Introduction
Breast density, assessed by mammography and expressed as a percentage of the mammogram occupied by radio-opaque 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.

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.

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
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 these 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...
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 similar estimates

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

| Authors/study, region | Subject age, years | Sample size | Measurement | Partition | OR (95% CI) | Follow-up, years | Adjustments |
|-----------------------|-------------------|-------------|-------------|-----------|-------------|-----------------|-------------|
| 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 ≥5% | 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*             | 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, and family history of breast cancer |
| Boyd et al./NBSS [14], Canada | 40-59          | 330         | a. Estimation | 0% versus ≥75% | a. 6.0 (2.8 to 13.0) | 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 | <10% versus ≥75% | a. 4.5 (1.9 to 11.0) | 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 | <10% versus ≥75% | a. 3.4 (1.1 to 10.3) | 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 | <10% versus ≥75% | a. 4.7 (3.0 to 7.4) | 6-8 | Age, parity, age at first birth, weight, height, number of births, age at menarche, and family history |

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*aReported as the number of case subjects/number of control subjects or as the number of pairs of case and control subjects. *Estimation means visual estimation by an observer (radiologist). †The most and least extensive categories of density from which odds ratios (ORs) were calculated. ‡Factors included in the analysis of risk associated with mammographic density. Factors controlled for by matching are also included. *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].

http://breast-cancer-research.com/content/13/6/223
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]).

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

| Categories of percent density, percentage | Number of pairs* | OR (95% CI) | P valueb |
|-------------------------------------------|------------------|-------------|----------|
| All                                       |                  |             |          |
| Case                                      | 1,112            | 1.00        |          |
| Control                                   | 1,112            | 1.00        |          |
| OR                                        | 1.00             | 1.00        |          |
| (95% CI)                                  | (0.9, 1.1)       | (0.9, 1.1)  |          |
| Screen-detected                           |                  |             |          |
| Case                                      | 717              | 1.00        |          |
| Control                                   | 717              | 1.00        |          |
| OR                                        | 1.00             | 1.00        |          |
| (95% CI)                                  | (0.9, 1.1)       | (0.9, 1.1)  |          |
| Non-screen-detected <12 monthsd           |                  |             |          |
| Case                                      | 124              | 1.00        |          |
| Control                                   | 124              | 1.00        |          |
| OR                                        | 1.00             | 1.00        |          |
| (95% CI)                                  | (0.9, 1.1)       | (0.9, 1.1)  |          |
| Non-screen-detected >12 monthse            |                  |             |          |
| Case                                      | 262              | 1.00        |          |
| Control                                   | 262              | 1.00        |          |
| OR                                        | 1.00             | 1.00        |          |
| (95% CI)                                  | (0.9, 1.1)       | (0.9, 1.1)  |          |

*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). P value for the Cochran-Armitage trend test. *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). *Cancers detected within 12 months of the last screening date. *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].
that PMD and lobular involution are independently associated with risk of breast cancer [38], and it appears (lobular involution) has been found to be inversely

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 × 10⁻³) and glandular area (P = 2 × 10⁻³) [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 woman’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 | ER status/phenotype | Size | Nodal status | Adjustments |
|------------------------|--------|-------------|-------------------|---------------------|------|--------------|-------------|
| 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 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, 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 |
| 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+ tumors only; Case analysis: Molecular subtype: no association | No association | No association | 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 | 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: 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 [80], Australia (2009) | Case only | 1,348 cases | Semi-automated | No association | n/a | No association | 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. [81], Europe (2007) | Case only | 759 cases | BI-RADS | No association | 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 | ER status/phenotype | Size | Nodal status | Adjustments |
|-----------------------|--------|-------------|-------------------|--------------------|------|-------------|-------------|
| 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 |

*No association: association is not statistically significant. 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+). Factors included in the analysis of risk associated with mammographic density or of the association of mammographic density with tumor characteristics. 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 | ER status/phenotype | Events | HR (95% CI) | Adjustments | Comments |
|-----------------------|------------------|-----------------|-------------------|--------------------|--------|-------------|-------------|----------|
| 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 |
| 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 |
| 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 |
| 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 |
| 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 | No association (HR not given) |

*Factors included in the analysis of mammographic density and risk of second breast cancer. 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 [70,72,77,79,81,82,84,87,88], 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.
58. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ: Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989, 81:1879-1886.

59. Chen J, Peer D, Ayagani R, Graubard B, Schairer C, Byrne C, Benichou J, Gail MH: Projecting absolute breast cancer risk in white women with a model that includes mammographic density. J Natl Cancer Inst 2006, 98:1215-1226.

60. Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K: Using clinical risk factors and mammographic density to estimate breast cancer risk: development and validation of a new predictive model. Ann Intern Med 2008, 148:337-347.

61. Martin LJ, Li Q, Melnichouk O, Greenberg C, Minkin S, Hislop G, Boyd NF: A randomized trial of dietary intervention for breast cancer prevention. Cancer Res 2011, 71:123-133.

62. Prestince RL: Surrogate endpoints in clinical trials: Definition and operational criteria. Stat Med 1988, 8:431-440.

63. Schwartz A, Gail M: The promise and peril of surrogate end points in cancer research. Nat Rev Cancer 2002, 2:19-27.

64. Cuzick J, Warwick J, Pinney E, Duffy SW, Cawthorn S, Howell A, Forbes JF, Warren RM: Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. J Natl Cancer Inst 2011, 103:744-752.

65. Woolcott GG, Coumeys KS, Boyd NF, Yaffe MF, Terry T, Mtiertan A, Bryant R, Ballard-Barbash R, Irvin MJ, Jones CA, Bras S, Cam MJ, KL, McNeely ML, Kvanin KH, Friedenich CM: Mammographic density change with 1 year of aerobic exercise among postmenopausal women: a randomized controlled trial. Cancer Epidemiol Biomarkers Prev 2010, 19:1112-1121.

66. Kerlikowske K, Cook AJ, Buist DS, Cummings SR, Vachon C, Vacek P, Miglioretti DL: Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. J Clin Oncol 2010, 28:3830-3837.

67. Greendale GA, Reboussin B, Slone S, Wasilauskas C, Pike MC, Ursin G: Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst 2003, 95:30-37.

68. Chleowski RT, Hendrik SL, Langer RD, Stefanick ML, Gass M, Lane D, Rodakobh RJ, Gilligan MA, Cyng MR, Thomson CA, Kandekarian J, Petrovitch H, Mtiertan A; WHI Investigators: Influence of estrogen plus progesteron on breast cancer and mamography in healthy postmenopausal women. The Women's Health Initiative Randomized Trial. JAMA 2003, 289:3243-3253.

69. Spencer DV, Ursin G, Parisky YR, Pearce JG, Shoue P, Pike A, Pike MC: Changes in mammographic densities induced by a hormonal contraceptive designed to reduce breast cancer risk. J Natl Cancer Inst 1994, 86:431-436.

70. Yaghjyan L, Colditz GA, Collins LC, Schnitt SJ, Rosner B, Vachon CM, Tamimi RM: Mammographic density and the risk of breast cancer recurrence after breast-conserving surgery. Cancer 2009, 115:5789-5787.

71. Cil T, Fishell E, Hanna W, Sun P, Rawlinson E, Nardon SA, McCready DR: Mammographic density and the risk of breast cancer recurrence after breast-conserving surgery. Cancer 2009, 115:5789-5787.

72. Ghosh K, Brandt KR, Sellers TA, Reynolds C, Scott CG, Maloney SD, Carstison MJ, Pankratz V, Vachon CM: Association of mammographic density with the pathology of subsequent breast cancer among postmenopausal women. Cancer Epidemiol Biomarkers Prev 2008, 17:872-879.

73. Faichign PA, Heusings K, Loehbeg CR, Winkel E, Lux MP, Schrauder M, Koscheck T, Bautz W, Schulz-Wendtland R, Beckmann MW, Bari M: Influence of mammographic density on the diagnostic accuracy of tumor size assessment and association with breast cancer tumor characteristics. Eur J 2006, 40:394-408.

74. Aelio EJ, Buist DSM, White E, Porter PL: Association between mammographic breast density and breast cancer tumor characteristics. Cancer Epidemiol Biomarkers Prev 2005, 14:662-668.

75. Morisihita M, Ohtsuru A, Hayashi T, Isomoto L, Itoyanagi N, Maeda S, Honda S, Yano H, Uga T, Nagayasu T, Kanematsu T, Yamashita S: Clinical significance of categorisation of mammographic density for breast cancer prognosis. Int J Oncol 2005, 26:1307-1312.

76. Roudoboux MA, Bailey JE, Wray LA, Helvie MA: Invasive cancers detected after breast cancer screening yielded a negative result: relationship of mammographic density to tumor prognostic factors. Radiology 2004, 230:42-48.

77. Hinton CP, Roebeck EU, Williams MR, Blamey RW, Gaves J, Nicholson RI, Griffiths K: Mammographic parenchymal patterns: value as a predictor of hormone dependency and survival in breast cancer. AJR Am J Roentgenol 1985, 144:1103-1107.

78. Nickson C, Kavanagh AM: Tumor size at detection according to different measures of mammographic breast density. J Med Screen 2009, 16:140-146.

79. Porter G, Evans AJ, Conmber EF, Burrell HC, James JJ, Lee AH, Chakrabarti J: Influence of mammographic parenchymal pattern in screening-detected and interval invasive breast cancers on pathologic features, mammographic features, and patient survival. AJR Am J Roentgenol 2007, 188:676-683.

80. Sala E, Solomon L, Warren R, McCann J, Duffy S, Ruben R, Day N: Size, node status and grade of breast tumors: association with mammographic parenchymal patterns. Eur Radiol 2000, 10:157-162.

81. Boyd NF, O'Sullivan B, Campbell JE, Fishell E, Simor I, Cooke G, Germanson T: Mammographic patterns and bias in breast cancer detection. Radiology 1982, 143:671-674.

82. Habel LA, Dagnan JJ, Lund SR, Salane M, Capra AM, Juliano RL: Mammographic density and breast cancer after ductal carcinoma in situ. J Natl Cancer Inst 2004, 96:1467-1472.

83. Habel LA, Capra AM, Acharacos NS, Janga A, Acton L, Fulgandia B, Quesenberry CP Jr: Mammographic density and risk of second breast cancer after ductal carcinoma in situ. Cancer Epidemiol Biomarkers Prev 2010, 19:2488-2495.

84. Park CC, Rembert J, Chev K, Moore D, Kerlikowske K: High mammographic breast density is independent predictor of local but not distant recurrence after lumpectomy and radiotherapy for invasive breast cancer. Int J Radiat Oncol Biol Phys 2007, 73:75-79.

85. Hwang ES, Miglioretti DL, Ballard-Barbash R, Weaver DL, Kerlikowske K: Invasive cancers detected after breast cancer screening yielded a negative result: relationship of mammographic density to tumor prognostic factors. Radiology 2004, 230:42-48.

86. Park CC, Rembert J, Chev K, Moore D, Kerlikowske K: High mammographic breast density is independent predictor of local but not distant recurrence after lumpectomy and radiotherapy for invasive breast cancer. Int J Radiat Oncol Biol Phys 2009, 73:75-79.

87. Hwang ES, Miglioretti DL, Ballard-Barbash R, Weaver DL, Kerlikowske K: Association between breast density and subsequent breast cancer among postmenopausal women. J Natl Cancer Inst 2007, 100:2587-2593.

88. Chiu SY, Duffy S, Yen AM, Tabar L, Smith RA, Chen HH: Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. Cancer Epidemiol Biomarkers Prev 2010, 19:1219-1228.

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