Breast Cancer RESEARCH

REVIEW

Mammographic density and breast cancer risk: current understanding and future prospects

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Abstract

Variations in percent mammographic density (PMD) reflect variations in the amounts of collagen and number of epithelial and non-epithelial cells in the breast. Extensive PMD is associated with a markedly increased risk of invasive breast cancer. The PMD phenotype is important in the context of breast cancer prevention because extensive PMD is common in the population, is strongly associated with risk of the disease, and, unlike most breast cancer risk factors, can be changed. Work now in progress makes it likely that measurement of PMD will be improved in the near future and that understanding of the genetics and biological basis of the association of PMD with breast cancer risk will also improve. Future prospects for the application of PMD include mammographic screening, risk prediction in individuals, breast cancer prevention research, and clinical decision making.

Introduction

Breast density, assessed by mammography and expressed as a percentage of the mammogram occupied by radiologically dense tissue (percent mammographic density, or PMD), reflects variations in breast tissue composition and is strongly associated with breast cancer risk [1]. Here, we review the evidence that PMD is a risk factor for breast cancer, histological and other factors associated with variations in PMD, and the biological plausibility of the associations with risk of breast cancer. We discuss the potential clinical applications of this risk factor in screening, in research on breast cancer prevention, and in risk prediction in individuals. Mammographic density has been the subject of a meta-analysis (see next section) [1] and a recent review [2] and readers are referred to these sources for additional information.

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Mammographic density and risk of breast cancer

The radiographic appearance of the breast on mammography varies among women, as illustrated in Figure 1, and reflects variations in breast tissue composition and the different x-ray attenuation characteristics of these tissues [3]. Fat is radiologically lucent and appears dark on a mammogram. Connective and epithelial tissues are radiologically dense and appear light. This appearance is usually expressed as a percentage of the breast area, or (as referred to here) as percent mammographic density (PMD).

In a systematic meta-analysis of data for more than 14,000 cases and 226,000 non-cases from 42 studies, McCormack and dos Santos Silva [1] reviewed the data on the association of PMD with risk of breast cancer. The authors found that PMD was consistently associated with risk of breast cancer. Associations were stronger in studies in the general population rather than symptomatic women, in studies of incident rather than prevalent cancer, and for percent density rather than Wolfe's classification. Wolfe was the first to describe differences in breast cancer risk associated with variations in the mammographic appearance of the breast [4,5]; he used four categories: N1 (predominately fat), P1 and P2 (ductal prominence in less than 25% or more than 25% of the breast, respectively), and DY (extensive 'dysplasia'). A quantitative method of measuring breast density, Cumulus, is illustrated in Figure 1. Thresholds placed at the edge of the breast (red line) and the edge of density (green line) are used to calculate PMD [6].

Table 1 summarizes selected features of the cohort studies, or studies nested within cohorts, that used quantitative methods to classify PMD [7-15]. The 10 studies shown were carried out in the US, Europe, or Canada and all found a statistically significant increase in risk associated with more extensive PMD after adjustment for other risk factors, and the increase in risk persisted for at least 8 to 10 years from the date of the mammogram used to classify PMD [9,15]. There is also evidence of a dose-response relationship (that is, of risk increasing with increasing PMD).

Other qualitative classifications, such as the four-category system developed by the American College of

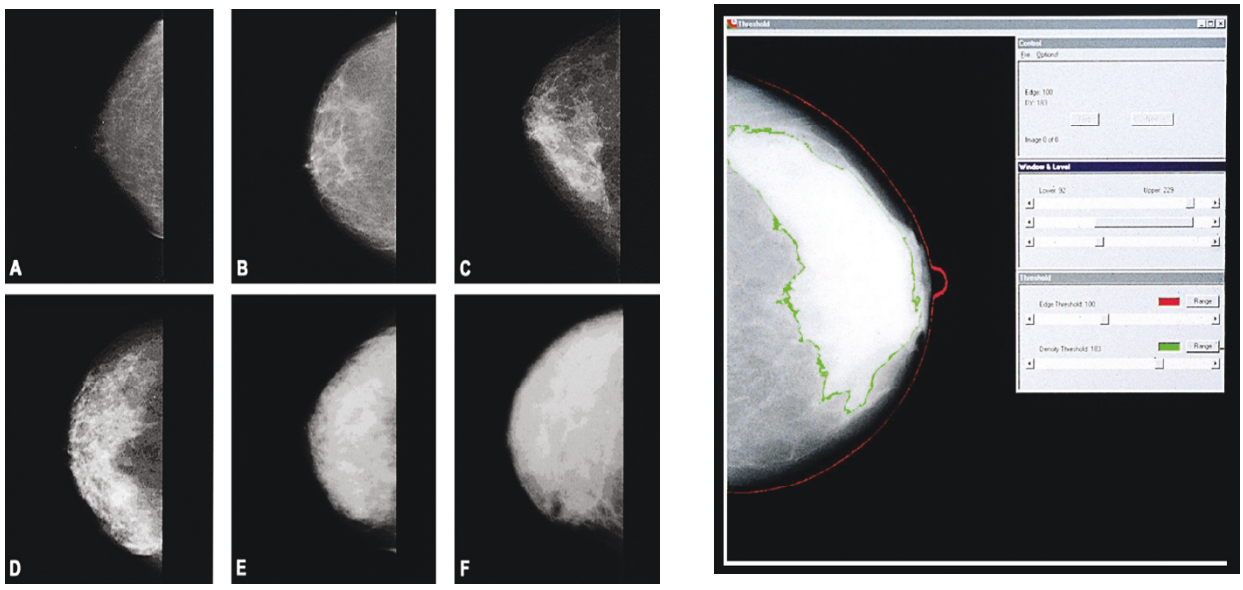

Figure 1. Examples of mammographic density. (a) 0% mammographic density, **(b)** less than 10%, **(c)** less than 25%, **(d)** less than 50%, **(e)** less than 75%, and **(f)** greater than 75%. On the right is an illustration of Cumulus in the measurement of mammographic density. The red line outlines the breast, and the green line outlines the area of density. Republished with permission from [2].

Radiology (Breast Imaging-Reporting and Data System, or BI-RADS), also create groups with different risks of breast cancer [16,17]. The BI-RADS classification of mammographic density has four categories: (1) almost entirely fatty, (2) scattered fibroglandular densities, (3) heterogeneously dense, and (4) extremely dense. BI-RADS is the only classification of mammographic density currently in clinical use in the US but, of the available methods, appears to be the least reliable. Reliability between readers is modest (kappa statistic = 0.56) [18], whereas the interclass correlation coefficient for trained readers using Cumulus is more than 0.9 [15]. Nonetheless, the BI-RADS classification does distinguish women at different risks for the development of breast cancer, and a summary by Cummings and colleagues [17] estimated a fourfold gradient in risk between BI-RADS categories 1 and 4.

As shown in Table 2, PMD is associated with risk of breast cancer both at screening and between screening examinations. In the three Canadian studies shown in Table 1 [15], the method of breast cancer detection was recorded by each of the programs. We used those classifications to subdivide the breast cancers into those detected at screening, those detected within 12 months of a negative screen, and those detected more than 12 months after a negative screening examination. In a comparison of those with less than 10% density and those with more than 75% density, the odds ratio was 4.74 (95% confidence interval (CI) 3.0, 7.4) for all cancers. In the 717 cases of breast cancer detected at screening, the odds ratio was 3.52 (95% CI 2.0, 6.2). In the 124 cases of breast cancer detected within 12 months of the last screening examination, the odds ratio for risk of breast cancer in those with more than 75% density was 17.81 (95% CI 4.8, 65.9). For cancers detected more than 12 months after the last screen, the odds ratio for those with more than 75% density was 5.68 (95% CI 2.1, 15.5). Within each category of detection, there was a monotonic increase in risk with each category of density, and the trend tests were all highly significant. Similar results were seen in each of the three screening programs.

More extensive PMD was thus associated with an increased risk of breast cancer at screening, in the presence of potential masking by density. The marked elevation in risk associated with PMD in the 12 months after a negative screening examination does, however, probably reflect the masking of tumors by density. The annual incidence of breast cancer associated with different degrees of density may be best estimated by combining the incident cancers detected at screening with those found by other methods in the 12 months following screening [15].

Comparison with other risk factors

Relative risk

Among other menstrual, reproductive, and familial risks of breast cancer, only age and BRCA carrier status are associated with larger relative risks of breast cancer than PMD (for example, [19]). The relative risk associated with density is substantially larger than the relative risk of

Table 1. Selected characteristics of cohort studies with quantitative classification of percent mammographic density

Authors/study, region	Subject age, years	Sample size[a]	Measurement[b]	Partition[c]	OR (95% CI)	Follow-up, years	Adjustments[d]
Kato *et al*. [7], USA	35-65	197/521	Planimetry	Upper versus lower tertile	3.6 (1.4 to 9.1)	5.5	BMI, parity, and menopause
Saftlas *et al*. [8], USA	35-74	266/301	Planimetry	<5% versus ≥65%	4.3 (2.1 to 8.8)	5	Age, weight, and parity
Byrne *et al*. [9], USA	35-74	1,880/2,152	Planimetry	0% versus ≥75%	4.3 (3.1 to 6.1)	10	Weight, age at first birth, family history, years of education, alcohol use, previous benign biopsies, and reproductive years
Torres-Mejia *et al*. [10], Europe	40-80	111/3,100	Computer-assisted	0.5% versus >46%	3.5 (1.4 to 5.2)	14	Age, education, parity, height, and BMI
van Gils *et al*. [11], Europe	>45	129/517	Automated	<5% versus >25%	2.9 (1.6 to 5.6)	10	Age and parity
Thomas *et al*. [12], USA	<50	547/472	Estimation	Upper versus lower quartiles	4.4 (3.0 to 6.7)	>6	Age and study
Maskarinec *et al*. [13], USA	60[e]	607/667	Computer-assisted	<10% versus >50%	3.6 (2.3 to 5.6)	7	Ethnicity, age, BMI, age at first birth, number of births, age at menarche, age at menopause, HRT, and family history of breast cancer
Boyd *et al*./NBSS [14], Canada	40-59	330	a. Estimation b. Computer-assisted	0% versus ≥75%	a. 6.0 (2.8 to 13.0) b. 4.0 (2.1 to 7.7)	7	Age, parity, age at first birth, weight, height, number of births, age at menarche, and family history
Boyd *et al*./SMPBC [15], Canada	40-70	398	a. Estimation b. Computer-assisted	<10% versus ≥75%	a. 4.5 (1.9 to 11.0) b. 4.4 (2.1 to 5.0)	6	Age, parity, age at first birth, weight, height, number of births, age at menarche, and family history
Boyd *et al*./OBSP [15], Canada	50-69	386	a. Estimation b. Computer-assisted	<10% versus ≥75%	a. 3.4 (1.1 to 10.3) b. 4.1 (2.0 to 8.6)	8	Age, parity, age at first birth, weight, height, number of births, age at menarche, and family history
Boyd *et al*./ Combined [15], Canada	40-70	1,114	a. Estimation b. Computer-assisted	<10% versus ≥75%	a. 4.7 (3.0 to 7.4) b. 4.4 (2.9 to 6.7)	6-8	Age, parity, age at first birth, weight, height, number of births, age at menarche, and family history

[a]Reported as the number of case subjects/number of control subjects or as the number of pairs of case and control subjects. [b]Estimation means visual estimation by an observer (radiologist). [c]The most and least extensive categories of density from which odds ratios (ORs) were calculated. [d]Factors included in the analysis of risk associated with mammographic density. Factors controlled for by matching are also included. [e]Average age. Table reproduced from [2]. BMI, body mass index; CI, confidence interval; HRT, hormone replacement therapy; NBSS, National Breast Screening Study; OBSP, Ontario Breast Screening Program; SMPBC, Screening Mammography Program of British Columbia. Republished with permission from [2].

breast cancer associated with a family history of the disease or any of the menstrual and reproductive risk factors.

Attributable risk

Because extensive PMD is common in the population and associated with a large relative risk, if the association with breast cancer risk is causal, the proportion of the disease attributable to this risk factor is expected to be substantial. According to data from three Canadian screening programs [15], the risks of breast cancer attributable to density of 50% or more were 16% for all cancers, 12% for screen-detected cancers, 40% for cancers detected within 12 months of a negative screen, and 16% for cancers detected more than 12 months after a screening examination.

For women below the median age of 56 years, the prevalence of density of 50% or more was about three times greater than in older women, in each category of detection, and the attributable risks of breast cancer were 26% for all cancers, 21% for screen-detected cancers, 50% for cancers detected within 12 months of a negative screen, and 28% for cancers detected more than 12 months after a screening examination. Similar estimates

Table 2. Mammographic density and risk of breast cancer according to method of detection: unmatched analysis and radiologists' classification of density

		Number of pairs[a]	Categories of percent density, percentage					*P* value[b]
			<10	10 to <25	25 to <50	50 to <75	>75	
All	Case	1,112	230	272	336	178	96	
	Control	1,112	362	270	290	144	46	
	OR[c] (95% CI)		1	1.75 (1.4, 2.2)	2.06 (1.6, 2.6)	2.43 (1.8, 3.3)	4.74 (3.0, 7.4)	<0.0001
Screen-detected	Case	717	173	171	219	102	52	
	Control	717	242	162	196	88	29	
	OR[c] (95% CI)		1	1.65 (1.2, 2.2)	1.77 (1.3, 2.4)	1.98 (1.3, 2.9)	3.52 (2.0, 6.2)	<0.0001
Non-screen-detected <12 months[d]	Case	124	12	22	33	32	25	
	Control	124	35	29	29	23	8	
	OR[c] (95% CI)		1	2.11 (0.9, 5.2)	3.61 (1.5, 8.7)	5.65 (2.1, 15.3)	17.81 (4.8, 65.9)	<0.0001
Non-screen-detected >12 months[e]	Case	262	43	79	80	42	18	
	Control	262	82	79	62	30	9	
	OR[c] (95% CI)		1	2.00 (1.2, 3.4)	2.64 (1.5, 4.6)	3.13 (1.6, 6.2)	5.68 (2.1, 15.5)	<0.0001

[a]Nine pairs were excluded from the screen or non-screen group analysis because of missing information on detection (n = 1) or the last mammogram date (n = 8). [b]*P* value for the Cochran-Armitage trend test. [c]Adjusted for age, body mass index, age at menarche, parity, number of live births, age at first birth, menopausal status, age at menopause, hormone replacement therapy (ever/never), breast cancer in first-degree relatives (0, 1, and 2+), study (National Breast Screening Study, Ontario Breast Screening Program, and Screening Mammography Program of British Columbia), and observation time (2 years, 2 to 4 years, and greater than 4 years). [d]Cancers detected within 12 months of the last screening date. [e]Cancers detected 12 months or more after the last screening date. Table reproduced from [15]. CI, confidence interval; OR, odds ratio. Republished with permission from [15].

of attributable risk have been calculated for PMD in the Breast Cancer Detection and Demonstration project [9]. These estimates of attributable risk are larger than for any other risk factor for breast cancer, including BRCA carrier status, which is estimated to be responsible for 5% or less of all breast cancer [20,21].

Biological plausibility of the association of mammographic density and breast cancer risk

Hypotheses concerned with the biological basis of the association of PMD with risk of breast cancer have been reviewed elsewhere [22] and will be discussed only briefly here. The change in PMD with age reflects the reduction in glandular tissue and accompanying increase in fat which occur with increasing age. This decline in the risk factor of density with age may seem paradoxical, as breast cancer incidence increases with age. However, cumulative exposure to PMD reflects cumulative exposure of breast stroma and epithelium to hormonal and growth factor stimuli to cell division. Cumulative exposure to PMD increases with age and may be related to the age-specific incidence of breast cancer [23].

As reviewed in [22], PMD is also less extensive in women who are parous and in those with a larger number of live births and is reduced by menopause. After adjustment for age and other potential influences, a family history of breast cancer is associated with a more extensive PMD [24]. PMD has consistently been found to be inversely associated with body weight. Greater birth weight and adult height have been shown to be positively associated with PMD [25,26] and with an increased risk of breast cancer [27]. With the exception of weight, PMD may be on the causal pathway for breast cancer for some or all of these other risk factors.

Many of the factors that are associated with PMD are also associated with alterations in exposure to hormones that may influence the number and proliferative state of epithelial and stromal cells in the breast. To date, most studies of blood levels of ovarian hormones have found either no association or an inverse association with PMD in premenopausal or postmenopausal women (reviewed in [22]). Positive associations with PMD have been found between serum levels of growth hormone and breast water (a surrogate for PMD) in young women from 15 to 30 years old [28], and serum insulin-like growth factor I (IGF-I) levels in premenopausal women and postmenopausal women, and with serum levels of prolactin in postmenopausal women (reviewed in detail in [22]).

Radiologically dense breast tissue – in addition to greater amounts of collagen and cells and greater stained

area (on immunohistochemistry) of IGF-I – also have greater amounts of the tissue inhibitor metalloprotease 3 (TIMP-3) [29]. Aromatase immunoreactivity is also associated with dense breast tissue [30]. The proteoglycans lumican and decorin have been associated with breast cancer and have also been found to be present in greater amounts in women with extensive PMD [31].

Mammographic density and risk of histological precursors to breast cancer

Mammographic density reflects the proportions of fat, stromal, and epithelial tissue in the breast and does not denote any histological abnormality [32,33]. Extensive mammographic density is, however, associated with increased risks for the development of most of the histological abnormalities that are non-obligate precursors of breast cancer. The breast lesions of ductal carcinoma *in situ* (DCIS), atypical hyperplasia, hyperplasia without atypia, and columnar cell lesions (CLLs) are, to different degrees, associated with an increased risk of breast cancer, and, as discussed below, risk of each type of lesion is also increased by extensive PMD.

In the Multiethnic cohort, women with more than 50% PMD had, compared with those with less than 10% PMD, an increased risk of both invasive breast cancer (OR = 3.58; 95% CI 2.3, 5.7) and DCIS (OR = 2.9; 95% CI 1.4, 5.9) [26]. A case control study in the Canadian National Breast Screening Study showed that, in women with more than 75% density, compared with those with no density, risk of *in situ* breast cancer and atypical hyperplasia combined was greater (OR = 9.7; 95% CI 1.7, 53.9), as was risk of hyperplasia without atypia (OR = 12.2; 95% CI 2.9, 50.1) [34]. Additional studies have also shown PMD to be associated with risk of DCIS [35,36].

CLL, thought to be the earliest recognizable histological feature that is a non-obligate precursor to breast cancer, has been found to be more frequent (OR = 2.2; 95% CI 1.03, 4.8) in biopsies from breasts with more than the median density of 30%. CLLs were also strongly positively associated with the percentage of the biopsy occupied by collagen ($P = 9.2 \times 10^{-5}$) and glandular area ($P = 2 \times 10^{-5}$) [37]. Age-related atrophy of breast lobules (lobular involution) has been found to be inversely associated with risk of breast cancer [38], and it appears that PMD and lobular involution are independently associated with risk of breast cancer [39].

Future prospects

Potential improvements in measuring breast tissue composition

All of the methods currently used to assess breast density by mammography have limitations. None takes into account the thickness of the breast, and all are based on the projected area, rather than the volume, of breast tissue. All current methods depend upon a trained observer and thus are subjective. These potential sources of error in measurement are likely to attenuate the observed associations between percent PMD and other risk factors for breast cancer and risk of the disease itself.

To date, three published case control studies have examined the association between percent PMD and risk of breast cancer by measuring breast tissue volumes. One used standard mammography form (SMF) software that uses information about the non-fat tissue in the breast, in conjunction with the thickness of the compressed breast and the breast imaging variables of tube voltage and exposure time, to generate estimates of breast tissue volumes [40]. In an alternative approach to the measurement of tissue volumes, we acquired images prospectively from mammography machines calibrated to allow examination of the relationship between the image signal in each pixel (that is, optical density or blackness of the processed film value), the exposure factors (that is, kilovoltage, milliampere-seconds, tube target, and beam filter), and the amount of radiation transmitted by the breast. Corrected breast tissue thickness and breast tissue volumes were calculated [41].

In two of these studies, the volume-based measures of percent density were associated with breast cancer risk, though less strongly than the area-based measures of percent density. It is not yet clear whether these results reflect as-yet-uncorrected errors in the measurement of breast tissue volumes or the failure to capture additional breast risk information that is present in the area-based measures. An alternative method of measuring percent fibroglandular tissue volumes by using single x-ray absorptiometry has been shown to more accurately predict breast cancer risk than percent dense area [42] but has not yet been replicated or applied to digital mammograms. Other methods of measuring tissue volumes are under development [43,44].

Potential alternatives to the assessment of breast tissue composition by mammography include measurement of the breast water (reflecting the stromal and epithelial tissue) and fat content by magnetic resonance (MR) and ultrasound tomography (UST). Both have been discussed elsewhere as alternatives to mammography in measuring density [2]. Percent PMD in the mammogram is strongly correlated both with percent water by MR (Spearman r = 0.85; $P < 0.001$) [45] and average sound speed by UST (Spearman r = 0.77; $P < 0.001$) [46].

Etiology of mammographic density

Because PMD is strongly associated with risk of breast cancer, factors that influence PMD may also contribute to the causes of breast cancer, and the identification of factors that change PMD may lead to the identification of factors that can reduce the incidence of breast cancer.

Age, parity, and menopausal status (see 'Biological plausibility of the association of mammographic density and breast cancer risk' section above) account for only 20% to 30% of the PMD variation observed in the population [47], and genetic factors might explain a proportion of variation (that is, the heritability) of PMD. Two large, twin studies have added to the evidence that PMD is a heritable quantitative trait. In one, 951 twin pairs (age range of 40 to 70 years) in Australia and North America were recruited, and mammograms and information on the factors associated with variations in PMD were collected. After adjustment for age and other covariates, the proportion of the residual variation in PMD accounted for by additive genetic factors (heritability) was estimated to be 63% (95% CI 59% to 67%) in the combined studies [48]. In a second study, with 553 twin pairs, the proportion of the residual variation in PMD heritability was estimated to be 53% [49]. Research now in progress seeks to identify genetic variants associated with PMD, and, of the 12 single-nucleotide polymorphisms reproducibly associated with risk of breast cancer, at least 3 have been found to be also associated with PMD [50,51].

Understanding of biological mechanisms

Epithelial and stromal cells, collagen, and fat are the tissue components that contribute to variations in PMD. The twin studies described in the previous section indicate that the quantities of these tissue components in the breast are determined largely by heritable factors. Furthermore, each component has properties that may influence the risk and progression of breast cancer.

Breast cancer arises from epithelial cells and the number and proliferative state of these cells may influence both the radiological density of the breast and the probability of genetic damage that can give rise to cancer. In addition, collagen and the stromal matrix are products of stromal cells, which may, through mechanical and other properties, facilitate tumor invasion. Interactions between stroma and epithelium are known to influence breast development and the changes in breast structure that take place during pregnancy, lactation, and involution and during tumorigenesis. The extracellular matrix, which comprises collagens, fibronectin, laminins, polysaccharides, and proteoglycans, plays a key role in these processes, and there is a large and rapidly growing body of literature on the molecules that mediate how the extracellular matrix influences the epithelium (see [52-55] for reviews). Proteoglycans (see 'Biological plausibility of the association of mammographic density and breast cancer risk' section above) bind growth factors, contribute to the mechanical integrity of tissues, may reflect the stiffness of breast tissue, and can modify tissue behavior [55]. To date, there has been limited application of these basic science findings to understanding the association between PMD and risk of breast cancer. Animal models now being developed may clarify the biological mechanisms that underlie the association of PMD with breast cancer risk.

Potential clinical applications of mammographic density

Mammographic screening

The evidence given above shows that women undergoing screening for breast cancer with mammography are heterogeneous with respect to cancer risk and the ease with which breast cancer can be detected by mammography. Women with extensive PMD are doubly disadvantaged as they are both at higher risk of developing breast cancer and at greater risk that cancer will not be detected by mammography, because of 'masking' by density of the radiological signs of cancer. In the presence of this underlying heterogeneity in the population undergoing screening, it does not seem likely that screening with a single modality and a single screening frequency will be optimal. It seems possible that, for women with extensive PMD, screening more often than once every 2 to 3 years and with modalities such as MR or UST in addition to mammography would improve cancer detection rates at screening and reduce the frequency of interval cancers. For women with radio-lucent breast tissue and a negative screening mammogram, in whom risk is lower and detection easier, re-screening less frequently than every 2 to 3 years might be safe. Research is required into optimizing screening frequency and modality according to the breast tissue characteristics of women. An approach to mammographic screening that starts at age 40 and that bases the frequency of screening on a women's age, breast density (by BI-RADS score), and other risk factors was recently advocated and shown to be cost-effective [56]. However, in an editorial accompanying that paper, a number of potential limitations of this approach were raised [57]. These limitations include lack of knowledge of the biological basis of the risk associated with mammographic density and of the effects of density on the risk and detection of breast cancer subtypes (see 'Breast cancer characteristics and clinical outcomes' section below).

Individual risk prediction

Currently, the most widely used method of predicting risk of breast cancer in individuals is the Gail model [58], which takes into account a woman's age, age at menarche, age at first live birth, number of previous benign breast biopsies, and number of first-degree relatives with breast cancer. Breast density is more strongly associated with breast cancer risk than the other variables included in the Gail model, and the addition of breast density, measured by a manual method tracing, to the Gail model increased

predictive accuracy, as shown by the concordance statistic, from 0.607 to 0.642 [59]. Tice and colleagues [60] developed a predictive model for breast cancer by using the BI-RADS classification; the model had a concordance statistic of 0.66. The Gail and Tice models have only moderate levels of risk prediction that might be improved by the improvements in measuring breast density described above.

Breast cancer prevention trials

In contrast to most other risk factors for breast cancer, mammographic density can be changed (as described below), suggesting that MD might be used as a surrogate marker in clinical trials of potential approaches to breast cancer prevention. Clinical trials of breast cancer prevention require large numbers of subjects and long periods of observation and thus are expensive. The number of subjects required in a breast cancer prevention trial can, however, be reduced by the selection of subjects at increased risk of breast cancer. We have carried out a long-term dietary intervention study in 4,690 women selected because they had mammographic density in 50% or more of the breast. During an average follow-up of 10 years (range of 7 to 17 years), invasive breast cancer was detected in 220 women, an observed age-specific incidence twice that of women of the same age in the Canadian population followed for the same length of time. However, a potential limitation of the selection of a high-risk group is that the results of such a trial may not be applicable to women who are not at increased risk [61].

It would make possible smaller, shorter, and less expensive trials of breast cancer prevention strategies if there were a breast cancer surrogate that after a short period of observation would allow the identification of interventions that would reduce breast cancer incidence. To be used as a surrogate for breast cancer, a biomarker such as PMD should meet the criteria proposed by Prentice [62] and further by Schatzkin and Gail [63]. These are that (a) the marker should be associated with risk of breast cancer, (b) the marker should be changed by the intervention, and (c) the change in the marker should mediate the effect of the intervention on breast cancer risk.

In a case control study nested within the first International Breast Cancer Intervention Study (IBIS), a randomized prevention trial of tamoxifen versus placebo, Cuzick and colleagues [64] showed that, compared with all women in the placebo group, those in the tamoxifen group who experienced a 10% or greater reduction in breast density had a 63% reduction in breast cancer risk, whereas those who took tamoxifen but experienced a reduction in PMD of less than 10% had no risk reduction. In the placebo arm, breast cancer risk was similar in subjects who experienced less than a 10% reduction in PMD and those who experienced a greater reduction. The authors conclude that the change in PMD 12 to 18 months after starting treatment is an excellent predictor of response to tamoxifen in the preventive setting [64].

These results (and others) show that PMD is associated with risk of breast cancer and is changed by intervention with tamoxifen. However, although the change in PMD was associated with the effect of tamoxifen on breast cancer risk, no evidence is given that the change in PMD mediated the effect of tamoxifen on breast cancer risk.

Even if it were convincingly shown that change in PMD did mediate the effects of tamoxifen on breast cancer risk, it should not be concluded that all other causes of a reduction in PMD will reduce risk of breast cancer. For example, as discussed above, average PMD decreases with increasing age whereas breast cancer incidence increases with age. A randomized controlled trial of physical activity for 1 year in postmenopausal women, which may reduce breast cancer risk, showed that PMD was increased as a result of the weight loss associated with the intervention [65].

Other interventions that are known to influence PMD and breast cancer risk include combined hormone therapy (but not estrogen alone), which increases PMD and risk of breast cancer [66-68], and a gonadotrophin-releasing hormone agonist reduces PMD in premenopausal women [69]. It is not yet known whether PMD can be used as a surrogate for breast cancer in any of these settings. In the IBIS trial, the association observed between change in PMD and reduction in breast cancer incidence with tamoxifen suggests that change in PMD after the initiation of hormone therapy might be useful in the prediction of effect in therapeutic settings.

Breast cancer characteristics and clinical outcomes

Tables 3 and 4 show, respectively, summaries of published studies that have examined the associations of breast density with tumor characteristics and the clinical course of breast cancer. To date, most studies examining the association of breast density with tumor characteristics have used a qualitative measure of density (for example, BI-RADS), lacked information on covariates, and differed in whether and how the cancer was detected (by screening or other means).

Tumor characteristics

Studies that have examined the association of breast density with tumor characteristics of estrogen receptor status, tumor size, and nodal status are summarized in Table 3. These studies vary in size, design, methods used to classify mammographic density, and factors adjusted for in analysis. Differences in these factors may contribute to the inconsistency of the results of the association of breast density with tumor characteristics.

Table 3. Summary of studies of the association of mammographic density and tumor characteristics

Authors, region (year)	Design	Sample size	Measurement of MD	Association with			Adjustments[c]
				ER status/phenotype[a]	Size[a,b]	Nodal status[a,b]	
Yaghjyan *et al*. [70], USA (2011)	Nested case control	1,042 cases 1,794 controls	Computer-assisted	Case control: Increased risk of ER^+ and ER^- tumors (greater for ER^-) Increased risk of PR^+ and PR^- and $HER2^-$ and $HER2^+$ tumors	Increased risk for tumors >2 cm but not for tumors <2 cm	Increased risk with $node^+$ and $node^-$ disease	Age, BMI, age at menarche, age at first birth, parity, age at menopause, HRT use, family history, history of benign breast disease, alcohol intake, and smoking
Conroy *et al*. [71], USA (2011)	Nested case control	607 cases 667 controls	Computer-assisted	Case control: Increased risk of ER^+ tumors only Case only: ER^+ > PMD than ER^- cases	n/a	n/a	Age, ethnicity, BMI, parity, age at first birth, age at menarche, menopausal status, HRT use, and family history
Ding *et al*. [72], Europe (2010)	Nested case control	370 cases 1,904 controls	Computer-assisted	Case control: Increased risk of ER^+ tumors only	Increased risk for tumors of all sizes	Increased risk with $node^+$ and $node^-$ disease	Age
				Case only: ER^+ > PMD than ER^- cases	No association	No association	
Olsen *et al*. [73], Europe (2009)	Cohort	694 cases 48,052 total	Mixed/dense versus fatty	Increased risk of ER^+ and ER^- tumors (greater for ER^+)	n/a	n/a	Age
Ziv *et al*. [74], USA (2004)	Cohort	701 cases 44,811 total	BI-RADS	Increased risk of ER^+ and ER^- tumors	n/a	n/a	Age, HRT use, BMI, parity, family history, menopause, and race
Ma *et al*. [75], USA (2009)	Case control	479 cases 376 controls	Computer-assisted	Case control: Increased risk of ER^+/PR^+, ER^-/PR^-, $HER2^-$, luminal A, and triple-negative tumors[d] Case analysis: Molecular subtype[d]: no association	n/a	n/a	Age, family history, BMI, age at menarche, parity, age at first birth, menopause, and HRT use
Gierach *et al*. [76], Europe (2010 abstract)	Case only	227 cases	Computer-assisted	No significant difference in PMD between luminal A, luminal B, $HER2^+$, basal-like, or unclassified tumors[d]	n/a	n/a	Not available (abstract only)
Arora *et al*. [77], USA (2010)	Case only	1,323 cases	BI-RADS	Molecular subtype: no association	No association	No association	Age
Yang *et al*. [78], USA (2008)	Case only	198 cases	BI-RADS	Molecular subtype[d]: no association	n/a	n/a	None
Cil *et al*. [79], Canada (2009)	Case only	335 cases	Wolfe score	No association	No association	No association	None
Nickson and Kavanagh [86], Australia (2009)	Case only	1,348 cases	Semi-automated	n/a	No association	n/a	Age, HRT use, and family history
Ghosh *et al*. [80], USA (2008)	Case only	286 cases	Computer-assisted	No association	No association	n/a	Age, parity, BMI, family history, and HRT use
Porter *et al*. [87], Europe (2007)	Case only	759 cases	BI-RADS	n/a	Positive (screen-detected)	No association	None
Fasching *et al*. [81], Europe (2006)	Case only	434 cases	BI-RADS	No association	Negative	No association	None

Continued overleaf

Table 3. Continued

Authors, region (year)	Design	Sample size	Measurement of MD	Association with			Adjustments[c]
				ER status/phenotype[a]	Size[a,b]	Nodal status[a,b]	
Aiello *et al*. [82], USA (2005)	Case only	546 cases	BI-RADS	No association	Positive	Positive	Age, BMI, menopause, and age at first birth
Morishita *et al*. [83], Japan (2005)	Case only	163 cases	BI-RADS	No association	No association	n/a	None
Roubidoux *et al*. [84], USA (2004)	Case only	121 cases	BI-RADS	No association	Positive	No association	Age
Sala *et al*. [88], Europe (2000)	Nested case control	875 cases	Wolfe	n/a	Positive	Positive	None
Hinton *et al*. [85], Europe (1985)	Case only	337 cases	Wolfe	DY pattern associated with greater frequency of ER^+ versus ER^- tumors	n/a	n/a	None
Boyd *et al*. [89], Canada (1982)	Case only	183 cases	Wolfe	n/a	No association	No association	None

[a]No association: association is not statistically significant. [b]Positive: higher percent mammographic density (PMD) associated with higher tumor size or higher frequency of positive nodal status ($node^+$); negative (inverse) association: higher PMD associated with smaller tumor size or lower frequency of positive nodal status ($node^+$). [c]Factors included in the analysis of risk associated with mammographic density or of the association of mammographic density with tumor characteristics. [d]Molecular subtypes determined by immunohistochemistry. BI-RADS, Breast Imaging-Reporting and Data System; BMI, body mass index; DY, dysplastic; ER, estrogen receptor; HRT, hormone replacement therapy; MD, mammographic density; n/a: not assessed; PR, progesterone receptor.

Table 4. Summary of studies of mammographic density and risk of second breast cancers

Authors, region (year)	Study population	Median follow-up	Measurement of MD	Results			Adjustments[a]	Comments
				Events[b]	Number	HR (95% CI)		
Habel *et al*. [91], USA (2010)	935 patients with DCIS	8 years	Planimeter Highest versus lowest quintile of dense area	All	228	1.8 (1.2 to 2.9)	Age, BMI, treatment, and diagnosis year	Similar HR in subgroups of age, BMI, treatment, and menopausal status
				Ips.	164	1.7 (1.0 to 2.9)		
				Cont.	59	3.0 (1.3 to 6.9)		
Hwang *et al*. [93], USA (2007)	3,274 patients with DCIS	39 months	BI-RADS High (3 or 4) versus low (1 or 2)	All inv.	133	1.4 (0.9 to 2.1)	Age and radiation treatment	No interaction of density with radiation treatment
				Ips. inv.	83	1.0 (0.6 to 1.6)		
				Cont. inv.	52	3.1 (1.6 to 6.1)		
Habel *et al*. [90], USA (2004)	334 patients with DCIS	11 years	Planimetry >75% versus <25% PMD	All	112	2.8 (1.3 to 6.1)	Age, BMI, and radiation treatment	No interaction with radiation treatment or menopausal status
				Ips.	80	3.0 (1.2 to 7.5)		
				Cont.	28	3.4 (0.7 to 16.2)		
Cil *et al*. [79], Canada (2009)	335 patients with invasive breast cancer	8 years	Wolfe score High versus low Wolfe score	Ips. inv.	34	5.7 (1.6 to 20.0)	Age, menopause, and radiation treatment	Association stronger in those who did not receive radiation treatment
				Dist. inv.	31	No association (HR not given)		
Park *et al*. [92], USA (2008)	136 patients with invasive breast cancer	7.7 years	Computer- assisted >75% versus <25% PMD	Ips. inv.	19	3.4 (1.6 to 7.5)	BMI	
				Cont./ Dist. inv.	25	No association (HR not given)		

[a]Factors included in the analysis of mammographic density and risk of second breast cancer. [b]Events include *in situ* and invasive cancer unless specified as invasive (inv.). All, all second breast cancers; BI-RADS, Breast Imaging-Reporting and Data System; BMI, body mass index; CI, confidence interval; Cont., second cancer in contralateral breast; DCIS, ductal carcinoma *in situ*; Dist, distant metastasis; HR, hazard ratio; Ips, second cancer in ipsilateral breast; MD, mammographic density; PMD, percent mammographic density.

Of 16 studies that examined the association of breast density with hormone receptor status or molecular phenotype [70-85], most found no associations. More extensive density was found to be associated with risk of ER^+ tumors in 6 studies [70-75] and of ER^- tumors in 4 studies [70,73-75]. Of 12 studies that examined tumor size in relation to breast density [70,72,77,79-84,86-89], 4 found larger tumors [82,84,87,88] and 1 found smaller tumors [81] associated with more extensive density. The remainder found no association. Ten studies examined nodal status [70,72,77,79,81,82,84,87-89], and 2 found nodal involvement to be more frequent in those with extensive density [82,88] and the remainder found no association. In addition, Yaghjyan and colleagues [70] found that the associations between breast density and breast cancer were stronger for *in situ* than for invasive tumors and for high-grade than for low-grade tumors.

Risk of second breast cancer

Studies that have examined risk of a second invasive or *in situ* breast cancer are summarized in Table 4. Four [79, 90-92] of the five [79,90-93] studies show an increased risk of a second cancer in the ipsilateral breast, and three [90,91,93] of the five show an increased risk in the contralateral breast. Only one [79] of the three [79,91,93] studies to examine the potential modifying role of radiation therapy found evidence that risk of a second breast cancer was higher in those who did not receive radiation.

Women with higher density have been shown to have a higher risk of dying from breast cancer compared with those with lower density, but this is due largely to the increased breast cancer incidence associated with density [73,94]. In terms of survival after a breast cancer diagnosis, one study reported a non-significant trend to better survival in women with dense breasts [68], and another reported that women with mixed/dense breasts had a significantly lower risk of death from any cause or from breast cancer specifically (case fatality rates of 60% and 53%, respectively) compared with women with fatty breasts [73].

Summary

There is now extensive evidence that extensive PMD is a strong risk factor for breast cancer and is associated with large relative and attributable risks for the disease. As discussed above (in the 'Breast cancer prevention trials' section), unlike most breast cancer risk factors, PMD can be changed. Work now in progress is likely to improve measurement of PMD, understanding of the genetics and biological basis of the association of PMD with breast cancer risk, and the clinical significance of change in PMD. Future prospects for the application of PMD include improvements in mammographic screening, risk prediction in individuals, breast cancer prevention research, and clinical decision making.

Abbreviations

BI-RADS, Breast Imaging-Reporting and Data System; CI, confidence interval; CLL, columnar cell lesion; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; IBIS, International Breast Cancer Intervention Study; IGF-I, insulin-like growth factor I; MR, magnetic resonance; OR, odds ratio; PMD, percent mammographic density; UST, ultrasound tomography.

Competing interests

MJY is a founding partner of, and holds shares in, Matakina Technology (Wellington, New Zealand), a company that develops software for measurement of breast density. The other authors declare that they have no competing interests.

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