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Background Parenchymal Uptake During Molecular Breast Imaging and Associated Clinical Factors

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Abstract

OBJECTIVE—The purposes of this study were to describe the prevalence of background parenchymal uptake categories observed at screening molecular breast imaging (MBI) and to examine the association of background parenchymal uptake with mammographic density and other clinical factors.

MATERIALS AND METHODS—Adjunct MBI screening was performed for women with dense breasts on previous mammograms. Two radiologists reviewed images from the MBI examinations and subjectively categorized background parenchymal uptake into four groups: photopenic, minimal-mild, moderate, or marked. Women with breast implants or a personal history of breast cancer were excluded. The association between background parenchymal uptake categories and patient characteristics was examined with Kruskal-Wallis and chi-square tests as appropriate.

RESULTS—In 1149 eligible participants, background parenchymal uptake was photopenic in 252 (22%), minimal-mild in 728 (63%), and moderate or marked in 169 (15%). The distribution of categories differed across BI-RADS density categories ($p < 0.0001$). In 164 participants with extremely dense breasts, background parenchymal uptake was photopenic in 72 (44%), minimal-mild in 55 (34%), and moderate or marked in 37 (22%). The moderate-marked group was younger on average, more likely to be premenopausal or perimenopausal, and more likely to be using postmenopausal hormone therapy than the photopenic or minimal-mild groups ($p < 0.0001$).

CONCLUSION—Among women with similar-appearing mammographic density, background parenchymal uptake ranged from photopenic to marked. Background parenchymal uptake was associated with menopausal status and postmenopausal hormone therapy but not with

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premenopausal hormonal contraceptives, phase of menstrual cycle, or Gail model 5-year risk of breast cancer. Additional work is necessary to fully characterize the underlying cause of background parenchymal uptake and determine its utility in predicting subsequent risk of breast cancer.

Keywords

breast density; hormone therapy; menstrual cycle; molecular breast imaging; MRI

Mammographic breast density, which refers to the relative amount of fibroglandular tissue compared with fat in the breast, has been found to both limit the sensitivity of mammography [1–3] and be independently associated with increased risk of development of breast cancer [4, 5]. Approximately 40–50% of screening-eligible women in the United States are estimated to have either heterogeneously dense or extremely dense breasts as classified according to the BI-RADS lexicon [6, 7]. Although mammographic density is a strong risk factor with relative risk of 4–6 (comparing women with extremely dense breasts with women with breasts with almost no dense tissue, incorporation of density into risk prediction models such as the Gail model has not been found to greatly improve discrimination of future risk, the reported C statistic being approximately 0.65 [4]. Thus, it is likely that the large population of women with dense breasts is on a wide spectrum of risk levels, diluting the utility of mammographic density in accurate prediction of risk for the individual patient.

Contrast-enhanced MRI not only depicts fibroglandular breast tissue, a finding similar to mammographic density, but also shows functional enhancement of fibroglandular tissue, termed background parenchymal enhancement (BPE) [8]. A recent study [9] showed that BPE on MR images can vary from absent to severe among women with similar mammographic density. In a report on women at high risk who underwent MRI screening, a higher level of BPE (classified as moderate or marked compared with minimal or mild) was a strong predictor of breast cancer odds, and BPE was a stronger predictor than amount of fibroglandular tissue assessed at the MRI examination alone [10]. Furthermore, BPE has been associated with exogenous and endogenous hormonal factors [11–14]. These findings suggest that assessment of the functional status of the fibroglandular tissue may improve discriminatory risk prediction relative to assessment of mammographic density alone.

Molecular breast imaging (MBI) is a nuclear medicine technique in which a gamma camera is used to image the preferential uptake of ^{99m}Tc -labeled sestamibi in highly metabolic cells in the breast. The addition of MBI to screening mammography in women with dense breasts has been shown to significantly increase the cancer detection rate compared with the rate with mammography alone [15, 16]. In a recent study, supplemental MBI increased the cancer detection rate per 1000 women screened from 3.2 with mammography alone to 12.0 with the combination ($p < 0.001$, supplemental yield of 8.8) [16]. Like BPE found with MRI, various levels of background parenchymal uptake in fibroglandular tissue of healthy breasts were found with MBI. These results led to the inclusion of four categories of background parenchymal uptake—photopenic, minimal-mild, moderate, and marked—in the lexicon for MBI interpretation [17, 18]. Studies of positron emission mammography

(PEM), another functional nuclear medicine technique for breast imaging, have also shown variable levels of background uptake of ^{18}F -FDG [19].

Anecdotal accounts of $^{99\text{m}}\text{Tc}$ -sestamibi uptake in normal breast parenchyma have used descriptors of “physiologic” or “patchy” uptake [20, 21]. To our knowledge, however, no formal evaluations of background parenchymal uptake, including the distribution of uptake and its association with clinical factors, have been conducted. We present the result of the first analysis to characterize background parenchymal uptake in women undergoing screening [22]. Our objectives were to describe the prevalence of background parenchymal uptake categories observed at adjunct screening MBI and to examine the association between background parenchymal uptake and mammographic density and other clinical factors, including endogenous and exogenous hormonal influences.

Materials and Methods

Study Design and Participants

Images from screening MBI examinations consecutively performed between April 2010 and March 2012 for a total of 1290 participants were retrospectively reviewed. These examinations were performed as part of an institutional review board–approved, HIPAA-compliant research protocol designed to evaluate the utility of MBI as an adjunct to screening mammography of women with dense breasts [16]. Informed consent was obtained. All participants were free of symptoms and had previous mammographic findings of heterogeneously dense or extremely dense breasts, according to the BI-RADS lexicon [7]. Participants with breast implants ($n = 7$) were excluded because background parenchymal uptake is difficult to assess with an implant present. To examine background parenchymal uptake in a healthy cohort at risk of incident breast cancer, participants with any invasive cancer or ductal carcinoma in situ diagnosed within 365 days after the study MBI ($n = 9$) and those with personal history of breast cancer ($n = 125$) were also excluded from analysis. Thus, the analysis set comprised 1149 participants.

Clinical Information Collected

Clinical information, including patient age, body mass index (BMI), menopausal status, and current use of systemic hormonal medications, was obtained through patient questionnaire and medical record. Menstrual status was categorized as premenopausal, perimenopausal, or postmenopausal (last menstrual period > 12 months before MBI or surgical menopause induced by bilateral oophorectomy). In premenopausal and perimenopausal patients, the date of onset of the last menstrual period was recorded when available. Additional data collected were as follows: age at menarche; age at first live birth and parity; personal history of breast biopsy with benign or high-risk findings and histopathologic result (whether atypia or lobular carcinoma in situ was diagnosed); and family history of breast cancer. These data were used for calculation of 5-year risk according to the Gail model.

Molecular Breast Imaging Acquisition and Interpretation

MBI was performed with IV injection of $^{99\text{m}}\text{Tc}$ -sestamibi; dispensed activity was 300 MBq (8 mCi). Immediately after injection, two views of each breast in craniocaudal- and

mediolateral oblique–analogous orientations were acquired with a dual-head direct-conversion gamma camera (LumaGEM, Gamma Medica; or Discovery NM 750b, GE Healthcare) for 10 minutes per view.

Images from each MBI examination were reviewed by one of two breast radiologists, both with more than 3 years of experience in MBI interpretation. Background parenchymal uptake, described as the degree of uptake in fibroglandular tissue compared with that in subcutaneous fat, was subjectively categorized as photopenic, minimal-mild, moderate, or marked, according to a validated lexicon for gamma imaging of the breast [17, 18]. Examples of each background parenchymal uptake category are shown in Figure 1. Interreader and intrareader agreement on categorization of background parenchymal uptake was assessed in a subset of 50 MBI examinations. The readers reread their own 25 examinations and the 25 examinations of the other reader.

Mammographic Density Analysis

Bilateral two-view mammograms were acquired with Selenia full-field digital systems (Hologic) and interpreted in the course of routine clinical practice at our institution. Density was assessed according to the BI-RADS classifications by the radiologist performing the clinical interpretation: 1, almost entirely fat; 2, scattered fibroglandular densities; 3, heterogeneously dense; and 4, extremely dense. Because women were recruited for MBI screening on the basis of having the finding of either heterogeneously dense or extremely dense breasts on the last mammogram, a small number of women had scattered fibroglandular densities ($n = 85$), and no women had the finding of almost entirely fat breast density on the study mammogram.

A quantitative measure of percentage density was performed on craniocaudal mammograms processed in DICOM format by an operator trained in using semiautomated software (Cumulus3, University of Toronto). The operator had more than 12 years of experience in using Cumulus software to assess percentage density with high intraoperator reproducibility (Lin concordance correlation coefficient for processed images, 0.87) [23] and consistent findings of strong associations between percentage density and breast cancer [24–27]. Percentage density assessed on both processed and raw mammograms has been found to have similar associations with breast cancer risk [23]. The operator adjusted window levels and thresholds to classify dense and nondense tissue and remove the off-breast area from analysis. Percentage density was calculated as the dense area divided by the total breast area.

Statistical Analysis

To assess interreader and intrareader agreement in categorization of background parenchymal uptake, the Cohen unweighted kappa statistic was calculated to assess the proportion of agreement expected beyond chance, where $\kappa = 1$ corresponds to perfect agreement and $\kappa = 0$ indicates agreement expected by chance alone.

We described the distribution of background parenchymal uptake categories in the study population and examined the association between background parenchymal uptake categories and the following patient characteristics: age; BMI; mammographic density (both

BI-RADS categories and percentage density); menstrual status; exogenous hormone use, including postmenopausal hormones (among postmenopausal women only) and systemic hormonal contraceptives (among premenopausal women only); and 5-year risk according to the Gail model, which entails a combination of graphical and numeric summaries. Moderate and marked background parenchymal uptake categories were combined because of the limited number of cases with marked uptake ($n = 39$). Kruskal-Wallis and chi-square tests were used as appropriate for testing differences in patient characteristics across background parenchymal uptake categories.

Because differences were observed in age and BMI across the background parenchymal uptake categories, comparisons of percentage density and 5-year Gail risk across background parenchymal uptake categories were performed with estimated (least-squares) means and 95% CIs, which were obtained from a full-factorial analysis of variance model consisting of BMI category (three levels), age group (two levels), and background parenchymal uptake categories (three levels). Type 3 estimates (i.e., weighting each of the 18 estimated means equally) were used to construct the estimated means. Statistical analyses were conducted with SAS software (version 9.3, SAS Institute). No adjustment for multiple testing was applied to reported p values, and $p < 0.05$ was interpreted as statistically significant.

Results

A total of 1149 participants were eligible. Background parenchymal uptake was assessed by one of two readers (one reader 680 patients and the other, 469). Substantial agreement was observed between and within readers, according to criteria established by Landis and Koch [28]. The interreader kappa value was 0.84 (95% CI, 0.71–0.97). The intrareader values were 0.87 (95% CI, 0.70–1) for one reader and 0.94 (95% CI, 0.81–1) for the other.

Background parenchymal uptake was photopenic in 252 (22%) patients, minimal-mild in 728 (63%), moderate in 130 (11%), and marked in 39 (3%). The distribution of each background parenchymal uptake category by patient characteristics is shown in Table 1. Background parenchymal uptake was associated with both age and BMI ($p < 0.0001$, for both). Women with moderate or marked background parenchymal uptake had the lowest mean age, and the women with photopenic background parenchymal uptake had the lowest mean BMI.

The frequency of BI-RADS density categories differed across background parenchymal uptake categories ($p < 0.0001$) (Table 1). These differences are shown in a mosaic plot (Fig. 2A) that illustrates the distribution of background parenchymal uptake by BI-RADS density and the relative proportion of women in each category. Although the proportion of women with minimal-mild background parenchymal uptake decreased across BI-RADS density categories, the proportion of women with photopenic background parenchymal uptake increased with increasing BI-RADS density, and the proportion of women with moderate or marked background parenchymal uptake increased with increasing BI-RADS density. Among the 164 women with extremely dense breasts, 72 (44%) had photopenic, 55 (34%) had minimal-mild, and 37 (22%) had moderate or marked background parenchymal uptake.

Background parenchymal uptake was associated with menopausal status. Approximately three fourths (70–71%) of women with photopenic or minimal-mild background parenchymal uptake were post-menopausal, and among women with moderate or marked background parenchymal uptake, approximately three fourths (76%) were premenopausal or perimenopausal ($p < 0.0001$) (Fig. 2B). Among postmenopausal women, background parenchymal uptake was associated with use of systemic estrogen or progesterone: women with moderate or marked uptake were more likely to be currently using hormones ($p < 0.0001$) (Fig. 2C). Among premenopausal and perimenopausal women, background parenchymal uptake was not statistically associated with hormonal contraceptive use ($p = 0.64$) or day of menstrual cycle ($p = 0.65$). Background parenchymal uptake also was not statistically associated with history of benign biopsy ($p = 0.40$) or first-degree family history of breast cancer ($p = 0.60$).

We performed adjusted analyses to account for age and BMI and found that percentage density was lowest in the women with minimal-mild background parenchymal uptake ($p < 0.001$). The estimated percentage densities for the photopenic background parenchymal uptake versus moderate to marked background parenchymal uptake groups were not statistically different ($p = 0.24$) (Table 1). The distribution of percentage density by age and BMI groups is shown in Figure S1. (Figures S1 and S2 can be seen in the *AJR* electronic supplement to this article, available at www.ajronline.org.) The general tendency of women with minimal-mild background parenchymal uptake to have lower percentage density was appreciable in all age and BMI combinations with the possible exception of women with BMI greater than 30 and age older than 50 years. We also examined the association between 5-year risk according to the Gail model and background parenchymal uptake category but found no significant differences. The estimated 5-year Gail risk ranged from 1.6 (95% CI, 1.4–1.8) for women with moderate or marked background parenchymal uptake to 1.7 (95% CI, 1.4–2.1) for those with photopenic uptake after adjustment for age and BMI ($p = 0.79$) (Table 1 and Fig. S2).

Discussion

In this evaluation of background parenchymal uptake, we found that in women with primarily dense breasts, a range of background parenchymal uptake was observed at MBI, indicating functional differences in the behavior of fibroglandular tissue among women with similar-appearing fibroglandular tissue on mammograms. In general, women with moderate or marked background parenchymal uptake were younger, more likely to be premenopausal or perimenopausal, and more likely to be using postmenopausal hormone therapy than were women with photopenic or minimal-mild background parenchymal uptake. Background parenchymal uptake was also associated with BMI, BI-RADS density category, and percentage density (minimal-mild background parenchymal uptake being the least dense) but was not statistically associated with day of menstrual cycle, history of benign biopsy, family history of breast cancer, or 5-year risk according to the Gail model. Whether background parenchymal uptake is predictive of subsequent breast cancer risk is yet to be determined but should be the focus of future research.

Most of the women undergoing adjunct MBI screening in this study had minimal-mild background parenchymal uptake, in which uptake in fibroglandular tissue is the same as in fat. Because background parenchymal uptake depicts the component of fibroglandular tissue that is functionally active (through uptake of ^{99m}Tc -sestamibi), it was expected that moderate or marked background parenchymal uptake would be more frequently observed in denser breasts, which are associated with the highest risk of breast cancer [4]. We observed, however, that a substantial proportion of women with the densest breasts had photopenic background parenchymal uptake, in which there is a lack of uptake in fibroglandular tissue, showing less uptake compared with fat. The question becomes: What is different between mammographically dense tissue with moderate or marked background parenchymal uptake and that with photopenic background parenchymal uptake? Interestingly, photopenic background parenchymal uptake was more frequent in postmenopausal women and those with lower BMI, a subgroup in whom breast cancer risk is known to be lower [29].

Background parenchymal uptake appears to be influenced by hormonal activity in the breast: moderate or marked uptake was more common in postmenopausal women using hormone therapy than in nonusers and in women with menstrual cycles (premenopausal or perimenopausal) than in postmenopausal women. However, among postmenopausal women, moderate or marked background parenchymal uptake was still observed in a small proportion of nonusers (18 of 587 [3%]), and photopenic background parenchymal uptake was observed in a substantial proportion of postmenopausal women using hormone therapy (25 of 145 [17%]), which could suggest variability in response to hormone therapy, as has been seen with percentage density on mammograms [30]. A number of studies have shown similar influence of menopausal status and use of postmenopausal therapy on MRI-depicted BPE [11–13].

A previous report showed that background uptake of ^{99m}Tc -sestamibi during MBI is influenced by menstrual cycle in premenopausal women, moderate or marked uptake being more likely to occur in the luteal phase than in the follicular phase [17, 31]. Likewise, menstrual cycle has been found to affect background enhancement on MR images, enhancement being lowest on days 7–14 of the menstrual cycle among women undergoing serial imaging throughout the cycle [14]. We did not find an association between background parenchymal uptake and day of menstrual cycle. This discrepancy may be explained by the fact that the participants in our study were at various phases in their cycles. Previous studies, however, assessed background parenchymal uptake during MBI examinations performed specifically during peak follicular and peak luteal phases in the same woman.

Background uptake can occasionally obscure tumors during MBI (Fig. 3), and therefore, efforts to minimize background uptake may be considered. It has been recommended that MBI be scheduled on days 7–10 of the menstrual cycle [17], although our current data do not support this recommendation. According to our results coupled with those in the literature, cessation of hormonal therapy for a few months before MBI may also be considered. An example of a patient in whom background parenchymal uptake decreased when hormone therapy was discontinued is shown in Figure 4. Likewise, BPE has been observed to obscure tumors at MRI [32].

The mechanism of ^{99m}Tc -sestamibi uptake in the breast is poorly understood. This radionuclide is a perfusion agent, most common to myocardial imaging. In cancer, uptake of ^{99m}Tc -sestamibi is associated with blood flow, tissue viability, mitochondrial activity, and mitotic activity of tissue [33–35]. Similarly, angiogenesis and vascular permeability are the basis of contrast enhancement of breast tumors for the gadolinium chelate agents used in MRI [36]. Our experience to date has shown that MBI uptake of ^{99m}Tc -sestamibi in breast cancers correlates with gadolinium MRI contrast enhancement. Further study is needed to verify that these contrast agents are correlated in benign background breast tissue. A recent report [37] supports a correlation between ^{99m}Tc -sestamibi uptake and gadolinium contrast enhancement in background parenchyma.

MRI screening is currently indicated only for women at high risk, such as those with *BRCA* mutations or greater than 20% lifetime risk based on family history risk prediction models. It is not recommended on the basis of breast density alone, primarily owing to concerns about variable specificity, high cost, and patients' refusal to undergo screening MRI [38–40]. With the recent finding that MBI interpretation can be rapidly learned [18] and performed at radiation doses low enough to be acceptable for screening [16, 41], it may be feasible to implement MBI on a widespread basis for women with mammographically dense breasts who do not meet the risk criteria to qualify for screening MRI. Thus, understanding of background parenchymal uptake will be central to future risk stratification in this population. Further work is necessary to fully characterize the underlying cause of background parenchymal uptake and determine its utility in prediction of subsequent development of breast cancer.

The underlying biologic link between breast density and risk is not yet clear. Fibroglandular tissue in the breast is not homogeneous but comprises both epithelium and supporting stroma in varying proportions among women. Although there are different hypothesized mechanisms by which these tissues influence breast cancer development, study results have indicated that cellular proliferation of epithelium, stroma, or both is associated with mammographic density [42, 43]. Lobular involution (the age-related atrophy of epithelium associated with reduction in breast cancer risk) has been inversely associated with mammographic density. Examination of biopsy specimens has shown that nondense breasts on mammography are more likely to have undergone complete lobular involution [44]. However, this relation is not exact; a substantial proportion of the densest breasts were found to also have undergone complete lobular involution. Because epithelium cannot be easily differentiated from stroma on a mammogram and lobular involution status cannot be evaluated, mammography is limited in the use of underlying tissue composition for predicting risk at the individual level. These issues underscore the need for functional imaging tools, such as MRI and perhaps MBI, which may help further delineate which mammographically dense fibroglandular tissue is likely to increase risk of breast cancer and which is not. Such functional imaging tools may allow appropriate individualization of supplemental screening and risk reduction strategies for women with dense breasts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Examples of background parenchymal uptake categories.

A, 65-year-old postmenopausal woman with no current exogenous hormone use. Molecular breast image shows photopenic background parenchymal uptake.

B, 55-year-old postmenopausal woman with no current exogenous hormone use. Molecular breast image shows minimal-mild background parenchymal uptake.

C, 50-year-old postmenopausal woman with no current exogenous hormone use. Molecular breast image shows moderate background parenchymal uptake.

D, 75-year-old postmenopausal woman with no current exogenous hormone use. Molecular breast image shows marked background parenchymal uptake.

E–H, Mammograms corresponding to **A–D** are categorized as heterogeneously dense and have quantitative percentage densities of 33–35%.

Fig. 2. Mosaic plots show distribution of background parenchymal uptake categories in molecular breast imaging as function of BI-RADS breast density ($p < 0.0001$) (**A**), menopausal status ($p < 0.0001$) (**B**), and use of postmenopausal hormone therapy ($p < 0.0001$) (**C**).

Fig. 3.

59-year-old woman with bilateral breast cancer obscured by marked background uptake at molecular breast imaging (MBI). **A** and **B**, Right (**A**) and left (**B**) mediolateral oblique MB images show bilateral moderate to marked background uptake. Both mammographic and MBI findings were interpreted as benign. Workup of palpable areas in both breasts resulted in diagnosis of 8-mm invasive ductal carcinoma in 12-o'clock position of right breast and 7-mm invasive lobular carcinoma in periareolar region of left breast.

Fig. 4. 62-year-old postmenopausal woman discontinuing hormone therapy with systemic estradiol. **A**, Molecular breast image shows moderate background parenchymal uptake while patient is using hormone therapy. **B**, Molecular breast image obtained 4 months after hormone therapy was discontinued shows minimal-mild background parenchymal uptake.

TABLE 1

Background Parenchymal Uptake as Function of Participant Characteristics

Characteristic	Background Parenchymal Uptake				<i>p</i> ^d
	All Categories (<i>n</i> = 1149)	Photopenic (<i>n</i> = 252)	Minimal or Mild (<i>n</i> = 728)	Moderate or Marked (<i>n</i> = 169)	
Mean age (SD)	57.5 (9.8)	58.5 (10.0)	58.8 (9.5)	50.4 (7.7)	< 0.0001 ^b (C < A, B)
Mean body mass index (SD)	25.6 (4.7)	23.3 (3.4)	26.2 (4.7)	26.5 (5.3)	< 0.0001 ^b A < B, C
BI-RADS density					< 0.0001 ^c
Scattered fibroglandular densities	85 (7)	9 (4)	68 (9)	8 (5)	
Heterogeneously dense	900 (78)	171 (68)	605 (83)	124 (73)	
Extremely dense	164 (14)	72 (29)	55 (8)	37 (22)	
Menopausal status					< 0.0001 ^c
Pre- or perimenopausal	417 (36)	76 (30)	213 (29)	128 (76)	
Postmenopausal	732 (64)	176 (70)	515 (71)	41 (24)	
Hormones, all women					0.04 ^c
Current use of systemic estrogen, progesterone, or both	171 (15)	28 (11)	109 (15)	34 (20)	
No current systemic use	978 (85)	224 (89)	619 (85)	135 (80)	
Hormones, postmenopausal women (<i>n</i> = 732)					< 0.0001 ^c
Current use of systemic estrogen, progesterone, or both	145 (20)	25 (14)	97 (19)	23 (56)	
No current systemic use	587 (80)	151 (86)	418 (81)	18 (44)	
Hormones, pre- or perimenopausal women (<i>n</i> = 417)					0.64 ^c
Current use of hormonal contraceptives	106 (25)	17 (22)	53 (25)	36 (28)	
No current use	311 (75)	59 (78)	160 (75)	92 (72)	
Day of menstrual cycle, pre- or perimenopausal women (<i>n</i> = 417)					0.65 ^c
Not available or beyond day 35	173	33	105	35	
Day 1–14 (estimate of follicular phase)	112 (46)	17 (40)	51 (47)	44 (47)	
Day 15–35 (estimate of luteal phase)	132 (54)	26 (60)	57 (53)	49 (53)	
Personal history of benign biopsy result					0.40 ^c
Yes	298 (26)	57 (23)	196 (27)	45 (27)	
No	851 (74)	195 (77)	532 (73)	124 (73)	

Characteristic	Background Parenchymal Uptake				<i>p</i> ^a
	All Categories (<i>n</i> = 1149)	Photopenic (<i>n</i> = 252)	Minimal or Mild (<i>n</i> = 728)	Moderate or Marked (<i>n</i> = 169)	
Family history of breast cancer					
One or more first-degree relatives	258 (22)	59 (23)	157 (22)	42 (25)	0.60 ^c
No first-degree relatives	891 (78)	193 (77)	571 (78)	127 (75)	
Model-based estimates adjusted for age and body mass index					
Mean percentage density (95% CI)	NA	32.0 (30.1–33.9)	27.4 (26.8–28.0)	30.7 (29.6–31.8)	< 0.001 (B < A, C)
Mean Gail model 5-year risk (95% CI)	NA	1.7 (1.4–2.1)	1.6 (1.5–1.7)	1.6 (1.4–1.8)	

Note—Unless otherwise indicated, numbers in parentheses are column percentages for each characteristic, and percentages are rounded. BMI = body mass index, NA = not applicable.

^a Post hoc comparisons are provided for continuous measurements if the overall Kruskal-Wallis test result was statistically significant. Statistically significant comparisons (unadjusted *p* < 0.05) are indicated by group letter (A = photopenic, B = minimal or mild, C = moderate or marked). Comparisons not listed were not statistically significant.

^b Kruskal-Wallis analysis.

^c Chi-square analysis.