

# Mammographic Density Correlation with Gail Model Breast Cancer Risk Estimates and Component Risk Factors

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## Abstract

**Background:** The Gail model is a validated breast cancer risk assessment tool that is primarily based on nonmodifiable breast cancer risk factors. Conversely, mammographic breast density is strongly correlated with breast cancer risk and responds to risk-modifying interventions. The purpose of our study was to correlate mammographic density with breast cancer risk as calculated by the Gail model and to examine the relative association of each of the model covariates to mammographic density.

**Methods:** The study included 99 participants of the National Surgical Breast and Bowel Project P-1 trial, ages 36 to 74 years, all of whom had a mammogram and Gail model risk estimates done upon trial entry. Baseline mammograms were retrieved and digitized, and mammographic density was assessed by both subjective and computer-assisted objective measures.

**Results:** Mammographic density was 2-fold higher in women with a >15% lifetime risk of breast cancer compared with those with <15% risk, by all density assessment methods. This was equivalent to a 3% to 6% increase in density per 10% increase in risk. Gail model covariates that measured benign or premalignant breast tissue changes accounted for the majority (41%) of the relationship with increased mammographic density. Seven percent of density was not explained by risk factors included in the Gail model.

**Conclusions:** The Gail model does not fully account for the association between breast density and calculated breast cancer risk. Because mammographic density is a modifiable marker, development of a breast cancer risk assessment tool that includes mammographic density could be beneficial for assessing individual risk. (Cancer Epidemiol Biomarkers Prev 2006;15(7):1324–30)

## Introduction

Relative breast density, as seen on mammogram, reflects differential amounts of stromal, epithelial, and fat tissues present within the breast. Stroma and epithelium are radiologically dense, whereas fatty tissue is radiolucent (1). Many studies have shown that women with certain "high-risk" mammographic density patterns have as much as a 6-fold increased risk for breast cancer (2-7). Newer methods of reading mammographic patterns have led to an understanding that the percentage of breast volume that is occupied by dense-appearing areas is the key variable in predicting risk (8-10).

The Gail model is a validated tool for breast cancer risk assessment that has been used to determine eligibility for breast cancer chemoprevention trials (11, 12). However, although breast cancer risk may be reduced with lifestyle modifications (13) and chemopreventive agents (11, 14, 15), the Gail model excludes all modifiable breast cancer risk factors except for the initiation of childbearing. In fact, in women who have completed childbearing, the only time-dependent breast cancer risk factors included in the Gail model are current age and the interval development of an indication for breast biopsy. Many of the same interventions that reduce breast cancer risk are also associated with reduced mammographic density (16-21).

The purpose of this study was to correlate mammographic density with breast cancer risk as predicted by the Gail model. We compared breast density to each of the covariates in the

Gail model to determine which risk factors are most associated with breast density. A review of breast cancer risk factors and risk-reducing interventions associated with mammographic breast density follows, supporting its potential as a modifiable biomarker of breast cancer risk.

## Materials and Methods

**Participant Recruitment.** National Surgical Breast and Bowel Project (NSABP) P-1 Breast Cancer Prevention Trial (BCPT) participants enrolled through the Puget Sound Oncology Consortium-Fred Hutchinson Cancer Research Center were contacted for participation in this study. BCPT enrolled 13,388 women ages  $\geq 35$  years between June 1, 1992, and September 30, 1997. These women were randomized to receive 5 years of tamoxifen or placebo for the primary prevention of breast cancer. Eligibility for BCPT required having a 5-year predicted risk by the Gail model for breast cancer of at least 1.67% or a history of lobular carcinoma *in situ* (LCIS), as well as a mammogram and a clinical breast examination within 180 days before randomization demonstrating no evidence of breast cancer. Participants were followed until March 24, 1998, when the trial met prespecified stopping rules, and the treatment assignment was unblinded (11).

After approval by the Fred Hutchinson Cancer Research Center institutional review board, 164 of the BCPT participants were recruited through the Puget Sound Oncology Consortium-Fred Hutchinson Cancer Research Center clinical site. Of those, 154 were available for contact for participation in the current study. A total of 115 of the women contacted consented to mammogram retrieval and digitization for this study. Women who developed breast cancer within 5 years of the prerandomization mammogram were excluded ( $n = 6$ , four in the placebo group, two in the treatment group). Also, women whose prerandomization mammogram was irretrievable were

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excluded ( $n = 10$ ). Mammograms for 99 women were included in the study.

**Gail Model Risk Estimate Determination.** During screening for BCPT, women provided demographic, health, and reproductive information on variables included in the Gail model: current age, age at menarche, age at first birth, number of first-degree relatives with breast cancer, number of breast biopsies, and history of atypical hyperplasia. Both 5-year and lifetime (until age 80 years) estimated risks for breast cancer were calculated for each individual by using the Gail model analysis program (22). As above, women with an estimated 5-year risk of breast cancer  $<1.67\%$  were excluded from BCPT (11).

**Mammogram Retrieval and Digitization.** A traditional screening mammogram set included four views. Mammographic films of both breasts, all views, were requested. Once the mammogram films were received, all participant identifiers were concealed and any wax markings were erased. Each set of cleaned films was assigned a film identification number. The films were then sent to the Fred Hutchinson Cancer Research Center Image Analysis Center, where they were digitized on an Epson Expression 836XL scanner at 200-dpi resolution, and saved in both TIF and BMP format. All original films were returned to the provider within 2 weeks. Digitized files were electronically sent to a designated study radiologist (C. Lehman) for density assessment. Although all views were digitized, only the right craniocaudal view was sent to the radiologist for density assessment. If that view was not available, then either the left craniocaudal, right mediolateral, or left mediolateral view was sent, in that order of priority. File names for the electronic digitized files included only the film identification and view, such that the radiologist was not only blinded to all participant identifiers but also to the treatment assignment and the date that the films were originally obtained.

**Mammographic Density Assessment.** For each film, two subjective methods of quantifying mammographic density were used: the American College of Radiology standardized four-point classification scheme, Breast Imaging Reporting and Data System (BIRADS; ref. 23), and an estimated percentage density on a continuous scale. Both of these measures were determined by a breast-imaging specialist with expertise in mammographic density assessment (C. Lehman). To calculate intraobserver reliability, 10% of all films were reblinded and sent for reassessment by the same breast-imaging specialist. The intra-observer within-subject correlation coefficient for subjective estimates of percent density was 0.91, and the concordance for the BIRADS readings was 0.90.

The five objective breast density assessment methods used included both computer-assisted planimetric (ImageQuant 5.0 software, Molecular Dynamics, Inc., Sunnyvale, CA) and thresholding methods (Cumulus 108 software, University of Toronto).

For the ImageQuant measurements, the gray scale was adjusted to clearly visualize the breast edge. The radiologist subsequently outlined the entire breast (region 1). The gray scale was then readjusted to enhance contrast between fatty and glandular tissue, and the radiologist traced around the total area of glandular tissue (region 2), as well as the dense glandular tissue (region 3). These regions are depicted in Fig. 1A. The ImageQuant software calculates an area estimate using the number of pixels for each region. To account for volume averaging from projecting the image of a three-dimensional breast onto a two-dimensional film, a volume estimate was also calculated. The software assigns each pixel a numerical value corresponding to the absorbance of the image at that point, and the summation of those values within a defined region is called the integrated pixel intensity (IPI) for that region. The software also computes a background value

from an area of the film onto which no breast tissue is projected. This background value is subtracted from the IPI to result in the final volume estimate for the region.

The objective density measures are then computed as follows based on proportional area and volume estimates of regions 2 and 3 compared with the entire breast:

*Area measures:*

TOA	total glandular region objective percent density by area number of pixels in region 2, divided by the number of pixels in region 1 $\times 100\%$
DOA	dense glandular region objective percent density by area number of pixels in region 3, divided by the number of pixels in region 1 $\times 100\%$

*Volume measures:*

TOV	total glandular region objective percent density by volume IPI within region 2, divided by the IPI within region 1 $\times 100\%$
DOV	dense glandular region objective percent density by volume IPI within region 3, divided by the IPI within region 1 $\times 100\%$

Cumulus 108 is an interactive computer program, developed at the University of Toronto, that uses a gray-scale thresholding technique to determine mammogram density (24). Pixels above and below thresholds set by the user are highlighted and counted to determine total and dense areas of the breast, respectively. Before proceeding, the technician outlines the back edge of the breast using the mouse to draw a line to exclude the pectoral muscle from analysis. Density is determined by adjusting two sliding scales that encompass a range of pixel brightness of the digitized image, as follows, and as depicted in Fig. 1B. First, the sliding scale is adjusted to select the pixel value that contrasts the edge of the breast tissue from the dark background of the film. The Cumulus software calculates the total area of the breast as the sum of all pixels below that threshold. Next, the sliding scale is adjusted to select the pixel value that contrasts the dense glandular areas within the breast from the nondense breast tissue. The Cumulus software calculates the dense area of the breast as the sum of all pixels above this second threshold. Percentage density (PD) is then calculated as the dense area of the breast divided by the total breast area and multiplied by 100%.

All computer-assisted objective density measures were highly reproducible. The within-subject correlation coefficients for the objective measures were as follows: 0.91 for TOA, 0.92 for DOA, 0.93 for TOV, 0.91 for DOV, and 0.93 for PD.

**Data Analysis.** To examine the association between mammographic breast density and Gail model risk, two clinically relevant risk groups were defined. Those having a calculated lifetime risk  $<15\%$  were classified as moderate-risk, and those with a lifetime risk of  $\geq 15\%$  were classified as high-risk. This 15% cutoff point was chosen based on the average population lifetime risk of breast cancer of 12.5%, such that high risk was approximately equivalent to a relative risk of  $\geq 1.2$ . Differences in BIRADS density score distribution across risk categories were examined using a  $\chi^2$  test for trend. Differences in mean values for the continuous density measures were examined between risk groups using two-sample  $t$  tests. The magnitude and direction of effect of small increments of Gail model risk on continuous mammographic density measures were examined by linear regression.

To consider breast density as a noninvasive marker of breast cancer risk, we constructed a family of regression models with

the density measure as the primary independent variable and calculated lifetime breast cancer risk according to the Gail model as the outcome variable. Partial correlation coefficients were used to determine the percentage of effect explained by those components.

## Results

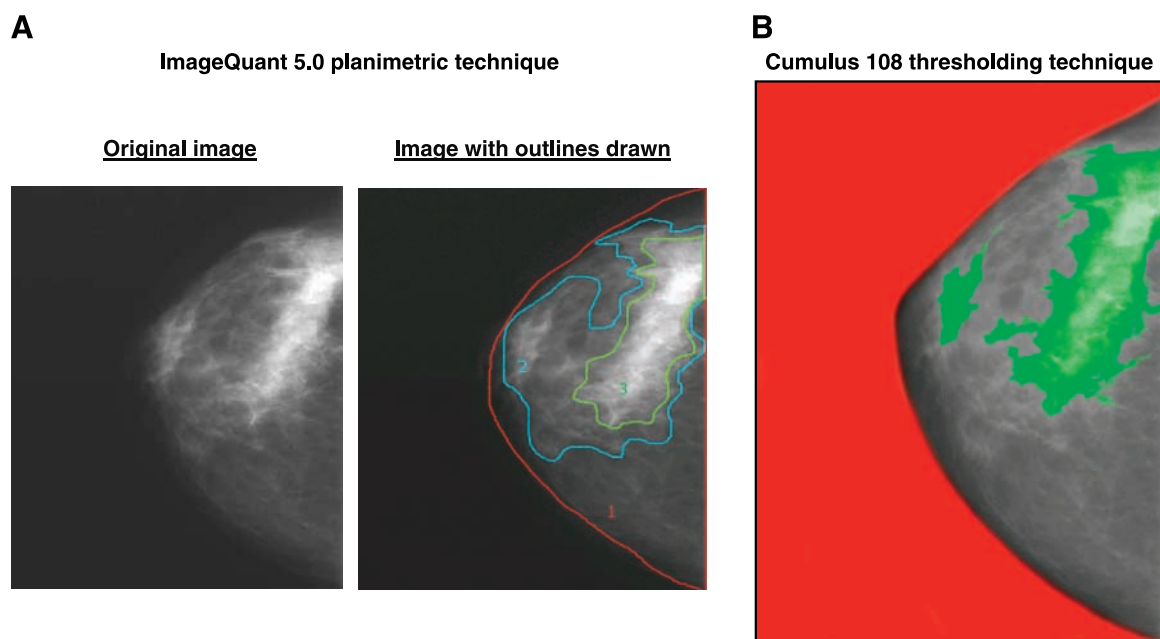
**Breast Cancer Risk Estimates and Risk Factors Included in the Gail Model.** Table 1 summarizes Gail model risk estimates and demographics of the study participants. The average age for the 99 subjects studied was 51.5 years (range 36-74 years). Of the 99 subjects, 45 were postmenopausal, 28 were premenopausal, 18 were perimenopausal, and 8 had unclear menopausal status at the time of trial entry. Breast cancer risk was greater than the eligibility criterion of the BCPT of  $\geq 1.67\%$  risk of developing breast cancer over the next 5 years as calculated by the Gail model: the average 5-year risk of our study population was 4.1% (range 1.8-13.7%). Because calculation of the Gail model lifetime risk calculation is conditional upon current age, it is possible for a woman to have less than population lifetime risk (12.5%), while still having an elevated 5-year risk. Consequently, for our study population, the average calculated lifetime breast cancer risk according to the Gail model was 23.5% (range 4.5-56.7%).

Results from component risk factors of the Gail model are also included in Table 1. Reproductive factors for our study population were similar to the average population, with an average age at menarche of 12.3 years and an average age at first birth of 24.1 years. A quarter of the participants were nulliparous, whereas the parous women had an average of 2.6 live births. A majority, approximately three-fourths, of participants had a family history of breast cancer, with an average of 1.4 affected first-degree relatives per participant. In addition, a large number of participants, approximately two-thirds, had at least one prior breast biopsy before BCPT entry, with an average of 1.7 biopsies per participant.

**Mammographic Density Estimates.** Table 2 summarizes the mammographic density findings. Nearly half of our cohort had mammograms categorized as "scattered fibroglandular densi-

ties" (BIRADS density score of 2) and one-third were labeled as "heterogeneously dense" (BIRADS density score of 3). Average subjectively estimated percent density was  $33.6 \pm 26.0\%$  (mean  $\pm$  SD). Mean digital planimetry-generated mammographic density readings using ImageQuant were as follows: area-based measurements TOA and DOA were  $42.0 \pm 21.8\%$  and  $18.0 \pm 17.4\%$ , respectively, and volume-based measurements TOV and DOV were  $56.2 \pm 24.9\%$  and  $28.6 \pm 24.0\%$ , respectively. Mean digital threshold-generated mammographic density using Cumulus (PD), an area-based measurement, was  $26.2 \pm 18.5\%$ , falling between the TOA and DOA planimetry-generated area-based measurements determined using ImageQuant.

**Association between Mammographic Density and Gail Model Risk.** Figure 2A plots the BIRADS density score distributions of women in the high Gail risk group and the moderate risk group. The high-risk group overall had significantly higher BIRADS density scores than the moderate-risk group ( $P = 0.018$ ,  $\chi^2$  for trend), with an average BIRADS density score of  $2.46 \pm 0.09$  (mean  $\pm$  SE) for the high-risk group compared with  $1.96 \pm 0.17$  for the moderate-risk group ( $P = 0.006$ , two-sided  $t$  test). Figure 2B displays the differences in average continuous density measures between the Gail risk groups. The mean subjectively estimated percentage density in the high-risk group was nearly double that of the moderate-risk group:  $38.2 \pm 3.1\%$  for the high-risk group compared with  $20.1 \pm 3.9\%$  for the moderate-risk group ( $P < 0.001$ , two-sided  $t$  test). The mean objectively determined percent density was also approximately 2-fold higher in the high-risk group than the moderate-risk group for both the Cumulus density assessment method (PD) and the ImageQuant methods that measured proportional dense glandular tissue (DOA and DOV). Specifically, we found the following average measurements: PD  $29.6 \pm 2.2\%$  versus  $16.1 \pm 2.7\%$ , DOA  $20.8 \pm 2.1\%$  versus  $9.7 \pm 2.3\%$ , and DOV  $32.7 \pm 2.9\%$  versus  $16.5 \pm 3.6\%$  for the high-risk group versus the moderate-risk group (all  $P \leq 0.01$  by two-sided  $t$  tests). The difference in mean objectively determined percent density between the risk groups was even more significant for the ImageQuant methods that measured proportional total



**Figure 1.** Computer-assisted mammographic density assessment methods. **A.** ImageQuant 5.0 planimetric technique. **B.** Cumulus 108 thresholding technique.



**Table 1. Gail model risk scores and risk factors included in the Gail model**

	<i>n</i>	Mean	SD (range)
5-year Gail risk	99	4.13%	4.10 (1.8-13.7)
Lifetime Gail risk*	99	23.5%	12.3 (4.5-56.7)
Current age (years)	99	51.5	8.5 (36-74)
Postmenopausal	45 (50%)	—	—
Age at menarche (years)	99	12.3	1.5 (9-16)
Parity	74 (75%)	2.6	1.2 (1-5)
Age at first birth	74 (75%)	24.1	4.8 (16-35)
No. first-degree relatives with breast cancer	76 (77%)	1.4	1.5 (0.5-5) <sup>‡</sup>
Prior breast biopsies	66 (67%)	1.7	1.4 (1-10)
History of atypical hyperplasia	19 (19%)	—	—
History of LCIS	10 (10%)	—	—

\*Population average = 12.5%.

<sup>†</sup>Defined as continuous absence of menstruation for at least 12 months, or if status post-hysterectomy, with follicle-stimulating hormone level in the postmenopausal range.

<sup>‡</sup>Half-siblings were counted as 0.5.

glandular tissue (TOA and TOV). Specifically, we found average TOA  $46.4 \pm 2.5\%$  versus  $29.0 \pm 3.7\%$  and TOV  $61.1 \pm 2.7\%$  versus  $41.8 \pm 4.8\%$  for the high-risk versus moderate-risk groups (both  $P \leq 0.001$  by two-sided *t* tests).

Linear regression analyses to approximate the effect of small increments of Gail model risk on mammographic density estimated a 3% to 6% increase in breast density per 10% increase in lifetime breast cancer risk as calculated using the Gail model (see Table 3). The subjectively estimated percent density and the volume-based objective measurements were the most highly correlated to Gail model risk: subjective density increased 5.2% per 10% increase in lifetime risk ( $P = 0.014$ ), DOV 5.2% ( $P = 0.008$ ), and TOV 6.2% ( $P = 0.002$ ). The area-based objective measurements calculated by ImageQuant were less highly correlated to Gail model risk, but findings were still statistically significant: TOA increased only 4.86% per 10% increase in lifetime risk ( $P = 0.007$ ), and DOA increased only 3.0% ( $P = 0.038$ ). The area-based measurement calculated by Cumulus (PD) was also significantly correlated to breast cancer risk according to the Gail model, but again less so than the volume-based measurements (3.4% increase per 10% increase in lifetime risk,  $P = 0.026$ ). These findings suggest that mammographic density assessment methodology must account for volume averaging to best correlate with Gail model breast cancer risk estimates.

**Association between Mammographic Density and Gail Model Components.** When the individual components of the Gail model were analyzed by partial correlation coefficients, it was noted that current age and history of premalignant breast disease (i.e., atypical hyperplasia or LCIS) accounted for the majority of the relationship between breast density and Gail model risk (see Table 4). Benign breast disease (the number of breast biopsies was a surrogate marker for this) represented another 8% of the density-risk relationship. Family history, assessed by the number of first-degree relatives affected with breast cancer, accounted for 12% of the risk. Nulliparity and delayed childbearing together accounted for approximately one-eighth of the risk, and early menarche represented only 2% of the relationship. However, 7% of the relationship remains unexplained by the breast cancer risk factors included in the Gail model. Other known breast cancer risk factors were tested, including menopausal status, hormone replacement or oral contraceptive use within 1 year of randomization, body mass index, exercise level, and tobacco and alcohol use, but none of these factors significantly altered regression coefficients beyond those in the risk factors already included in the Gail model.

Table 4 also examines the relative relationships between the components of the Gail model and breast density determined by the various assessment methods. All mammographic density methods were highly correlated to current age (all

$P < 0.001$ ), family history (all  $P < 0.05$ ), and premalignant breast disease (all  $P < 0.001$ ), the three factors that explained the majority of the relationship between breast density and Gail model risk. There were no observable differences between density assessment methods.

## Discussion

We found that mammographic density was significantly higher in women who were estimated to have a  $\geq 15\%$  lifetime breast cancer risk, according to the Gail model, than those with  $< 15\%$  risk. This was the case with all mammographic density assessment methods studied, which included two subjective and five objective measures. With each method, the magnitude of the difference between high and moderate risk groups was approximately 2-fold. This was equivalent to a 3% to 6% increase in density per 10% increase in Gail model lifetime risk. Of the computer-assisted objective measures, the volume-based measures, TOV and DOV, were the most correlated to breast cancer risk calculated by the Gail model.

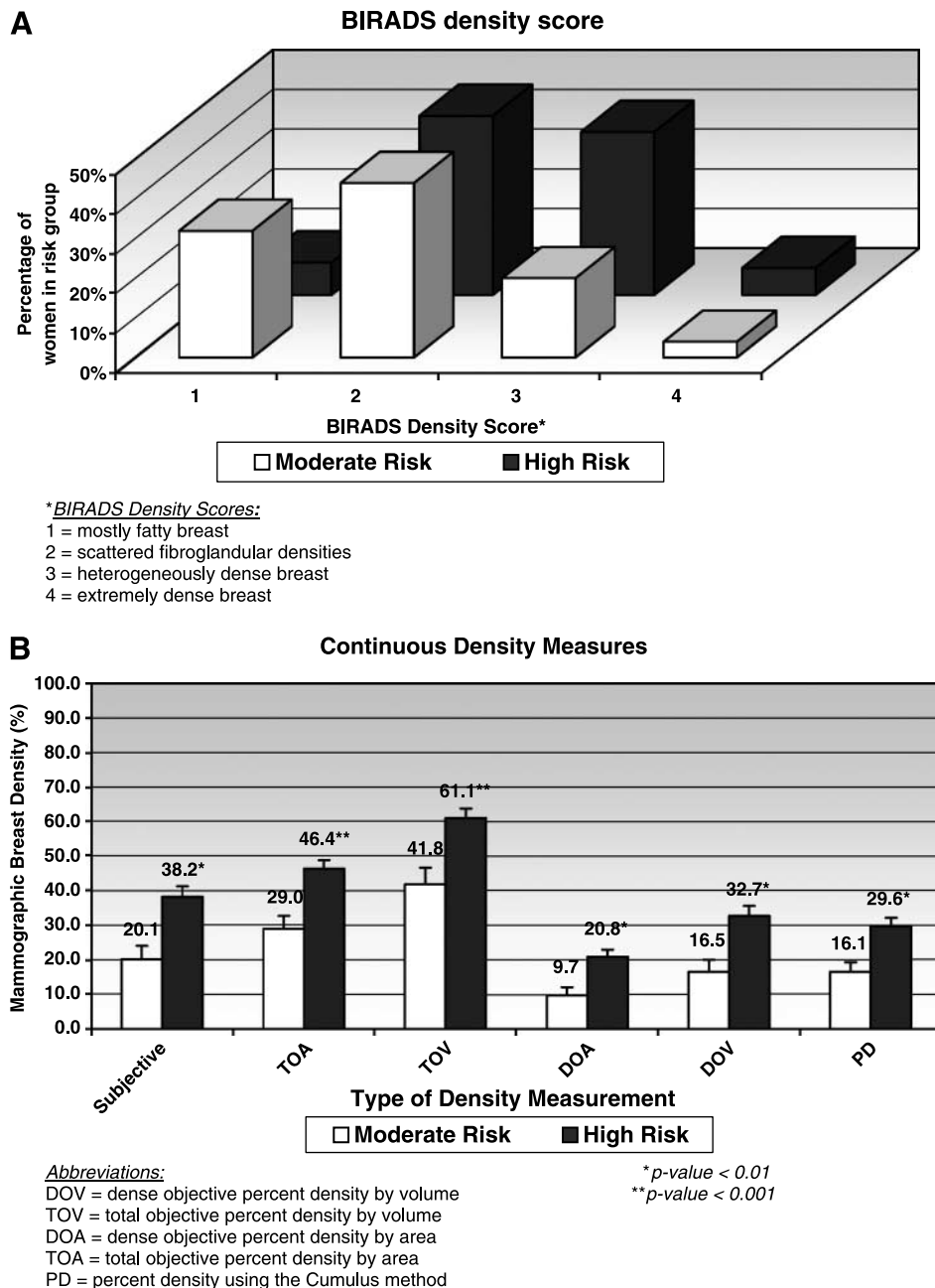
In general, breast cancer risk factors may be divided into four main categories: (a) hereditary factors; (b) lifetime history of hormonal exposure; (c) benign breast changes; and (d) environmental, lifestyle, or other factors that influence (b) and/or (c). The covariates used in the Gail model may be similarly categorized: (a) hereditary factors—number of first-degree relatives with breast cancer; (b) lifetime history of hormonal exposure—early menarche, nulliparity, and late age at first birth; (c) breast tissue changes—history of atypical hyperplasia or LCIS and number of prior breast biopsies; and (d) indirect influential factors—current age, which allows time for exposure

**Table 2. Mammographic density estimates**

BIRAD score	<i>n</i>	Percent (%)	
1 Mostly fatty breast	14	14.1	
2 Scattered fibroglandular densities	44	44.4	
3 Heterogeneously dense	35	35.4	
4 Extremely dense breast	6	6.1	
<i>Total</i>	99	100.0	

Continuous measures	<i>n</i>	Mean (%)	SD (range)
Subjective percent density	99	33.6	26.0 (2-95)
TOA	99	42.0	21.8 (1.1-88.6)
TOV	99	56.2	24.9 (2.2-95.5)
DOA	99	18.0	17.4 (0.13-73.4)
DOV	99	28.6	24.0 (0.13-91.2)
PD	99	26.2	18.5 (0.6-72.5)



**Figure 2.** Breast density and Gail model risk. **A.** BIRADS density score. **B.** Continuous density measures.

to hormones and environment, and allows time to reach the average age of penetrance for breast cancer susceptibility genes.

Other studies have defined the relationship between mammographic density and hereditary factors, but not in the context of a summary breast cancer risk model, where categories of risk can be compared (25-28). Our examination of the covariates used in the Gail model by partial correlation coefficients revealed that factors related to breast tissue changes were the most correlated to breast density. Premalignant histologic findings, including atypical hyperplasia and LCIS, explained one-third of the relationship between breast cancer risk estimates and breast density. The number of prior breast biopsies, a marker for other benign breast tissue changes, explained an additional 8% of the relationship. Age, a marker for duration of multiple exposures, was the second most influential risk factor, accounting for one-fourth of the relationship between breast cancer risk estimates and breast density. Factors influencing lifetime hormonal exposure was the third most significant risk category, representing 14% of

the risk-density relationship. Hereditary risk, measured by the number of first-degree relatives with breast cancer, represented 12% of the risk-density relationship and was the least significant risk category.

Several other studies have also found significant correlations between mammographic density and premalignant histology, namely hyperplasia, atypia, and LCIS (29-31). Other studies have suggested a relationship between breast density and stromal proteins, which likely serve as breast epithelial mitogens (32-34). Future studies that include mammographic density evaluations on cohorts with parallel and prospectively obtained mammograms and breast tissue for histologic correlation would add to our understanding of the *in vivo* biology of carcinogenesis, and would establish the usefulness of mammographic density as a predictive marker for the development of breast cancer and premalignant intermediates. Correlations between mammographic density and prospectively observed early neoplastic changes in the breast would be more meaningful than correlations with risk estimates calculated by

**Table 3. Association between continuous scale breast density and Gail model risk**

Measure	Risk group mean		Difference	95% CI	Regression	
	Moderate	High			$\beta^*$	P
Subjective percent density	20.12	38.20	+18.08	+8.11 to +28.05	0.52	0.014
TOA	29.00	46.44	+17.44	+8.53 to +26.68	0.48	0.007
TOV	41.82	61.07	+19.25	+8.05 to +30.44	0.62	0.002
DOA	9.73	20.80	+11.07	+4.85 to +17.28	0.30	0.038
DOV	16.45	32.72	+16.27	+7.12 to +25.41	0.52	0.008
PD	16.07	29.57	+13.50	+6.48 to +20.52	0.34	0.026

\* $\beta$  coefficients represent percentage change in density for every percentage increase in lifetime breast cancer risk as predicted by the Gail model.

using a breast cancer risk assessment model, such as the Gail model, which has been used to determine eligibility for NSABP breast cancer chemoprevention trials (both BCPT and STAR). Because mammographic density is a noninvasive biomarker that is not subject to the sampling errors of breast tissue sampling, whether by nipple aspirate, ductal lavage, fine needle aspirate, or core biopsy, this information could support the use of mammographic density as a surrogate endpoint in future breast cancer prevention trial.

Our study was based on a geographic subgroup of the BCPT, which may limit its predictive value. Because BCPT eligibility was based on a 5-year breast cancer risk of  $\geq 1.67\%$  as calculated by the Gail model, and the Gail model includes multiple risk variables within different categories of risk, it is unclear whether all the components of the Gail model within our study sample are representative of those found in the general population of women at increased risk for breast cancer. More studies of this nature are needed to validate our findings.

Also, the fact that the Gail model was the only breast cancer risk assessment tool used in the BCPT limits our ability to correlate other breast cancer risk factors with breast density. It is unclear how mammographic density relates to other summary measures of breast cancer risk, which emphasize different risk factor categories. For instance, the Claus model places its entire emphasis on hereditary risk factors, including both first- and second-degree relatives affected by breast cancer, and taking into account their ages of diagnosis (35). The Gail model only includes the number of first-degree relatives and does not include age of onset. However, it does include nonhereditary breast cancer risk factors, such as early breast tissue changes and hormonal factors, which we found to explain much of the association between the model's breast

cancer risk estimates and breast density. BRCAPRO is another breast cancer risk assessment tool commonly used in clinical practice. This model uses Mendelian genetics and Bayesian statistics and includes consideration of a family history of bilateral breast cancer and ovarian cancer, unlike the Gail or Claus models (36). However, although its treatment of family history information is more thorough than the other models, it does not consider the nonhereditary risk factors accounted for by the Gail model (37). Tyrer et al. (38, 39) recently developed a breast cancer risk model that may be a more comprehensive summary measure of breast cancer risk, and this is being developed further to include mammographic density.<sup>4</sup> Our findings suggest that it will be important to consider the method of assessing mammographic density. Specifically, volume-based measures seem to be more highly correlated to breast cancer risk, at least as estimated by the Gail model breast cancer assessment model.

A limitation of all currently existing models is that none include a comprehensive set of breast cancer risk factors. Notably missing are such established risk factors as hormone replacement therapy, elevated circulating estrogens and androgens, increased adiposity (for postmenopausal women), alcohol use, and a sedentary lifestyle. Mammographic density has been noted to correlate with hormone use, hormone levels, body mass index, and diet, all of which are modifiable breast cancer risk factors (40-43).

Because large prospectively followed cohorts have reported a linear association between increasing mammographic density and breast cancer risk (4, 5), and all of the existing breast

<sup>4</sup> J. Cuzick, personal communication.

**Table 4. Partial correlation coefficients of components of the lifetime Gail breast cancer risk score with mammographic density**

	SD		DOV		TOV		DOA		TOA		PD		Average r	Proportion of variance explained (%)
	r	P	r	P	r	P	r	P	r	P	r	P		
(a) Hereditary factors														
No. first-degree relatives affected by breast cancer	0.2333*	0.025	0.2255*	0.031	0.2364*	0.023	0.2305*	0.027	0.2368*	0.023	0.2328*	0.026	0.2328	12
(b) Hormonal exposure														
Early menarche (<age 12 years)	0.0381	0.718	0.0403	0.703	0.0309	0.770	0.0455	0.666	0.0354	0.738	0.0479	0.650	0.0397	2
Nulliparity	-0.1414	0.179	-0.1474	0.161	-0.1376	0.191	-0.1406	0.181	-0.1297	0.218	-0.1405	0.182	-0.1395	7
Late age at first birth (>age 30 years)	-0.1018	0.334	-0.1156	0.273	-0.1069	0.310	-0.1055	0.317	-0.0979	0.353	-0.1075	0.308	-0.1059	5
(c) Breast tissue changes														
No. prior breast biopsies	0.1561	0.137	0.1726	0.100	0.1534	0.144	0.1792	0.087	0.1639	0.118	0.1594	0.129	0.1641	8
History of AH or LCIS	0.6417*	0.000	0.6383*	0.000	0.6427*	0.000	0.6399*	0.000	0.6416*	0.000	0.6454*	0.000	0.6416	33
Remaining correlation between density variable and Gail risk	0.1193	0.257	0.1505	0.152	0.1542	0.142	0.1097	0.298	0.1092	0.300	0.1346	0.201	0.1296	7
(d) Current age	0.5148*	0.000	0.5092*	0.000	0.4792*	0.000	0.5228*	0.000	0.4942*	0.000	0.5056*	0.000	0.5043	26

Abbreviations: r, partial correlation coefficient; P, probability of type I error; SD, subjective density; AH, atypical hyperplasia.

\* $P < 0.05$ .

cancer risk assessment models are primarily based on non-modifiable risk factors besides childbearing, development of a breast cancer risk assessment tool that includes mammographic density may provide a more precise measurement of individual breast cancer risk. A recent report using breast density assessed by BIRADS score found that the addition of breast density to the Gail model increased its concordance statistic for predictive accuracy of breast cancer (44). More precise measures of breast density, such as those described herein, could further improve the currently available prediction models of breast cancer risk and should be evaluated. Our findings suggest that continuous volume-based measures may be the most promising. These measurements were the most highly correlated to the breast cancer risk estimates calculated by the validated Gail model.

Computer-assisted thresholding methods do not require manual tracing of outlines, as do planimetric methods, such as ImageQuant, requiring less analysis time per mammogram set. However, the Cumulus method currently available only includes an area-based assessment. The University of Toronto group, who developed the Cumulus thresholding mammographic density measurement tool, is currently working on a volumetric density assessment method using the thresholding technique (45), which may prove to be more useful for future studies that involve mammographic density.

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