB, history of previous biopsies; KRCT, the Koppaberg randomised control trial; OR, odds ratio; OCP, oral contraceptive; OBSP, the Ontario Breast Screening Program; PD, percent density; POR, place of residence; P, parity; PSM, number of prior screening mammogram; MS, menopausal status; MD, mammographic density; MSP, mammography screening program; NCC, nested case-control; NK, not known; NHS, Nurses' Health Study; NBCSP, Navarre Breast Cancer Screening Program; NSABP, national surgical adjuvant breast and bowel project; NS, nodal status; NBSS, the National Breast Screening Study; IQOR, inter-quintile odds ratio; IBCIS-I, the International Breast Cancer Intervention Study I trial; R, race; RR, relative risk; SS, study site; S, smoking; SR, screening round; SYB, single year of birth; SPCPMC, screening program at the California Pacific Medical Center; SMPBC, the screening mammography program of British Columbia; TR, treatment group; TS, tumour size; TBFM, time between baseline and final mammogram; WEBC, weekend to end breast cancer; XS, cross-sectional study; YESP, year of entry to the screening program.

Table 2. Published literature on the association of mammographic density with breast cancer prognosis and survival

First author, y [ref.]	Study design. Study population characteristics. Matching variables if applicable (Match). Variables adjusted for in analysis (Adj)	No. cases: noncases	Age (y)	Mammo-graphic feature	Key Finding
Eriksson, 2013 [114]	CC. SRCR, 1993-95. Adj: AAM, BMI, HRT, TS, NS, ERS, PRS, G, MOD.	1,774: 946	50-74	Cumulus	No association was found between density and survival.
Maskarin ec, 2013 [25]	NCC. MEC, USA, 1993-96. Adj: AAD, E, R, BMI, SOD, RRx, MS, CM, HS, HRT.	607: 980	NK	Cumulus	MD did not predict survival; RRx improved BC-specific survival.
Gierach, 2012 [26]	Cohort: BCSC, USA, 1996-2005. Adj: AAD, SOD, BMI, MOD.	9,232:1 7,339	30+	BIRADS	High MD was not related to risk of death from BC.

Abbreviations: AAM, Age at menopause; AAD, age at diagnosis; BMI, body mass index; BIRADS, Breast Imaging Reporting and Data Systems; BC, breast cancer; BCSC, breast cancer surveillance consortium; CC, case-control; CM, co-morbidity; G, grade; HS, hormonal status; HRT, hormonal replacement therapy; ERS, estrogen receptor status; E, ethnicity; PRS, progesterone receptor status; MD, mammographic density; MOD, mode of detection; MEC, multi-ethnic cohort; MS, menopausal status; NK, not known; NS, nodal status; NCC, nested case-control; R, race; RRx, radiation treatment; SRCR, Swedish Regional Cancer Registries; SOD, stage of disease; TS, tumour size.

Table 3. Published literature on the association of mammographic density with breast cancer recurrence or new primary occurrence

First author, y [ref.]	Study design. Study population characteristics. Matching variables if applicable (Match). Variables adjusted for in analysis (Adj)	No. cases: noncases	Age (y)	Mammo-graphic feature	Key Finding
Sandberg, 2013 [115]	NCC. SBCR, Sweden. 1976-2005. Match: FUT, Rx. Adj: A, AT, NDAD.	211:247	NK	Cumulus	≥10% reduction in MD was A/W a lower risk of developing BC than those women whose MD remained stable, independent of the therapy given.
Habel, 2010 [29]	XS. KPNC, USA, 1990-97. Adj: A, BMI, RRx, AT, R, MS, Fhx, HOBD, TS, G.	935: 286	20- 84	BIRADS	High MD was A/W increased risk of subsequent BC in either breast in patients who had DCIS.
Buist, 2010 [28]	Cohort: BCSC, USA, 1996-2006. Adj: AT, A, S, Re.	17,286: 8,354	18- 80+	BIRADS	Women with greater MD had higher second primary rates.
Cil, 2009 [27]	XS. WCH, Canada, 1987-88. Adj: A, MS, RRx.	355: 232	35- 87	Wolfe	High MD was A/W increased risk of local recurrence (10-year risks: 21% vs. 5% for density >50% and density <25%), HR=5.7)
Hwang, 2007 [30]	Cohort: BCSC, USA, 1993-2005. Adj: AAD, RRx.	3,274:1, 157	30- 93	BIRADS	High MD was A/W increased hazard for contralateral but not ipsilateral BC during a median follow-up period of 39 months in 133 women who developed invasive BC.

Abbreviations: A, age; AT, adjuvant therapy; A/W, associated with; AAD, age at diagnosis; BC, breast cancer; BIRADS, Breast Imaging Reporting and Data Systems; BMI, body mass index; DCIS, ductal carcinoma *in situ*; FUT, follow-up time; Fhx, family history of breast cancer; G, grade; HOBD, history of benign breast disease; HR, hazard ratio; KPNC, patients recruited at Kaiser Permanente Northern California; MD, mammographic density; MS, menopausal status; NCC, nested case-control; NDAD, non-dense area at diagnosis; NK, not known; Re, registry; Rx, treatment; R, race; RRx, radiation treatment; SBCR, Stockholm Breast Cancer Register; S, stage; TS, tumour size; WCH, patients who underwent breast-conserving surgery at the Women's College Hospital; XS, cross-sectional study.

Table 4. Published literature on the effect of hormonal replacement therapy on mammographic density

First author, y [ref.]	Study design. Study population characteristics. Matching variables if applicable (Match). Variables adjusted for in analysis (Adj)	No. cases: noncases	Age (y)	Mammo-graphic feature	Key Finding
Couto, 2012 [31]	XS. NBCSP, Norway, 2004. Adj: AAS, P, AAFB, BMI, Fhx,	2, 424:452	50-69	CAM	MD was positively A/W HRT use.
Lowry, 2011 [116]	Cohort: READ, USA, 2009-2010. Adj: A, BMI, P, Fhx, R.	1, 168:303	45-80	Cumulus	1-2 months of HRT cessation did not affect adjusted PD.
Chen, 2010 [117]	Cohort: KCGMH, 1994-2001, Taiwan. Adj: AHT, AAM, DR, HRT, BMI.	468:947	43-69	BIRADS	MD and regimen of HRT did not show significant association.
Kerlikowske, 2010 [24]	Cohort: BCSC, USA, 1996-2006. Adj: A, BMI, HRT, MS.	12,090:573,279	30-80+	BIRADS	BIRADS-4 MD was A/W increased BC risk, particularly among oestrogen +progestin users in women aged 55 to 59 years (5-year risk 4.2%).
Nielsen, 2010 [118]	Cohort: EEST, Denmark. Adj: TCBD.	42:43	45-65	BIRADS	1mg of oestrogen + 2mg of drospirenone in postmenopausal women for up to 2 years was A/W increased MD (10% to 26% from baseline to 2 years).
Stuedal, 2009 [119]	XS. NBCSP, 2003. Adj: AAS, P, BMI.	724:205	50-69	CAM	Use of estradiol and norethisterone acetate was A/W increased (6-8.8% increase) MD.
van Duijnhoven, 2007 [34]	Cohort: EPIC-NL, EPIC-UK, 1993-97. Adj: A, BMI, AM, MS, P, Fhx, OCP, S, AC, PA.	795:781	49-71	Cumulus	The absolute mean decline in PD with aging (median time 3.0 years) was larger in never users of HRT (7.3%), than in oestrogen therapy users (6.4%) and combined HT users (3.5%).
Bremnes, 2007 [120]	Cohort: GMSP, Norway, 2001-02. Adj: AAS, P, BMI.	1,007:22	55-71	CAM	Women using the continuous estradiol (E(2)) plus norethisterone acetate (NETA) combination had a mean PD significantly higher than never users (6.1% absolute difference).

Abbreviations: AAS, age at screening; A/W, associated with; A, age; AHT, age at the start of hormonal therapy; AAM, age at menopause; AM, age at menarche; AC, alcohol consumption; BMI, body mass index; CAM, computer-assisted method; DR, duration of regimen; EEST, Estradiol Efficacy and Safety trial; EPIC-NL, the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition; Fhx, family history of breast cancer; GMSP, the governmental mammographic screening program; HRT, hormonal replacement therapy; KCGMH, Keelung Chang Gung Memorial Hospital; OCP, oral contraceptive; PD, percent density; P, parity; PA, physical activity; MD, mammographic density; MS, menopausal status; NBCSP, Navarre Breast Cancer Screening Program; R, race; READ, Radiological Evaluation and Breast Density trial; S, smoking; TCBD, temporal changes in breast density with changes in serum estradiol level; XS, cross-sectional study.

Table 5. Published literature on the association of mammographic density with breast cancer subtypes and tumour characteristics

First author, y [ref.]	Study design. Study population characteristics. Matching variables if applicable (Match). Variables adjusted for in analysis (Adj)	No. cases: noncases	Age (y)	Mammo-graphic feature	Key Finding
Bertrand, 2013 [51]	CC. MMHS, MCMAM, SFMR, NHS, 1989-2008. Adj: Study, A, BMI, P, Fhx, HRT.	3,414: 7,199	Mean: 57	Cumulus	MD is positively associated with BC of all subtypes, particularly with BC of large size and positive lymph nodes in all age groups, and ER-negative status in women <55 years of age.
Eriksson, 2012 [121]	Cohort: CAHRES, 1993-95. Adj: A, BMI, HRT, AM, AAM, OCP, P, B, Fhx, MOD.	2,720: 625	50-74	Cumulus	No association found between MD and tumour phenotype, except for TS which was partially confounded by MOD.
Eriksson, 2012 [122]	Cohort: CAHRES, 1994-96. Adj: age, MS, HRT, Fhx, OCT, TS.	110: 414	32-86	Cumulus	No association found between MD and BC molecular subtypes.
Heusinger, 2012 [48]	Cohort: BC database, Franconia, 1995-2009. Adj: AAD, BMI, P, G, HRT.	2,410: 2,700	<45-70	CAM	PD appears to be inversely A/W ER expression and positively A/W PR expression.
Phipps, 2012 [123]	Cohort: BCSC, USA, 1999-2008. Adj: AEP, R, Fhx, HOBD.	13,797: 1,040,669	40-84	BIRADS	MD was positively and similarly A/W BC of all subtypes.

Yaghjyan, 2011 [23]	CC. NHS, USA, 1989-2004. Adj: AAD, BMI, AM, P, AAFB, HRT, AAM, AC, Fhx, S.	1,042:1,794	Mea n: 60.2	Cumulus	≥50% MD showed a 3.39-fold increased risk of BC compared to <10% MD. The associations were stronger for: <i>in situ</i> (vs. invasive) tumours, high-grade, larger (>2cm) tumours, ER-negative (vs. positive) tumours.
Conroy, 2011 [124]	NCC: MEC, USA, 1993-96. Match: A, R. Adj: AAS, R, P, AAFB, AM, MS, HRT.	667:607	Mea n 62	Cumulus	Mean PD was significantly greater for ER-positive and PR-positive tumours.
Anora, 2010 [125]	Cohort: MSKCC, USA, 2005-07. Adj: A.	1,323: NK	27-91	BIRADS	BIRADS-4 dense breasts occurred more commonly in younger women, more often mammographically occult.
Passaperuma, 2010 [126]	CC. HRSP, Canada, 1997-2008. Adj: A, MT.	46:376	25-65	Cumulus	High MD was not A/W increased BC risk in women with BRCA mutations.
Ding, 2010 [127]	CC. NHSBCS, UK, 1998-2004. Match: A. Adj: A.	370:1,904	50-75	Cumulus	≥50% MD was A/W 2.63-fold risk of developing BC compared to MD <10%. High MD was also A/W ER- positive tumours.
Gierach, 2010 [128]	Cohort: NCICGB, USA. Adj: A, BMI, AM, P, AAFB, MS, HRT, HOPB.	143:119	25-56	CAM	No difference found in MD between unaffected BRCA mutation carriers and women at low-to-average risk of BC.
Ma, 2009 [129]	CC. WCRES, USA, 1994-98. Match: A, R. Adj: R, MS, AM, P, AAFB, HRT.	479:376	35-64	CAM	PD was positively A/W luminal-A and triple-negative BCs.
Ghosh, 2008 [130]	XS. PBCS, USA, 1997-2001. Adj: A, BMI, HRT, Fhx, AAFB, P.	286:799	40+	CAM	MD was not A/W TS, histological type, ER/PR receptor status, mitotic activity or nuclear pleomorphism.

Abbreviations: A, age; AM, age at menarche; AAM, age at menopause; AAD, age at diagnosis; AEP, age at entry to the program; AC, alcohol consumption; A/W, associated with; AAFB, age at first birth; BC, breast cancer; BMI, body mass index; BIRADS, Breast Imaging Reporting and Data Systems; B, breastfeeding ever; BCSC, breast cancer surveillance consortium; ER, estrogen receptor; Fhx, family history of breast cancer; G, grade; HRT, hormonal replacement therapy; HOPB, history of benign disease; HRSP, high-risk screening program; HOPB, history of previous biopsies; OCP, oral contraceptive; P, parity; PR, progesterone receptor; PBCS, post-menopausal breast cancer study; MOD, mode of detection; MS, menopausal status; MEC, multi-ethnic cohort; MSKCC, Memorial Sloan-Kettering Cancer Centre; MT, mutation type; MMHS, the Mayo Mammography Health Study; MCBCS, the Mayo Clinic Breast Cancer Study;

MCMAM, the Mayo Clinic Mammography Study; NHS, Nurses' Health Study; NCC, nested case-control; NK, not known; NHSBCS, national health service breast cancer screening program; NCICGB, national cancer institute's clinical genetics branch breast imaging study; R, race; S, smoking; SPORE, the San Francisco Bay Area Breast Cancer; SFMR, the San Francisco Mammography Registry; TS, tumour size; WCRES, Women's contraceptive and Reproductive Experiences Study; XS, cross-sectional study.

Table 6. Published literature on mammographic density assessment and acquisition techniques

First author, y [ref.]	Study design. Study population characteristics. Matching variables if applicable (Match). Variables adjusted for in analysis (Adj)	No. cases: noncases	Age (y)	Mammo-graphic feature	Key Finding
Pollán, 2013 [131]	CC. SC, Spain, 2007-2010. Match: A. Adj: A, BMI, MS, Fhx, P, HRT.	655: 2,845	45-68	DM-Scan vs. Cumulus	DM-Scan, a new semiautomatic tool and Cumulus were high concordant (CCC: 0.80-0.84) in assessing MD.
Seo, 2013 [132]	Cohort: SMC, Korea. 2011.	193: 463	35-72	VBD vs. BIRADS	VBD showed a significant positive correlation with BIRADS by radiologists (Spearman's $p = 0.754$, $p < 0.001$)
Li, 2012 [133]	CC. SC, Sweden, 1993-95. Match: EADC. Adj: A, BMI, HRT, P, AAS, AAM.	3,345: 843	50-74	automated measure vs. Culumus	A high correlation between the Cumulus measure and the automated measure ($r = 0.884$) in an external test set.
Spayne, 2012 [134]	XS. VBCSS, USA, 1996-2006. Adj: BMI.	11,755: NK	50+	BIRADS	BIRADS had an intra-radiologist percent agreement of 77.2%.
Tagliafico, 2012 [100]	Cohort: NICR, Italy, 2010.	50: NK	35-83	BIRADS	MD appeared to be underestimated on digital breast tomosynthesis.
Berg, 2012 [135]	Cohort: ACRIN USA, 2004-06.	6666, 2,662: 147	25-91	BIRADS	Ultrasound identified an additional 3.7 cancers per 1000 screens and MRI identified 14.7 per 1000 screens.

Moon, 2011 [98]	XS. SC, Korea, 2007-08.	40: NK	Mean 50.9	PD	ABUS and MRI showed high correlation for MD assessment.
Corsetti, 2011 [136]	Cohort: SC, USA, 2001-06.	8,865	NK	BIRADS	US had a CDR (additional) of 4.4/1000 screens in dense breasts.
Thompson, 2009 [137]	XS. MARIBS, UK, 2006.	599: 238	31-49	Cumulus	MRI PD is well correlated with mammographic PD ($r = 0.76$) but overall gives estimates 8.1 percentage points lower ($p < 0.0001$).
Nickson, 2009 [138]	XS. SC, Australia, 1993-96. Adj: A, HRT, Fhx, MOD.	1,348	50-69	TT	PMD, MD and MD adjusted for non-dense area showed similar positive and significant association with TS.
Boyd, 2009 [139]	CC. MSH, WCH, PMH (USA); SHSC, OBSP (Canada), 2000-03. Match: A. Adj: A, AAFB, BMI, P, MS.	364:656	Mean 59	Cumulus	Measurement of the breast tissue volume did not improve BC risk prediction.
Tagliafico, 2009 [140]	XS. SC, Italy, 2007.	160: 735	NK	FAM & SAM vs. BI-RADS	FAM and SAM correlated well with BIRADS and demonstrated good intra- and inter-observer variability.
Heine, 2008 [141]	CC. SC, the Mayo Clinic, USA, 1997-2001. Match: A, FSED, MS, RC. Adj: A, BMI, P, HRT, MS.	372:713	Mean: 61	FAM vs., Cumulus, BIRADS	FAM showed good correlation with Cumulus and BIRADS.
Pisano, 2008 [142]	XS: DMIST, USA & Canada.	42,760: 6,768	NK	BIRADS	Digital mammography performed better than film for women younger than 50 with dense breasts.
McCormack, 2007 [143]	XS. SC, UK, 2004. Adj: A, BMI, P, HRT.	976:24	53-65	SMF vs. Cumulus	Reliability of a single measurement was lower in the SMF than in the threshold method.

Abbreviations: A, age; AAS, age at screening; AAM, age at menopause; ABUS, automated breast ultrasound; AAFB, age at first birth; ACRIN, American College of Radiology Imaging Network; BC, breast cancer; BMI, body mass index; BIRADS, Breast Imaging Reporting and Data Systems; CC, case-control; CCC, concordance correlation coefficients; CDR, cancer detection rate; DMIST, the Digital Mammographic Imaging Screening Trial; EADC, expected age distribution among cases; Fhx, family history of breast cancer; FAM, fully automated method; FSED, final screening exam date; HRT, hormonal replacement therapy; OBSP, Ontario Breast Screening Program; P, parity; PD, percent density; PMH, Princess Margaret Hospital; MS, menopausal status; MD, mammographic density; MRI, magnetic resonance imaging; MARIBS, multicentre magnetic resonance imaging breast screening study; MOD, mode of detection; MSH, Mount Sinai Hospital; NK, not known; NICR, National Institute for Cancer Research; RC, residence; SMC, Samsung medical center; SC, screening centre; SHSC, Sunnybrook

Health Sciences Centre; SAM, semi-automated method; SMF, standard mammogram form; TT, semi-automated technique: threshold technique; TS, tumour size; WCH, Women's College Hospital; US, ultrasound; VBD, automated volumetric breast density; VBCSS, Vermont Breast Cancer Surveillance System; XS, cross-sectional study.

Table 7. Published literature on the effect of breast cancer hormonal treatment on mammographic density

First author, y [ref.]	Study design. Study population characteristics. Matching variables if applicable (Match). Variables adjusted for in analysis (Adj)	No. cases: noncases	Age (y)	Mammo-graphic feature	Key Finding
Li, 2013 [144]	CC. CAHRES, 1993-95. Adj: AAD, BMI, HRT, ERS.	278: 432	50-74	CAM	Poor function of CYP2D6 was A/W less reduction in MD with tamoxifen Rx.
Henry, 2013 [145]	Cohort: ELPh trial, USA, 2005-09. Adj: A, BMI, AT, HRT.	259: 244	35-84	BIRADS	Mean PD reduction was 17.1% to 15.1% with AI therapy in 2/3 of patients, more pronounced in women with baseline PD \geq 20%.
Li, 2013 [92]	CC. SBCR, 1993-95. Adj: AABM, HRT, BMI, ERS, TS, G, NS.	1,295: 2,050	50-74	Cumulus	>20% reduction in MD post tamoxifen Rx was A/W a reduced risk of death due to BC of 50%.
Vachon, 2013 [146]	CC. NCIC CTG, NCCTG, MC, USA. Match: AABM, BMI.	369: 205	41-91	Cumulus	14% of 387 patients had a MD reduction of at least 5% after an average of 10 months of AI Rx and the reduction was similar with that of matched controls.
Kim, 2012 [93]	Cohort: WBPD, Korea, 2003-06. Adj: A, TS, NS, AT, G.	1,065:477	24-77	Cumulus	MD reduction was significantly A/W recurrence-free survival after at least 2 years of tamoxifen or AI.
Prowell, 2011 [147]	Cohort: SKCCC, USA, 2004-06. Adj: A, R, BMI, DS, G, HS.	53:1	Mean 62.5	Cumulus	18 women had \geq 20% MD reduction after 12 months of anastrozole 1 mg daily.
Cuzick, 2011 [91]	NCC. IBIS-I, 1992-2001. Adj: A and MD at entry to IBIS-I, BMI.	123: 942	35-70	Cumulus	\geq 10% MD reduction correlated to a 63% reduction in BC risk after tamoxifen Rx (20mg/d) for \geq 12 months.
Cigler,	Cohort: NCIC CTG,	44:23	55+	Cumulus	2.5mg of letrozole daily for 12

2010 [148]	Canada. Adj: A, BMI.					months with another 12 months follow-up did not affect MD.
Mousa, 2008 [149]	Cohort: women from private clinics, Canada. 2006-07. Adj: A, BMI.	40:16	54-74	BIRADS		Letrozole 2.5mg TDS + HRT for a year was A/W a reduction in MD; whereas there was no change in MD in women who took HRT alone.
Eilertsen, 2008 [150]	Cohort: RET, Norway, 2002-05. Adj: A, BMI.	178: 180	45-65	CAM		Raloxifene or Tibolone oral Rx for 12 weeks were not A/W changes in MD.

Abbreviations: AAD, age at diagnosis; A/W, associated with; A, age; AT, adjuvant therapy; AI, aromatase inhibitor; AABM, age at baseline mammogram; BC, breast cancer; BMI, body mass index; BIRADS, Breast Imaging Reporting and Data Systems; CC, case-control; CAHRES, the Cancer Hormone Replacement Epidemiology in Sweden study; DS, disease stage; ERS, oestrogen receptor status; ELPh, Exemestane and Letrozole Pharmacogenomics; G, grade; HRT, hormonal replacement therapy; HS, hormonal status; IBIS, the International Breast Cancer Intervention Study; PD, percent density; MC, the Mayo Clinic; NS, nodal status; NCIC CTG, National cancer institute of Canada clinical trials group; NCCTG: north central cancer treatment group; NCC, nested case-control; Rx, treatment; R, race; RET, raloxifene, oestrogen, tibolone study; SBCR, Swedish breast cancer register; SKCCC, Sidney Kimmel comprehensive cancer centre; TS, tumour size; TDS, three times per day; WBPD, web-based patient database.

Table 8. Published literature on the biology of mammographic density

First author, y [ref.]	Study design. Study population characteristics. Matching variables if applicable (Match). Variables adjusted for in analysis (Adj)	No. cases: noncases	Age (y)	Mammo-graphic feature	Key Finding
Chew, 2013 [39]	PC. PMSVH, Melbourne, Australia. 2012.	10: NK	38-57	BIRADS	HD human tissues had reduced stromal, increased adipose tissue compared to LD tissue during murine postpartum involution.
Rice, 2012 [61]	NCC. NHS, USA. 1989-1990, 1996-99. Match: A, MS, HRT. Adj: A, Fhx, AM, P, AAFB, S, AC, BMI.	1,219: 597	43-70	Cumulus	Plasma IGF-1, IGFBP-3 and GH levels were not A/W MD.
Heusinger, 2012 [58]	XS. SC, Franconia, Germany, 1995-2008. Adj: A, BMI, P, HRT.	1,975: 1,989	Mean 59.3	PD	No significant differences in PD between women with BC who had low and high Ki-67 values.

DeFilippis, 2012 [62]	PC. <i>In vitro</i> cell culture.	NK	NK	NK	CD36 is repressed in tumour and high MD stroma.
Chew, 2012 [73]	PC. PMSVH, Melbourne, Australia. 2011.	10: NK	35-59	BIRADS	High and low MD human mammary tissues maintained their histological differential in murine biochambers.
Ghosh, 2012 [52]	PC. MC, USA. 2006-08.	59: 179	40-82	BIRADS	Dense tissue comprised of greater mean areas of epithelium and stroma, less fat than LD tissue.
Lin, 2011 [53]	PC. PMSVH, Melbourne, Australia. 2010. Adj: A, BMI, MS.	12:3	35-48.3	BIRADS	HD regions had higher relative gland counts, higher stromal and lower fat compositions than LD tissue.
Walker, 2009 [151]	XS. MEGF, Britain, 1991-97. Adj: MV, AAS, LAB, BMI, SST, S, AAFB, P.	342:458	39-41	Cumulus	The positive association between endogenous oestrogen and MD was attenuated after adjustment for BMI.
McCormack, 2009 [152]	XS. SC, UK. 2005-06. Adj: A, BMI, LAB, ATC,	270: 210	50-65	Cumulus	Oestrogen, leptin, IGF levels were not A/W MD in postmenopausal women.
Verheus, 2009 [59]	PC. MEC, USA.	159: 120	Mean: 59.8	Cumulus	No association found between MD and expression of steroid receptors and proliferation markers.
Provenzano, 2008 [63]	PC. BTMSC in mouse mammary tissue.	NA	NA	NA	Increased stromal collagen in mouse mammary tissue increased tumour formation about 3-fold ($p<0.00001$).
Johansson, 2008 [153]	XS. CPT, Italy, 1998-2000. Adj: A, BMI.	174: 52	52	Cumulus	MD was found to be A/W circulating estradiol levels.
Harvey, 2008 [60]	CC. SC, USA. 1991-98. Match: A, YOM. Adj: A, HRT.	28: 299	Mean 61.7	CAM	HD in women using HRT was correlated with greater fibrous stroma and lobule type 1.
Bremnes, 2007 [154]	Cohort: NBCSP, Norway, 2001-02. Adj: AAS, AM, AAM, P, AAFB, Fhx, S, AC, HRT, LAB, BMI.	722:319	55-71	Cumulus	A positive association was found between plasma SHBG levels and mammographic densities among 722 postmenopausal women.
Khan, 2007 [155]	XS. HRKMC, USA. 2003-06. Adj: A, MS, BMI, P, PBC.	344: NK	20-78	Cumulus	MD exhibited no correlation with Ki-67 expression or cytomorphology.
Maskarinec, 2007 [156]	XS. SCs, USA, Japan and Norway. Adj: A, BMI, P, MS.	1,327: NK	Mean 53.9	Cumulus	No significant association was found between PD and IGF-I or prolactin levels among pre-and postmenopausal women.

Verheus, 2007 [157]	XS. Prospect-EPIC, The Netherlands. 1993-97. Adj: A, BMI, AM, AAM, AC.	684: 923	49-69	Cumulus	Higher premenopausal IGF-I levels were A/W a smaller decrease in dense area and a smaller increase in the fat area over menopause.
Bremmes, 2007 [158]	XS. SC, Norway, 2001-02. Adj: A, P, BMI, AAM, HRT.	977:64	55-71	CAM	Plasma IGF-I and IGFBP-3 were positively associated with PD.

Abbreviations: A, age; AAFB, age at first birth; AC, alcohol consumption; AM, age at menarche; AAS, age at screening; ATC, age at the time of blood collection; AAM, age at menopause; A/W, associated with; BC, breast cancer; BMI, body mass index; BIRADS, Breast Imaging Reporting and Data Systems; BTMSC, bi-trangenic tumour model with increased stromal collagen; CPT, clinical prevention trial; CC, case-control; CAM, computer-assisted method; EPIC, European Prospective Investigation into Cancer and Nutrition cohort; Fhx, family history of breast cancer; GH, growth hormone; HD, high density; HRT, hormonal replacement therapy; HRKMC, high-risk clinic at the University of Kansas medical centre; LD, low density; LAB, laboratory assay batch; PMSVH, women undergoing prophylactic mastectomy at St Vincent's Hospital; PC, pre-clinical; P, parity; PD, percent density; PBC, prior breast cancer; MS, menopausal status; MD, mammographic density; MC, the Mayo Clinic; MEGF, the mammography, oestrogen and growth factors study; MV, mammography view; MEC, multi-ethnic cohort; NCC, nested case-control; NHS, Nurses' Health Study; NK, not known; NA, not applicable; NBCSP, Navarre Breast Cancer Screening Program; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; S, smoking; SC, screening centre; SST, sample storage time; SHBG, sex hormone binding globulin; SC, screening centre; XS, cross-sectional study; YOM, year of mammogram.

Table 9. Published literature on the genetic variations of mammographic density

First author, y [ref.]	Study design. Study population characteristics. Matching variables if applicable (Match). Variables adjusted for in analysis (Adj)	No. cases: noncases	Age (y)	Mammo-graphic feature	Key Finding
Sun, 2013 [84]	Cohort: PWBCS, 2000-2003. Adj: A, BMI.	121: NK	20-74	Cumulus	Inactive subtype of extratumoral gene expression was A/W increased MD.
Ozhand	Cohort: NPCSP, 1996-	2,755:	50-69	CAM	9 tagging SNPs in the <i>IL6</i> gene had

[159]	, 2013	2005. Adj: A, BMI	4,419			an effect of 3-5% on MD per variant allele.
[160]	Lee, 2013	Cohort: SBSP, Singapore. Adj: AAM, BMI.	2,164: 1,538	NK	NK	161 SNPs in 15 hormone metabolism pathway gene regions were not A/W MD.
[161]	Lee, 2013	XS. SBSP, Singapore, 1993-98. Adj: A, BMI, DG.	3,695: 82	45-74	CAM	TGFβ1 genetic variations were found to be A/W PD.
[162]	De Aguiar, 2012	Cohort: SC, Brazil. 2005-06.	890: NK	45-69	BIRADS	MD in postmenopausal women was significant A/W the combined GSTM1 and GSTT1 null genotypes.
[163]	Stone, 2012	CC. ATR, 1995-99. Adj: A, BMI.	327: 272	40-70	Cumulus	Genetic components of MD variation are established before mid-life and MD measures are highly correlated over time.
[83]	Stevens, 2012	XS.MC, USA. Adj: A, BMI.	1,241: 5,777	NK	Cumulus	RS1265507 on 12q24 was A/W PD.
[81]	Vachon, 2012	XS. DENSNP Consortium, USA. Adj: A, BMI, MS.	5,110:1 1,785	NK	Cumulus	The C-allele of rs3817198 in LSP1 was positively A/W BC and MD.
[164]	Varghe se, 2012	Cohort: GWAS, UK. Adj: A, BMI, PS.	3,628:5 ,190	NK	Cumulus	PD and BC have a shared genetic basis that is mediated through a large number of common variants.
[165]	Greenw ood, 2011	Cohort: ATR. Adj: A, P, MS, HRT, BMI.	3,253: 699	Mean 52.8	PD	Maximum LOD from the GWS was on chromosome 7q32.3-q34 (LOD32) and 12.11.22-q13.11 (LOD 3.3).
[166]	Maskar inec, 2011	Cohort: mother and daughter pairs, USA. Adj: R, BMI, A,	101: 203	38.7-64.3 (moth ers); 10.2-16.9 (daug hters)	BIRADS	No association was found between percent and absolute fibroglandular volume of mothers and daughters.
[167]	Giacom azzi, 2011	Cohort: MSP, Brazil. Adj: AAS, AAM, AM, AAFB, P, R, BMI.	750: NK	40-69	BIRADS	HD was A/W more frequently in premenopausal women with the risk genotypes <i>STK15 F3II AA</i> and <i>AT</i> .
[168]	Sung, 2010	Cohort: HTS, Korea, 2005-07. Adj: A, BMI, S, AC, AAFB, AM, P, B, HRT, MS.	730: 667	30+	Cumulus	PD demonstrated high heritability in Korean women.

Odefrey, 2010 [169]	XS. ATSMDS, 2004-09. Adj: A, BMI.	2,288: NK	40-70	Cumulus	rs3817198 (LSP1) and rs13281615 (8q) were A/W dense area and PD.
Yang, 2010 [170]	PC. FTB, USA.	66: NK	29-88	BIRADS	High MD was A/W reduced TGF β signaling and increased COX2 expression in high risk women.
de Moura Ramos, 2009 [171]	XS. UNIFESP-EPM, 2008. Adj: A, BMI, MS, P, AAM.	120: NK	NK	BIRADS	Polymorphism XbaI may be strongly related to MD ($p=0.02$).
Crandall, 2009 [172]	Cohort: SWAN, USA. Adj: A, R, P, BMI, S.	451:64 3	42-52	PD	The CYP1B1 rs162555 CC genotype was A/W a 9.4% higher MD than the TC/TT genotype ($p = 0.04$). The CYP19A1 rs936306 TT genotype was A/W 6.2% lower MD than the TC/CC genotype ($p = 0.02$).
Kataoka, 2009 [173]	CC. MSP, UK. 2002-07. Adj: AAS, BMI, S, AC, AAM, AM, MS, P, B, AAFB, HOBD.	746: NK	37-79	Cumulus	Sister-sister pairs and monozygotic twin pairs showed that MD had a strong heritable basis.
Chambro, 2009 [174]	XS. UNIFESP-EPM, Brazil. 2006. Adj: A, P, BMI.	123: NK	NK	BIRADS	Wild-type PROGINs and mutated CYP17 taken together were A/W a 4.87 times higher chance of having dense breasts ($p=0.030$).
Woolcott, 2009 [175]	NCC. MEC, USA, 1993-96. Match: R, YAG. Adj: A, R, BMI.	361:46 4	45-75	Cumulus	The polymorphism rs12443621 in TOX3 was associated with PD.
Douglas, 2008 [176]	Cohort: Sister-pairs study, USA, 2005-07. Adj: A, MS, BMI, AM, AAM.	550: 474	40-88	CAM	Genetic effects accounted for >33% of the total variance of MD.
Tamimi, 2008 [177]	XS. NHS, USA. 1989-1990. Adj: A, BMI.	1,121: NK	33-55	Cumulus	No association between the 11 BC susceptibility loci and MD was seen.
Diorio, 2008 [178]	XS. MSP, Canada, 2001. Adj: AAS, BMI, P, S, HOPB.	741:46	Mean 46.8	Cumulus	Women carrying increasing number of copies of the rare allele of IGF-I rs1520220 and rs6220 SNPs had increased PD.
Verheul, 2008 [179]	Cohort: Prospect-EPIC, 1993-97. Adj: A, BMI, P, HRT, S, OCP, AAFB.	656: 1,272	50+	PD	Common genetic variations in the IGF-1 gene were not A/W MD.
Vachon, 2007 [180]	XS. MGBCP, USA. 1990-96. Adj: A.	583:30 6	46-70	Cumulus	The maximum LOD for linkage score from the GWS was on chromosome 5p (likely to account for up to 22% of variation in MD).

Stone, 2007 [181]	XS. ATSMDS. Adj: A, BMI, P, HRT, S, MS.	457: 499	40-70	CAM	Each additional copy of the HSD3B1 Asn(367)Thr variant allele was A/W lower PD.
Olson, 2007 [182]	XS. MC, USA. Adj: A, GL, BMI, MS, P.	550: 182		Cumulus	CYP19 variants were not A/W MD.
Tamimi, 2007 [183]	XS. NHS, USA, 1998. Adj: A, BMI, AC, P, Fhx, HOBD, MS, HRT.	1,121:2 1	42-78	Cumulus	Two haplotype-tagging SNPs in IGF1, rs1520220 and rs2946834, showed a strong association with MD.

Abbreviations: A, age; AAM, age at menopause; ATR, Australian twin registry; AAS, age at screening; AAFB, age at first birth; AC, alcohol consumption; ATSMDS, the Australian twin and sisters mammographic density study; A/W, associated with; AM, age at menarche; BC, breast cancer; BMI, body mass index; BIRADS, Breast Imaging Reporting and Data Systems; B, history of breastfeeding; CC, case-control; CAM, computer-assisted method; COX, cyclooxygenase; DG, dialect group; EPIC, the European Prospective Investigation into Cancer and Nutrition study; FTB, frozen tissue bank; Fhx, family history of breast cancer; GWAS, genome-wide association studies; GWS, genome-wide scan; GL, geographic location; HRT, hormonal replacement therapy; HD, high density; HTS, the healthy twin study; HOBD, history of benign disease; HOPB, history of previous biopsies; OCP, oral contraceptive; PD, percent density; PWBCS, population-based Polish Women's breast cancer study; PS, population stratification; P, parity; PC, pre-clinical; LOD, logarithm of odds; MD, mammographic density; MC, the Mayo Clinic; MS, menopausal status; MSP, mammography screening program; MGBCP, multigenerational families ascertained through a breast cancer proband; NBCSP, Navarre Breast Cancer Screening Program; NK, not known; NHS, Nurses' Health Study; IL, interleukin; IGF, insulin-like growth factor; R, race; SBSP, Singapore breast screening project; SNP, single nucleotide polymorphism; SWAN, the study of Women's Health across the nation; SC, screening centre; S, smoking; TGFB1: Transforming Growth Factor Beta 1; UNIFESP-EPM, patients from the Climacterium Sector and the Diagnostic Section of the Department of Gynecology, Federal de São Paulo, Escola Paulista de Medicina; XS, cross-sectional study; YAG, 5-year age group.

Table 10. MD classification and measurement systems

MD Assessment Method	Classification
BI-RADS	The breast parenchyma is given a score of 1-4: 1= predominantly fat; 2= scattered fibroglandular densities; 3= heterogeneously dense; 4= extremely dense.
Wolfe	The breast parenchyma is divided into 4 risk patterns: N1= predominantly fat; P1= mainly fat with a few prominent ducts; P2= prominent duct patterns involving at least one half of the parenchyma; DY= extremely dense.
Tabár	The breast parenchyma is divided into 5 risk patterns based on 4 mammographic building blocks: nodular, linear, homogeneous and radiolucent tissue respectively I= [25%,15%,35%,25%] II= [2%,14%,2%,82%] III= Similar to II in composition + periductal fibrosis IV= [49%,19%,15%,17%] V= [2%,2%,89%,7%]
Cumulus	Interactive thresholding software that relies on the user to select the whole breast and dense tissue areas on digitized mammographic images. It calculates the pixel sizes of selected areas based on a grey scale and convert the results to square centimetres. Percent dense area = dense area/ whole breast area Non-dense area = whole breast area – dense area