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RISK AND PREVENTION (ME WOOD, SECTION EDITOR)

Mammographic Density: Intersection of Advocacy, Science, and Clinical Practice

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Abstract

Purpose of Review Here we aim to review the association between mammographic density, collagen structure, and breast cancer risk.

Recent Findings While mammographic density is a strong predictor of breast cancer risk in populations, studies by Boyd show that mammographic density does not predict breast cancer risk in individuals. Mammographic density is affected by age, parity, menopausal status, race/ethnicity, and body mass index (BMI). New studies normalize mammographic density to BMI and this may provide a more accurate way to compare mammographic density in women of diverse race and ethnicity. Preclinical and tissue-based studies have investigated the role collagen composition and structure in predicting breast cancer risk. There is emerging evidence that collagen structure may activate signaling pathways associated with aggressive breast cancer biology.

Summary Measurement of film mammographic density does not adequately capture the complex signaling that occurs in women with at-risk collagen. New ways to measure at-risk collagen potentially can provide a more accurate view of risk.

Keywords Mammographic density · Breast cancer risk · Mammographic density notification · Collagen · Tissue tensile forces · TACS

Introduction

Population-based studies consistently show that high mammographic breast density is associated with a 2- to 6-fold increased risk of breast cancer [1••]. Studies of postmenopausal women in the NSABP Study of Tamoxifen and Raloxifene (STAR) showed that high breast density was significantly associated with increased breast cancer risk [2].

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Mammographic density, while relatively easy to measure, is the sum of complex variables that change during a woman's lifetime. Low mammographic density is associated with increasing age and body mass index (BMI); high mammographic density is associated with young age, low BMI, and with hormone use; mammographic density also varies between racial and ethnic groups. For example, an athletic 20-year-old woman with a BMI of 20 may have high mammographic density but this does not reflect increased risk, but rather that the woman is young and has a low BMI. Conversely, mammographic density in an obese woman may be low, but the actual breast collagen structure may be associated with high rather than low risk for breast cancer.

High mammographic density on film-based mammographic screening has been consistently associated with the risk of "missed" or interval breast cancer as high mammographic density can mask the presence of a breast cancer. Alternatively, the majority of biologically aggressive triple-negative breast cancers (TNBC) are not associated with mammographic calcifications; in the absence of a breast mass,

TNBC are not easily detected by mammogram, regardless of low or high mammographic density.

Mammographic density has been the subject of intense lobbying and advocacy. A majority of states have passed laws (or are in the process of passing laws), requiring physicians to tell a woman whether she has mammographically dense tissue [3]. These laws state that women should be informed that dense breast tissue can (1) hide tumors on a mammogram, (2) increase the risk of breast cancer, and (3) require additional screening tests, such as ultrasound and breast magnetic resonance imaging (MRI) [3, 4].

These new laws are not without controversy. Some professional groups argue that the measurement of mammographic density is subjective and not highly reproducible in a community setting [4]. To further complicate issues, there are no accepted methods to standardize mammographic density measurements for variables that affect density including age, BMI, race, ethnicity, and breast size [1••]. While breast MRI can be recommended, the American Cancer Society Breast MRI guidelines do not recommend breast MRI screening for women with high breast density in the absence of established clinical risk factors (> 20% lifetime risk) [5].

Here, our goal is to provide a review of the published literature on mammographic density and breast cancer risk, the biological basis of mammographic density, and review tissue-based and preclinical studies linking collagen structure with activation of signaling events that promote aggressive breast cancer biology.

Measurement of Breast Density

Breast density reflects breast composition, particularly, the relative ratio of fibroglandular to adipose (fat) tissue (Fig. 1a, b). Fibroglandular tissue includes the (1) ducts and glands of the breast and (2) connective tissue between ducts and glands (Fig. 1a, b). Adipose tissue appears dark on a mammogram and is considered "low" density. Areas of brightness on mammogram are considered to be "dense" and have high fibroglandular tissue content.

In 1976, Wolfe first demonstrates the association between mammographic density and breast cancer risk [6]. Breast density can be measured by film mammogram, digital mammography, and MRI. However, most studies predicting breast cancer risk have utilized film mammography [7]. Density is typical reported using (1) the original Wolfe grading system, (2) percentage of mammographic density tissue, and/or (3) BIRADS assessment of density. Percentage density that is determined subjectively by a radiologist is shown the strongest predictor of breast cancer risk [8••]. The most widely used density reporting method in the USA today is the BIRADS classification: (1) BIRADS-1; predominately fatty, (2) BIRADS-2; scattered density, (3) BIRADS-3; heterogeneous density, and (4) BIRADS-4; extremely dense.

For women with BIRADS 4 mammographic density (extreme density), the sensitivity and specificity of mammography are 63 and 89% respectively. This compares with 87 and 97% sensitivity and specificity for women with BIRADS1 (predominately fatty) breasts [9]. While MRI can be used to screen for breast cancer in women with high breast density, American Cancer Society finds insufficient evidence for (or against) the use of MRI in women with high breast density alone and no additional risk factors [5].

Breast Composition and Biological Determinants of Mammographic Density

Mammographic density is determined by the differential ability of X-rays to penetrate human breast tissue. While breasts can feel dense or not dense on clinical examination, there is no direct correlation between breast density as assessed by clinical breast exam and mammographic breast density [1••].

The human breast is composed of epithelial cells, connective tissue/fibroblasts, adipose cells, endothelial cells, and immune cells (Fig. 1a, b). X-rays readily penetrate adipose tissue; a high volume of adipose tissue correlates with low mammographic density; adipose tissue appears "black" on mammography (low density) [1••]. In contrast, epithelial and stromal tissues are radio-opaque compared with adipose tissue and appear "white" on a mammogram (high density) [1••].

While the majority of breast cancers are epithelial in origin, the relative volume of breast collagen to adipose cell is the major predictor of mammographic density. Recent studies show that during breast cancer initiation, there is a desmoplastic reaction consisting of (1) activation and recruitment of stromal cells, and (2) collagen deposition. Regions of the breast undergoing desmoplastic reaction demonstrate increased mammographic density.

Modifiers of Mammographic Density

Mammographic density decreases with increasing age and increasing BMI. High mammographic density is associated with hormone use, low BMI, and young age [1••]. The majority of White women less than 25 years old have high mammographic density (BIRADS 3,4) [10]. For women less than 40, 81% have high mammographic density (BIRADS 3,4) [10]. As women age, there is a decrease in mammographic density but an increase in breast cancer risk and incidence [10], underscoring the importance of correcting for both age and BMI in breast cancer risk assessment studies [10].

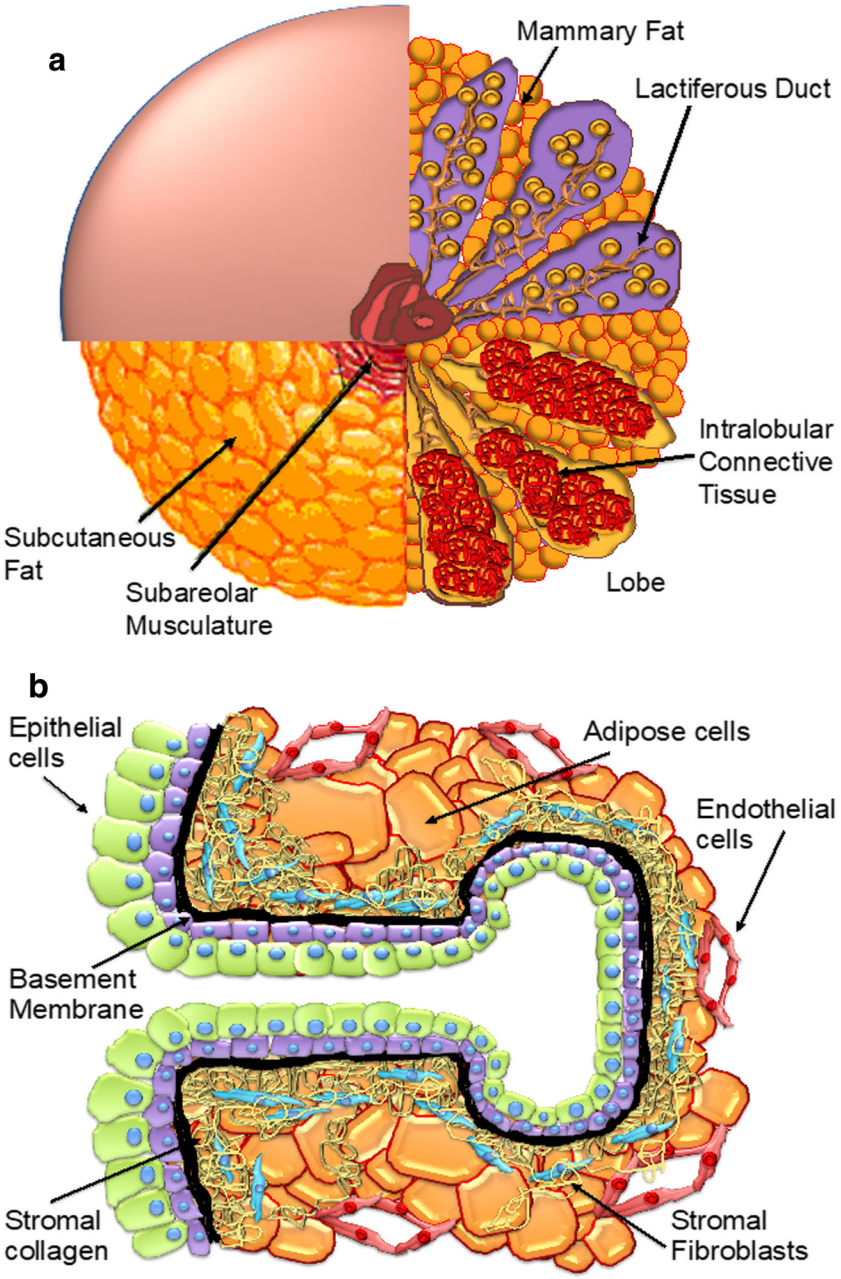

Fig. 1 **a**, **b** The human breast composition is a complex structure. **a** Progressive quadrant dissection (counterclockwise) of the human breast reveals subcutaneous fat, breast lobes containing intralobular connective tissue, and the lactiferous ducts and mammary fat. **b** The terminal ductal lobular unit of the human breast contains epithelial cells, basement membrane, stromal fibroblasts, adipose cells, endothelial cells, and immune cells. Each cell type contributes to the breast density of an individual woman. **c**–**f** Recent research provides evidence that collagen structure may play a key role in breast cancer survival and perhaps breast cancer risk. **c**, **d** Normal collagen is curly. **e**, **f** High-risk collagen is aligned, stiff, and exerts tension (high tissue tensile forces) on adjacent epithelial cells. **e**, **f** Second harmonic generation imaging of collagen structure in human breast biopsies containing in invasive breast cancer. Image in **d** depicts curly normal collagen. Image in **f** depicts high-risk aligned TASK-3 collagen. **g** Tensile or compression forces on epithelial cells, cell-cell junctions, and basement membrane. **h** High tissue tensile forces result in mechanoresponsive signaling, mechanotransduction signaling, and alterations in intrinsic forces

Combination hormone replacement therapy (estrogen and progesterone) is consistently associated with an increase in mammographic density [11]. High mammographic breast cancer density predicts breast cancer risk in women with a first-degree relative who has had breast cancer [12]. In *BRCA1* or *BRCA2* mutation-carriers, however, the association between high mammographic density and breast cancer risk was less strong [12].

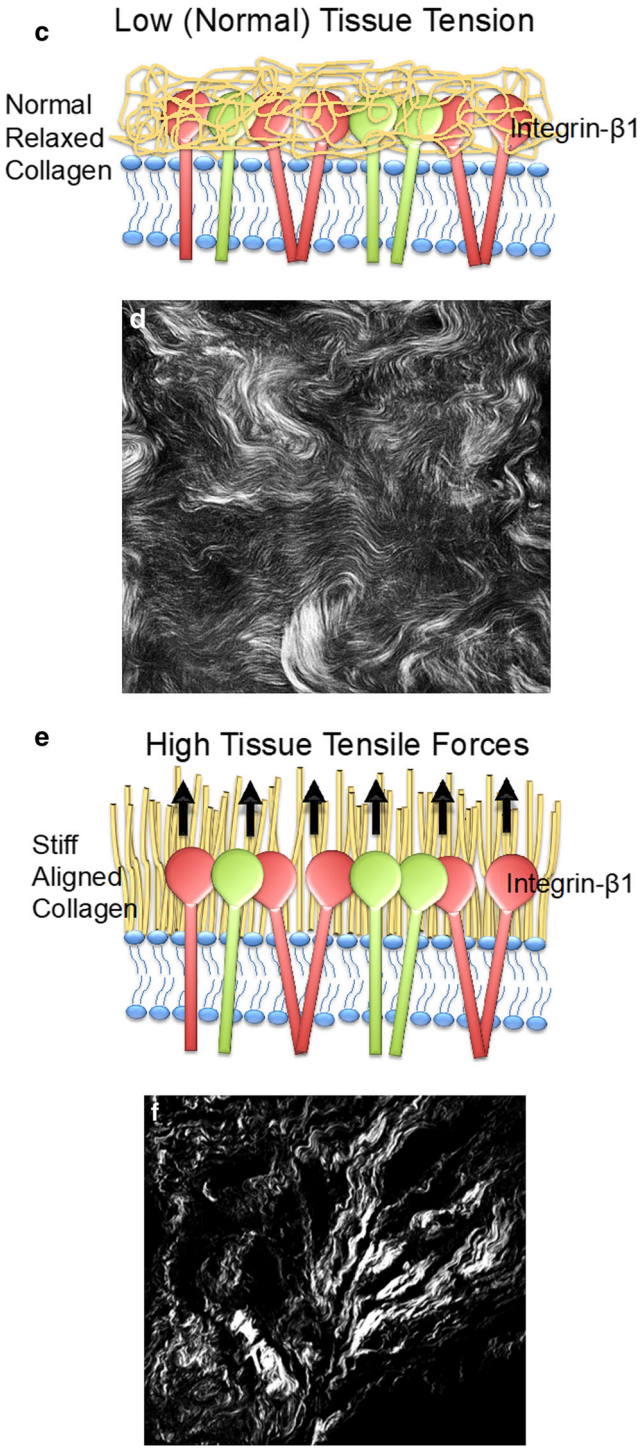

Fig. 1 (continued)

Population-Based Studies of Mammographic Density and Increased Breast Cancer Risk

Over 40 population-based studies demonstrate an 2- to 6-fold increased risk of breast cancer in women high mammographic density (Table 1) [21••]. Originally, this association was thought to be due to the difficulty of detecting breast cancer in mammograms with extremely or heterogeneously dense tissue, termed "masking bias" [22]. Subsequent studies showed that masking bias is not the only factor that accounts for the higher breast cancer incidence observed in mammographically dense breast tissue [1••, 23••].

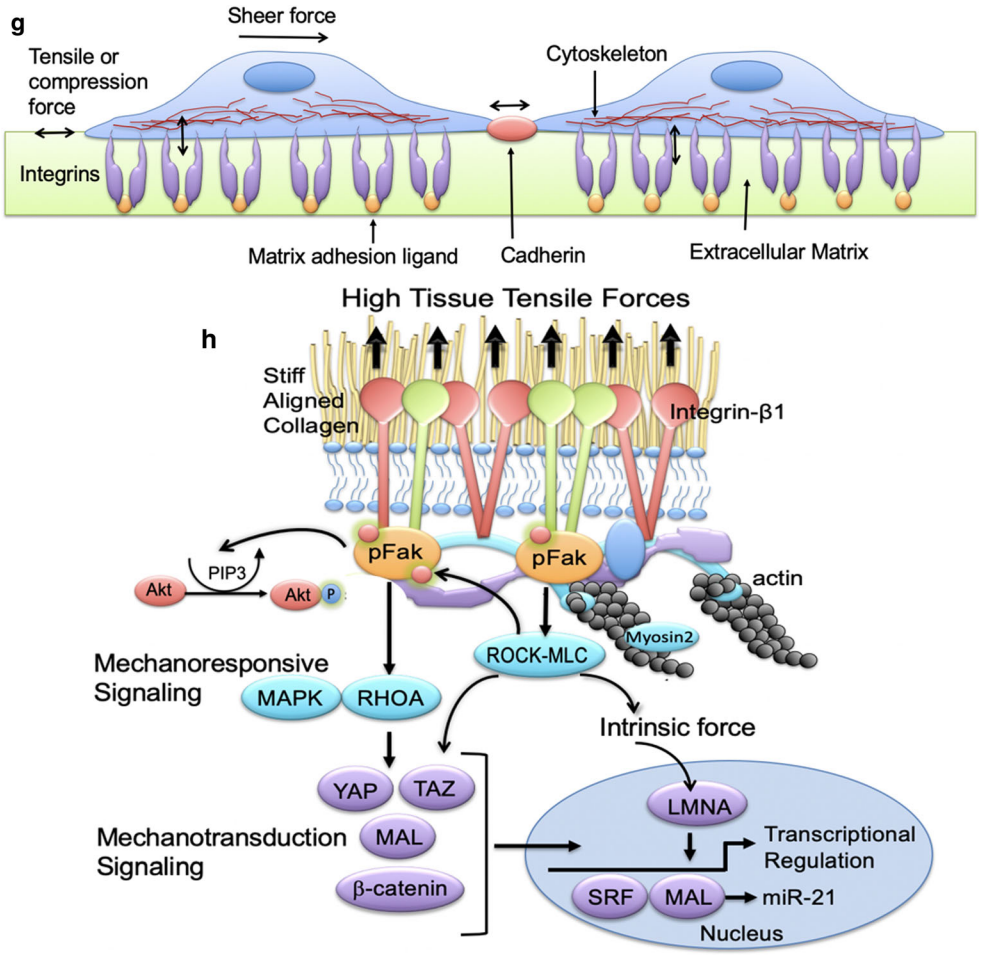

Fig. 1 (continued)

In additional population-based studies, the association between mammographic density and breast cancer risk appears to hold across ethnic groups. However, the relationship appears to be weaker in Asian women versus non-Hispanic Whites or Black/African American women [21••]. Asian women have relatively higher mammographic density than non-Hispanic Whites or Black/African American women [21••]. However, when adjustments are made for age and BMI, absolute breast density in Asian women is significantly lower than the age/BMI-corrected mammographic density of non-Hispanic Whites and Black/African American women [24, 25]. In one study, mammographic density-associated risk was greatest in patients with BMI > 30 [25]. These observations underscore the importance of correcting for both age and BMI when assessing breast density [21••].

High-Mammographic Density, Masking, and Biology

It is well established that breast cancer screening is complicated by the presence of increased mammographic density. Using film mammography from the 1970s, Whitehead et al., first demonstrated that high mammographic density had a "masking" effect [6, 26]. This "masking" effect was hypothesized to obscure early detection; dense mammograms are more radio-opaque ("white"); many cancers also are radio-opaque and appear "white" on mammograms; therefore, the greater the mammographic density (increased "whiteness"), the more difficult it would be to detect a "white" cancer lesion.

Interval cancers are cancers diagnosed within 12 months of a normal screening radiological study. In a landmark study, Boyd et al., investigated the relationship between mammographic density and the diagnosis of an interval cancer [23••]. As compared with women with low mammographic density (< 10%), women with high mammographic density (> 75%) had an increased risk of breast cancer (odds ratio, 4.7; 95% confidence interval [CI], 3.0 to 7.4). For women < 56 years of age, 26% of all breast cancers and 50% of cancers detected < 12 months after a negative screening mammogram test were attributable to density in 50% or more of the mammogram. This study provides evidence that high mammographic density is strongly associated with the risk for subsequent diagnosis of an interval cancer.

Table 1 Mammographic density, breast cancer risk, modulation of density, and risk

Study author	Sample/ trial size	Age of subjects (years)	Study: follow-up trial: duration (years)	MD classification	Study: risk associated with MD^ trial: Variable# and effect on MD and risk^
Byrne [13]	1880:2125	35–74	10	Percent	OR for > 75% versus 0%. PrM and PoM. 4.5 (3.2–6.4)
Vacek [14]	61,844	< 40–> 75	3.1	BIRADS	RR for extremely dense versus entirely fatty PrM, 4.6 (1.7–12.6) and PoM, 3.9 (2.6–5.8)
Ziv [15]	44,811	Mean, 54	3.8	BIRADS	HR for BIRADS 4, 2.09 (1.6–2.75)
Boyd [1••]	1114	40–70	8	Percent	OR for < 10% versus > 75% 4.7 (3.0–7.4)
Eng-Wong [16]	27	Mean, 43	1–3	Percent	Raloxifene: no change in MD. Risk not evaluated.
Conroy [17]	722	Median, 46	Mean, 5.6	Percent	Physical activity: annual decline of 1.1% in density (decrease in non-dense breast area and no change in dense breast area). Risk not evaluated.
Woolcott [18]	320	50–74	1	Percent and volume	Aerobic exercise: no change in percent dense area (following adjustment changes in % body fat). Risk not evaluated.
Martin [19]	4690	30–65	Mean, 10	Percent (all patients in trial had ≥ 50% MD)	Reduced fat diet: no effect on risk
Cuzick [20••]	123:942	< 45–> 60	1–2	Percent	Tamoxifen: 46% of patients had a ≥ 10% reduction in MD. Those patients had a 63% reduction in risk.

Numbers reported as total cases or cases:controls. ^ Risk reported as breast cancer incidence. # Variable is intervention that occurred in the setting of a trial. *MD*, mammographic density; *OR*, odds ratio; *RR*, relative risk; *HR*, hazard ratio; *PrM*, premenopausal, *PoM*, postmenopausal

Studies in Individuals

Studies of 13,409 postmenopausal participants in the NSABP Study of Tamoxifen and Raloxifene in postmenopausal women showed that high BIRADS breast density was significantly associated with increased breast cancer risk when considered in conjunction with Gail score but provided only slight improvement to the Gail score for predicting the incidence of invasive breast cancer [2]. This study calculated the receiver operator curve (ROC) and area under the curve (AUC) for the ability of mammographic density to predict breast cancer risk. The ROC curve is a plot of the test true-positive rate (*y*-axis) against the corresponding false-positive rate (*x*-axis), i.e., sensitivity against specificity. The curve is built from test performance at different "diagnostic thresholds." While mammographic density can be high/not high, mammographic density has range of values. If the diagnosis of breast cancer is increasingly likely with higher values, the proportion of patients ultimately diagnosed depends on applying a diagnostic threshold that denotes a positive test. In such analysis, an AUC of 0.5 (0.5 slope = line of identify) means that a positive test result will have an equal chance of being predictive vs. not predictive (true-positive vs. false-positive). In the studies by Boyd's group, while mammographic density was positively associated with breast cancer risk, the AUC was 0.55, only slightly above the line of identity (AUC = 0.5). Gail score had an AUC = 0.63 and Gail Score + Density had an AUC = 0.64. These studies highlight the weak predictive power mammographic density has in predicting breast cancer risk for an individual woman.

Clinical Guidelines for MRI Screening in Women with High Breast Density

The American Cancer Society clinical guidelines for breast MRI screening state that high breast density alone, in the absence of other risk factors, is not an indication of breast MRI screening [5]. Whether there is a place for breast MRI screening in women with high mammographic density remains a subject of intense debate; therefore, women with high mammographic density should be encouraged to enroll in clinical trials.

Can Density Be Modified?

Mammographic density generally decreases with age and breast cancer risk generally increases with age. Mammographic density declines with age due to a (1) decrease in glandular tissue and (2) simultaneous increase in adipose tissue [1••]. This paradox has led investigators to hypothesize that cumulative exposure to high breast density throughout a woman's lifespan (rather than at one point in

time) may be the ultimate predictor of breast cancer risk [1••]. Consistent with this hypothesis is that women who continue to have high mammographic density at age 50 and beyond have a higher risk of breast cancer, relative to women who only have high breast density when they were less than 50 years old [17].

Increased physical activity is associated with a reduced risk of breast cancer (independent of BMI). While the impact of exercise on breast cancer risk is well established, the impact of physical activity on mammographic density is less clear. A recent trial evaluating 722 multi-ethnic women (mean 46 years old) found no association between physical activity and reduction in mammographic density [17]. A second trial in postmenopausal women evaluating the potential impact of exercise on mammographic density that (1) weight loss was associated with an increase in mammographic density; however, (2) there was no significant change in the total volume of breast density [18, 19]. A Spanish study of over 3500 women provided evidence that weight gain in adulthood was associated with increased mammographic density [27].

The relationship between mammographic density and hormones is well established. After menopause, female hormone production decreases and mammographic density also decreases. Many studies show that combination hormone replacement therapy (estrogen and progesterone) is associated with an increase in mammographic density. The impact of estrogen therapy alone, however, on breast density is less clear [28]; the association between estrogen and increased mammographic density is weakest in (1) younger women and (2) women with an elevated BMI.

Pregnancy is also known to modify mammographic density. Parity decreases mammographic density; each additional birth results in a decrease of 16% in mammographic density [29]. High mammographic density is positively associated with older maternal age at first birth and inversely associated with the length of time that a woman breastfeeds.

The potential association between pregnancy, estrogen/progesterone, and mammographic density led to clinical trials testing whether anti-hormone chemoprevention (e.g., tamoxifen) could reduce both breast cancer risk and breast density. Well-powered clinical trials including both premenopausal and postmenopausal women demonstrate that tamoxifen significantly reduces breast density and the incidence of breast cancer [20••, 30]. In the International Breast Cancer Intervention Study, Cuzick et al. showed that 46% of women who took tamoxifen for 12 months experienced a 10% or greater reduction in breast density [20••]. In women who received tamoxifen, this observed reduction in breast density correlated with a 63% reduction in breast cancer risk. However, women who received tamoxifen and had less than 10% reduction in breast density had no corresponding reduction in breast cancer risk. This study has provided support for the hypothesis that a decrease in breast density can serve as a surrogate maker for breast cancer risk reduction. While the use of mammographic density as a surrogate endpoint for chemoprevention trials has gained acceptance, the molecular mechanism underlying the reduction in breast cancer risk is not understood.

Collagen Structure, Breast Cancer Risk, and Mammographic Density

The biological mechanisms by which breast density may increase breast cancer risk are only just beginning to be understood. High mammographic density is associated with increased collagen deposition. Up until recently, collagen was felt to be a relatively inert structural protein that did not contribute substantially to cancer initiation and progression. Recent studies, however, provide evidence that collagen fibers may act as a conduit or "super highway" that traffic breast cancer cells within the mammary gland [31, 32]. These studies raise the question of whether mammary collagen structure (as opposed to mammographic density) may be a more accurate predictor of breast cancer risk.

Increased mammographic density is characterized by an increased in X-ray absorbance throughout the entire breast [31]. Generalized, high mammographic density is distinct from the focal events that accompany breast cancer initiation and progression. During breast cancer initiation, there is a focal stromal response (desmoplastic reaction) characterized by (1) increased collagen matrix deposition and (2) stromal cell recruitment and activation [33, 34]. Increased cell density/numbers and increased collagen deposition both increase mammographic density. Mammographic imaging and ultrasound are inadequate to distinguish whether a focal increase in mammographic is due to an increase in cell number and/or an increase in collagen deposition. Since tumor cells invade in collagen-rich stroma, it is important to develop molecular tools that can detect early interactions between premalignant and malignant breast epithelial cells and collagen matrix [35–38]. Therefore, techniques that identify and characterize features of the epithelial-stromal interaction at the single cell level are of great diagnostic potential.

Studies in mouse models first identified and classified sequential collagen alterations as potential markers of mammary carcinoma initiation and progression. Collagen alterations that were associated with carcinogenesis are called tumor-associated collagen signatures (TACS) [38, 39] (Fig. 1c–f). During cancer initiation, mouse mammary tumors first exhibit a localized increase in the deposition of collagen near the tumor lesion (TACS-1) [40, 41]. As tumors increase in size, there is a straightening of collagen fibers aligned parallel to the tumor boundary (TACS-2) [38]. During the final stage of carcinogenesis, there is remodeling and reorientation of collagen such that multiple collagen fibers are bundled and aligned

perpendicular to the tumor boundary (TACS-3) [38]. Studies by the late Patricia Keely, Matthew Conklin, and Kevin Eliceiri show that TACS-3 collagen fiber alignment is significant; regions containing TACS-3 correspond to sites of focal invasion into the stroma [38, 39]. This group and others have shown that tumor cells preferentially invade along straightened, aligned collagen fibers [32, 38, 42, 43, 44••].

Collagen alignment can now be detected through second harmonic generation (SHG) imaging. During imaging, two photons of incident light interact with the non-centrosymmetric structure of collagen fibers such that the resulting photons are half the wavelength of the incident photons [45] (Fig. 1d, f). This non-linear coherent process is non-fluorescent and will specifically image collagen, whereby the SHG signal can be separated from endogenous fluorescence through the use of narrow bandpass filters centered at one-half the laser wavelength [31]. Thus, SHG does not requires labeling or staining; SHG imaging can be used in lieu of stains for collagen, such as Masson's trichrome or picrosirius red stain [31]. SHG generates contrast in an image based solely on the presence of collagen and is influenced by the properties of collagen itself such as the degree of cross-linking, fiber thickness, and alignment of overlapping fibers (ordered versus disordered) [31, 46–52]. Keely, Conklin, and Eliceiri used SHG to test for TACS-3 in breast cancer biopsy samples [31]. Their studies show that TACS-3 collagen is an independent predictor of poor survival in non-Hispanic White women with breast cancer and provide evidence that collagen structure is associated with breast cancer initiation and poor survival [31].

Syndecan-1 interacts with constituents in the extracellular matrix, including collagen fibers [53••]. A recent study tested whether (1) stromal syndecan-1 expression and (2) orientation of collagen fibers surrounding ductal carcinoma in situ (DCIS) predict local DCIS recurrence [53••]. The study evaluated collagen fiber alignment and syndecan-1 expression in 227 women diagnosed with DCIS in 1995 to 2006 followed through 2014 (median, 14.5 years; range, 0.7–17.6) [53••]. Stromal collagen alignment was evaluated from diagnostic tissue slides using SHG microscopy [53••]. Greater fiber angles surrounding DCIS lesions, but not syndecan-1 staining intensity, were related to poor prognostic features including (1) positive HER2 ($p = 0.002$) amplification, (2) comedo necrosis ($p = 0.03$), and (3) ER- ($p = 0.002$) and PR- ($p = .0.02$) status [53••]. Although collagen alignment and stromal syndecan-1 expression did not predict recurrence, collagen fibers perpendicular to the duct perimeter were more frequent in DCIS lesions with features typical of poor prognosis [53••].

Mammographic density correlates with an abundance of collagen-rich fibroglandular tissue. The structural, molecular, and mechanical consequences, however, of high collagen remain poorly defined [54]—it is unclear whether increased collagen alone drives risk or whether specific structural properties of collagen are the key drivers.

Experimental Assessment of Collagen, Tensile Force, and Molecular Signaling

Aligned stromal collagen has been shown to increase the stiffness of the extracellular matrix (ECM) [55]. Increased stromal collagen stiffness increases the "pull" or "stretch" that the stroma exerts on mammary epithelial cells (increased tissue tensile forces) [55]. When the cells sense these mechanical cues, they activate integrins, the interface that mediates cell-ECM interaction. Activation of integrins promotes their clustering, oligomerization, and maturation into focal adhesions [56–60]. Focal adhesions are composed of mechanosensor proteins such as talin and vinculin, in addition to signal transduction proteins such as focal adhesion kinase (FAK), SRC, PI3K, adapter proteins, and actin linker proteins such as filamin and alpha-actin. The later proteins physically link integrins to the cytoskeleton [61, 62]. Upon integrin oligomerization, talin and vinculin association is fostered and FAK and SRC are activated [56, 63, 64••]. Downstream signaling of FAK and SRC stimulates Rho proteins, which in turn activate Rho-associated protein kinases (ROCK) that subsequently lead to cytoskeletal reinforcement and acto-myosin contractility [56]. Rho-GTPase-dependent myosin contractility is mediated by phosphorylation of myosin light chain (MLC) of myosin II. The cytoskeletal response of acto-myosin contractility is the intrinsic force generated inside the cells in response to increased stiffness (exogenous force) (Fig. 1g, h) [55, 56, 61].

Simultaneously, focal adhesion formation and signaling of FAK and SRC via interaction of growth factor receptors (GFRs) and G protein-coupled receptors (GPCRs) lead to MAPK or ERK activation (Fig. 1g, h) [56, 64••, 65]. ERK activation in response to stiff microenvironment leads to enhanced growth of mammary epithelial cells in vivo and in vitro and activation of proliferation signature genes [64••, 66]. Rho GTPase activation in response to stiff mechanical forces is known to activate other pathways that are involved in breast cancer and aggressive biology [55]. For instance, Rho GTPases also signal to phosphoinositide 3-kinase (PI3K) which promotes cellular proliferation via Akt signaling [67]. In response to force, ERK and Jun N-terminal kinase (JNK) activate transcription factors that include p53, STAT1, STAT3, MYC, cAMP response element-binding protein (CREB), and nuclear factor–KB (NF-KB) [55]. Moreover, transcriptional regulators YAP and TAZ are activated in response to stiff mechanical cues in response to Rho GTPases and acto-myosin cytoskeletal tension [68]. Activation of beta-catenin in response to stiff ECM is also reported to be dependent on integrin/FAK stimulation (Fig. 1h) [69]. Most of these pathways and transcription factors are involved in initiation/progression of aggressive forms of breast cancer such as triple-negative breast cancer.

Inside the nucleus, a mesh of intermediate filaments called laminins interacts with both the cytoskeleton and the

chromatin [70]. These laminins respond to mechanical cues sensed by the cells at focal adhesions and transmitted through the cytoskeleton [71]. The cytoskeleton is physically linked to the nucleus via LINC (linker of nucleoskeleton and cytoskeleton) complexes [71]. In response to ECM stiffness, LINC complexes are reinforced and type-A laminins (LMNA) are stabilized, increased, and assembled to counteract the external mechanical force [71, 72]. Upon actin polymerization, MAL is shuttled from the cytoplasm and accumulates in the nucleus [73]. MAL, a coactivator of the transcription factor serum response factor (SRF), activates SRF to turn on genes regulating cellular motility and contractility such as vinculin, actin, and SRF itself [74], contributing to a tension-induced "inside-out signaling." Thus, the nucleus feeds back to the cytoskeleton to balance the extrinsic and intrinsic forces (Fig. 1h) [71].

Conclusions

In population-based studies, increased breast density is associated with a 2- to 6-fold increased risk of breast cancer. While mammographic density correlates with breast cancer risk in population-based studies, mammographic density does not accurately predict breast cancer risk in individuals. Mammographic density declines with increasing age and increasing BMI. Mammographic density is increased with women who take combination hormone replacement therapy and decreases with tamoxifen chemoprevention. There is evidence that a decrease in breast density in women taking tamoxifen is associated with a reduction in breast cancer risk. The relative ratio of adipose:fibroglandular tissue volume roughly correlates with mammographic density. While absolute collagen content is associated with mammographic density, the more accurate predictor of mammographic density is collagen alignment and collagen stiffness. Recent studies investigating downstream signaling pathways activated by stiff/aligned collagen hold promise for better defining the mechanism(s) that underly breast cancer risk.

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Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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