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Epidemiology

Mammographic breast density and the Gail model for breast cancer risk prediction in a screening population

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Summary

Background. Estimating an individual woman's absolute risk for breast cancer is essential for decision making about screening and preventive recommendations. Although the current standard, the Gail model, is well calibrated in populations, it performs poorly for individuals. Mammographic breast density (BD) may improve the predictive accuracy of the Gail model.

Methods. Prospective observational cohort of 81,777 women in the San Francisco Mammography Registry presenting for mammography during 1993 through 2002 who had no prior diagnosis of breast cancer. Breast density was rated by clinical radiologists using the Breast Imaging Reporting and Data System classification (almost entirely fat; scattered fibroglandular densities; heterogeneously dense; extremely dense). Breast cancer cases were identified through linkage to Northern California Surveillance Epidemiology End Results (SEER) program. We compared the predictive accuracy of models with Gail risk, breast density, and the combination. All models were adjusted for age and ethnicity.

Results. During 5.1 years of follow-up, 955 women were diagnosed with invasive breast cancer. The Gail model had modest predictive accuracy (concordance index (c-index) 0.67; 95% CI 0.65–0.68). Adding breast density to the model increased the predictive accuracy to 0.68 (95% CI .66–.70, $p < 0.01$ compared with the Gail model alone). The model containing only breast density adjusted for age and ethnicity had predictive accuracy equivalent to the Gail model (c-index 0.67, 95% CI 0.65–0.68).

Conclusion. The addition of breast density measured by BI-RADS categories minimally improved the predictive accuracy of the Gail model. A model based on breast density alone adjusted for age and ethnicity was as accurate as the Gail model.

Background

Medicine is rapidly moving to basing recommendations for preventive therapy on an individual's absolute risk of disease. Current guidelines for cholesterol lowering therapy [1] and aspirin use to prevent heart attacks [2] recommend thresholds for treatment based on risk calculated using the Framingham equation [3]. Similarly, the United States Preventive Services Task Force (USPSTF) recommendations for primary prevention of breast cancer are based upon the 5-year risk of developing breast cancer calculated using the Gail model [4].

The Gail model is a multivariable statistical model that uses age, age at menarche, age at first live birth, family history of breast cancer, and number of breast biopsies to estimate breast cancer risk among individuals without a prior history of breast cancer [5]. It was modified to use during recruitment for the Breast Cancer Prevention Trial using Surveillance Epidemiology End Results (SEER) data to update the underlying incidence rates and allow for different rates based on race [6]. The Gail model has been shown to accurately estimate the proportion of women who will develop breast cancer when used in large groups [6–8]. However, it does not discriminate well at the individual level between a woman who will develop breast cancer and a woman who will not develop breast cancer [8]. Nonetheless, the United States Preventive Services Task Force recommends breast cancer risk estimation for all women considering chemoprophylaxis for breast cancer using the Gail model to estimate risk [4]. Given the narrow therapeutic index of tamoxifen for most women considering chemoprophylaxis [9], discovering new strategies to improve the identification of women who would benefit most from chemoprophylaxis is clinically important. Adding information from biological

measurements, such as mammographic breast density, to the risk model may improve prediction of the short-term risk of breast cancer.

Mammographic breast density is one of the strongest risk factors for breast cancer risk. Studies have consistently demonstrated that women with increased mammographic breast density have higher risk of breast cancer compared with women of similar age with lower breast density [10–12]. The risk of breast cancer remains increased at least 10 years after the determination of breast density on a mammogram [11]. The objective of this study was to test the hypothesis that the combination of breast density with the Gail model has better predictive accuracy than the Gail model alone.

Methods

Design and study cohort

The San Francisco Mammography Registry (SFMR) is a community-based registry formed as part of the National Cancer Institute's Breast Cancer Surveillance Consortium [13]. The SFMR (http://mammography.ucsf.edu/SFMR/) includes 18 radiology facilities in San Francisco and Marin Counties: 14 hospital-based facilities with four managed by a Health Maintenance Organization, 1 radiology group practice, 1 facility operated by a solo physician, 1 clinic-based practice, and 1 mobile mammography program. Only one facility is an academic institution. The present analysis included women who underwent screening mammography examination in San Francisco County between January 1993 and December 2002. Institutional review board approval for data collection, linkage, and data security was obtained at the University of California San Francisco and at each participating facility in the registry.

Current US Food and Drug Administration guidelines state that women 35 years and older with Gail model risk ≥1.67% are eligible for prophylactic tamoxifen. Thus, we included in the cohort women age 35 years and older who had a reading of mammographic density associated with at least one of their mammograms taken prior to January 1, 2002. For women with multiple mammograms in the registry, the first mammogram was used for this analysis. The Gail model was developed and validated in women without a history of breast cancer who had previously normal mammograms. Thus, we excluded all women who had a diagnosis of breast cancer prior to their first mammographic density measurement, women diagnosed with breast cancer within 6 months of their initial mammogram, and women who died within 6 months of their initial mammogram. We tested the sensitivity of our results by varying this time window from 0 to 24 months and repeating our analyses. Women diagnosed with ductal carcinoma *in situ* were excluded from the primary analysis, but included in a subsequent model to assess the robustness of the results.

Measurements

Demographic information and a breast health history were collected from women by self-administered questionnaire at each screening mammography visit. The questionnaire includes age of menarche, history of prior mammography, race/ethnicity, questions about history of breast cancer, menopausal status, parity, history of breast cancer in first-degree relatives and age at diagnosis of the woman's relative.

The radiologists received no special training for this study and were unaware of the Gail risk for women when reading their mammograms. Community radiologists at each site classified breast density on screening mammograms using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS®) categories [14] of almost entirely fat, scattered fibroglandular densities, heterogeneously dense, and extremely dense. We described the reproducibility of BI-RADS® density measurements in a prior publication [15]. Briefly, the reproducibility was good for the same radiologist on repeat reading (kappa = 0.72, 83% agreement) and for two different radiologists (kappa = 0.59, 75% agreement). The reproducibility of breast density readings in the SFMR over time was similar for women with 2 mammograms obtained less than 1 year apart (kappa = 0.63, n = 21,214) or 1–2 years apart (kappa = 0.59 n = 81,293). A decline in reproducibility over time is expected because of the decrease in breast density with aging.

Ascertainment of breast cancer cases

Breast cancer outcomes (invasive cancer and ductal carcinoma *in situ*) were obtained through linkage with the regional population-based Surveillance, Epidemiology, and End Results (SEER) program. The most recent linkage was performed in August 2004, which included at least 95% of breast cancer reporting through December 31, 2002.

Vital status

Vital status was obtained through linkage with the California Vital Statistics (California Department of Health Services). The most recent linkage was performed in June 2004, which provided date of death through December 31, 2002.

Statistical analysis

Data for risk factors were categorized according to the methods used for the Gail model. All missing data were coded according to the approach used by the FORTRAN program used by the NCI Risk Disk (BCPT.FOR, May 12, 2000). Specifically, for the number of first degree relatives with breast cancer, missing values were categorized as 0; for age at menarche missing values were categorized as >14, for age

at first birth missing values were categorized as <20; and for number of breast biopsies missing values were categorized as 0. Women with unknown race/ethnicity were excluded from the analysis. We elected to impute data using the method of the NCI FORTRAN program because of the large number of women with missing data for age at menopause (n = 60,455, 74% of cohort). Analyses restricted to participants with complete data for all variables are included for comparison. No data were available about atypical hyperplasia from – breast biopsies. In the original Gail model, 7.8% of the participants with benign biopsies had atypical hyperplasia [5]. Given that 12% of our participants reported prior biopsy, less than 1% of our cohort would have their risk changed with knowledge of their biopsy results. The BI-RADS 2 category was used as the reference group for breast density because it was the largest group.

We used Cox proportional hazards models to compare time to development of breast cancer. All models were adjusted for age and ethnicity. The proportional hazards assumption was assessed using log–log plots and including interaction terms with time for each predictor variable. All predictors met the proportional hazards assumption. The initial model included the risk factors used in the Gail model including the interaction terms for age and number of biopsies and for age at first live birth and family history [5,6]. We recalculated the coefficients for the Gail model predictor variables using participants in the SFMR cohort with complete data to prevent biased comparisons with the models including breast density. Indicator variables for breast density were added to create a second model. The models were compared using the likelihood ratio test. Using these models, we calculated a risk score for each woman by summing the product of the model coefficients by the woman's value for each variable in the model.

The two models were compared using the concordance index (c-index) [16]. The c-index is a measure of the ability of these models to separate women who developed breast cancer from those women who did not. Values for the c-index can range from 0.5 to 1. A value close to 1 would indicate that women diagnosed with breast cancer consistently had risk scores higher than those who remained disease free. A value of 0.5 would indicate that the model does no better than chance. Standard errors used to calculate 95% confidence intervals around the c-index were estimated using the method of DeLong [17].

Breast cancer incidence was calculated by quintiles of the risk score defined by each model. We also calculated the incidence of breast cancer by breast density categories within quintiles of the Gail model risk score to look for evidence for an interaction. All statistical tests were two-sided with a p-value ≤ 0.05 considered statistically significant. All analyses were performed using STATA version 8.2 (STATA Corp., College Station, TX).

Results

Breast density was recorded for 81,777 women with screening mammograms throughout the study period. During a median of 5.1 women-years of follow-up, 955 women were diagnosed with invasive breast cancer. Women had a mean age at enrollment of 55.9 years and a broad ethnic distribution including Caucasians (40%), Asians (31%), African Americans (8%), and Latinas (9%) (Table 1). As expected, breast cancer cases were more common among older, Caucasian women with more first degree relatives with breast cancer, later age at first live birth, greater number of breast biopsies and higher breast density.

The coefficients for predictors included in the Gail model calculated using data from this cohort were similar to those reported in the original Gail model, except for age at menarche (Table 2). Adding breast density to the Gail model significantly improved the model fit ($p < 0.0001$) without any significant effect on the coefficients for variables used in the Gail model (Table 2). Women with high breast density had a higher risk of invasive breast cancer (RH BI-RADS 4 to BI-RADS 1 = 3.2, 95% CI 2.3–4.5). The c-index for the Gail model was 0.67 (95% CI 0.65–0.68) indicating modest predictive accuracy. Adding breast density to the model increased the c-index slightly (0.68, 95% CI 0.66–0.70, $p < 0.01$ compared to the Gail model alone). The receiver operating characteristic curves for prediction of breast cancer are shown in Figure 1. The area under the curve (equivalent to the c-index) for the combined model is modestly greater than for the Gail model alone. The results were similar when the outcome included ductal carcinoma *in situ* and when the window of exclusion for early diagnosis of breast cancer was varied from 0 to 24 months. Limiting the analysis to women with complete information for all Gail model variables increased the discriminatory accuracy of both models modestly (0.70 for Gail model, 0.71 for Gail model plus breast density, $p = 0.03$), but did not affect the magnitude of the difference.

Figure 2 shows the incidence of breast cancer stratified by breast density within quintiles of the Gail model risk score. Both measures were strongly associated with breast cancer incidence ($p < 0.0001$). There was no interaction between the Gail model risk and breast density ($p = 0.31$), and the relative risks for the breast density were fairly consistent across quintiles of Gail risk.

Table 3 presents the average incidence of breast cancer for women stratified by quintiles of predicted risk. About 40% of the cases of breast cancer occurred in women in the highest quintile of risk (20% expected by chance alone) when the Gail model was used to predict risk. The relative hazard for the highest risk quintile compared to the lowest quintile was 4.5 (95% CI 3.6–5.8). In contrast, 42% of the cases were in the highest quintile when breast density was added to the model and

Table 1. Baseline characteristics of the cohort

Risk factor	Overall *n* (%)	No breast cancer *n* (%)	Breast cancer *n* (%)
Age groups, years			
35–44	20,652 (25)	20,517 (25)	135 (14)
45–54	25,123 (31)	24,840 (31)	283 (30)
55–64	15,592 (19)	15,364 (19)	228 (24)
65+	20,410 (25)	20,101 (25)	309 (33)
Ethnicity			
Caucasian	32,434 (40)	31,860 (39)	574 (60)
African American	6317 (8)	6255 (8)	62 (6)
Latina	7515 (9)	7468 (9)	47 (5)
Asian	25,110 (31)	24,939 (31)	171 (18)
Other including mixed	10,401 (13)	10,300 (13)	101 (11)
First degree relatives with breast cancer			
0	60,281(74)	59,613 (74)	668 (70)
1	9006 (11)	8807 (11)	199 (21)
≥2	1085 (1)	1052 (1)	33 (3)
Missing	11,406 (14)	11,351 (14)	55 (6)
Age at menarche			
≥14	7014 (9)	6905 (9)	109 (11)
12, 13	11,147 (14)	10,951 (14)	196 (21)
<12	3172 (4)	3116 (4)	56 (6)
Missing	60,445 (74)	59,851 (74)	594 (62)
Age at first birth			
<20	10,084 (12)	9993 (12)	91 (10)
20–24	27,056 (33)	26,751 (33)	305 (32)
25–29, nulliparous	23,221 (28)	22,867 (28)	354 (37)
≥30	11,053 (14)	10,897 (13)	156 (16)
Missing	10,364 (13)	10,315 (13)	49 (5)
Number of breast biopsies			
0	54,285 (66)	53,708 (66)	577 (60)
1	6238 (8)	6124 (8)	114 (12)
≥2	2293 (3)	2244 (3)	49 (5)
Missing	18,962 (23)	18,747 (23)	215 (23)
Breast density[a]			
1	7890 (10)	9107 (10)	60 (6)
2	36,543 (45)	41,388 (45)	398 (42)
3	31,282 (38)	33,929 (37)	410 (43)
4	6062 (7)	6595 (7)	87 (9)

[a] Using the Breast Imaging Reporting and Data System (BI-RADS) density categories: 1 = Almost entirely fat; 2 = Scattered fibroglandular densities; 3 = Heterogeneously dense; 4 = Extremely dense.

the relative hazard increased to 5.9 (95% CI 4.6–7.8). Breast density alone, adjusted for age and ethnicity, had a relative hazard for the highest risk quintile compared to the lowest quintile of 5.6 (95% CI 4.4–7.3) and similar predictive accuracy to the Gail model (c-index 0.67, 95% CI 0.65–0.68).

Discussion

Breast density is reported with mammography interpretation primarily to indicate the possibility of reduced sensitivity to detect cancer in women with dense breasts [18,19]. In this study, adding mammographic breast density to the complex model used to calculate the Gail risk for women minimally improved the predictive accuracy of the model (from *c*-index of 0.67 to 0.68). One of the remarkable findings from this analysis was the power of breast density alone, adjusted for age and ethnicity, to predict incident breast cancer. We found that the predictive accuracy of the breast density model was similar to the Gail model. If confirmed in other prospective studies, BI-RADS density (adjusted for age and ethnicity) could provide an easily obtained estimate of risk of breast cancer for patients and their clinicians, to guide discussions and decisions about breast cancer risk, screening, and prevention.

The established breast cancer risk factors used in the Gail model have been shown to be associated with

Table 2. Comparison of original Gail model[a] risk factor relative risks for breast cancer to those calculated using the San Francisco Mammography Registry

Risk factor		Gail	Model 1		Model 2	
		RR	RR	(95%CI)	RR	(95% CI)
Age at menarche						
≥14		1.00	1.00	(Referent)	1.00	(Referent)
12–13		1.10	0.98	(0.83–1.15)	1.01	(0.86–1.19)
<12		1.21	0.96	(0.69–1.33)	1.02	(0.73–1.41)
Age < 50 years						
No previous biopsy		1.00	1.00	(Referent)	1.00	(Referent)
Previous biopsy		1.70	1.22	(0.82–1.82)	1.19	(0.80–1.78)
>1 previous biopsy		2.88	1.49	(0.67–3.31)	1.42	(0.64–3.16)
Age ≥50 years						
No previous biopsy		1.00	1.00	(Referent)	1.00	(Referent)
Previous biopsy		1.27	1.24	(0.99–1.56)	1.19	(0.94–1.50)
>1 previous biopsy		1.62	1.54	(0.97–2.45)	1.41	(0.88–2.24)
Age at first birth	# 1° rel.					
<20	0	1.00	1.00	(Referent)	1.00	(Referent)
	1	2.61	2.89	(1.82–4.57)	2.80	(1.77–4.43)
	2+	6.80	8.33	(3.32–20.9)	7.83	(3.13–19.6)
20–24	0	1.24	1.27	(1.09–1.48)	1.22	(1.05–1.42)
	1	2.68	2.98	(2.11–4.21)	2.80	(1.98–3.95)
	2+	5.78	6.99	(3.86–12.7)	6.40	(3.54–11.6)
25–29	0	1.55	1.62	(1.20–2.18)	1.50	(1.10–2.03)
	1	2.76	3.08	(2.18–4.36)	2.80	(1.97–3.98)
	2+	4.91	5.87	(3.60–9.57)	5.24	(3.21–8.56)
30+	0	1.93	2.05	(1.31–3.22)	1.83	(1.16–2.89)
	1	2.83	3.18	(2.00–5.07)	2.80	(1.75–4.49)
	2+	4.17	4.93	(2.43–9.99)	4.28	(2.10–8.74)
Breast density[b]						
1					0.59	(0.36–0.98)
2					1.00	(Referent)
3					1.41	(1.11–1.78)
4					1.94	(1.31–2.89)

[a] All models are additionally adjusted for age and ethnicity. [b] Using the Breast Imaging Reporting And Data System (BI-RADS) density categories. 1 = Almost entirely fat; 2 = Scattered fibroglandular densities; 3 = Heterogeneously dense; 4 = Extremely dense. Gail = relative risks as reported in original Gail model [5]. Model 1 = Gail model fitted to this dataset: *c*-index 0.67 (95% CI 0.65–0.68). Model 2 = Gail model plus breast density: *c*-index 0.68 (95% CI 0.66–0.70).

mammographic breast density. Older age at birth of first child predicts higher breast density [20–22], whereas pregnancy at an early age appears to permanently lower breast density [21,23,24]. Early age at menarche [23], number of breast biopsies [25,26], and number of first degree relatives with breast cancer [27] also are associated with extent of breast density. Breast density is associated with established breast cancer risk factors not incorporated in the Gail model such as alcohol intake [21], parity [21,23,28], and hormone therapy use [21,23,28]. Breast density also has been shown to be a heritable trait [29] with approximately 60% of the variance explained by genetic factors [29,30]. Thus, mammographic breast density appears to reflect the cumulative effect of many established hormonal and reproductive risk factors for breast cancer, but is also an independent risk factor for breast cancer.

Mammographic breast density is one of the strongest independent predictors of breast cancer risk with a high population attributable risk [10,11]. One limitation of our study is the use of a qualitative rating of breast density assessed by numerous radiologists without specific training or standardization. Based on prior reports, we expect high variability between radiologists [15]. Studies using a quantitative measure of breast density [10,11] usually report a stronger association with breast cancer than studies using qualitative measures [31]. However, even with a qualitative measure of breast density, the association with breast cancer risk is strong. Misclassification of the readings may attenuate the association with breast cancer, implying that a more reproducible and quantitative measure of breast density could further improve the predictive accuracy of risk models incorporating breast density.

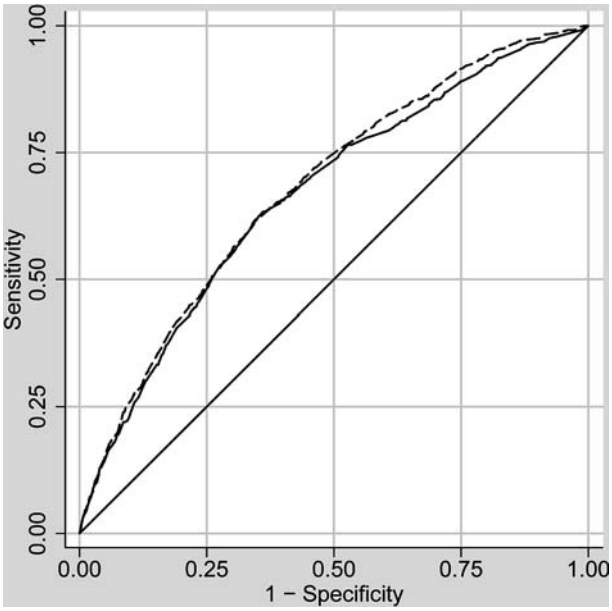

Figure 1. Receiver operating curves for predicting breast cancer: Gail model versus Gail model plus breast density. The received operating characteristic (ROC) curves for the Gail model alone (continuous line) and for the Gail model plus mammographic breast density results (dashed line). Areas under the curves are 0.67 (95% CI 0.65–0.68) for the Gail model alone and 0.68 (0.66–0.70) for the Gail model plus breast density. The straight line represents the ROC curve expected by chance alone.

The composition of the cohort strengthens our conclusions in several ways. This study includes a large sample size with pre- and post-menopausal women of diverse racial and ethnic groups. Furthermore, this cohort is derived from a general screening population, rather than a group of women volunteering to participate in a study. Thus the results are likely generalizable to the US population as a whole since at least 85% of women have had at least one mammogram [32]. We limited the cohort to women ≥35 years of age, the age cutoff used for the US Food and Drug Administration indication for the use of tamoxifen for primary prevention of breast cancer. Over 40% of women in the cohort are under age 50. A risk benefit analysis of tamoxifen use, based on data from the Breast Cancer Prevention Trial [9], reported that tamoxifen was overall most beneficial in these younger women because they were at much lower risk for the adverse effects of tamoxifen (stroke, venous thromboembolic disease, uterine cancer) and they had a longer life expectancy.

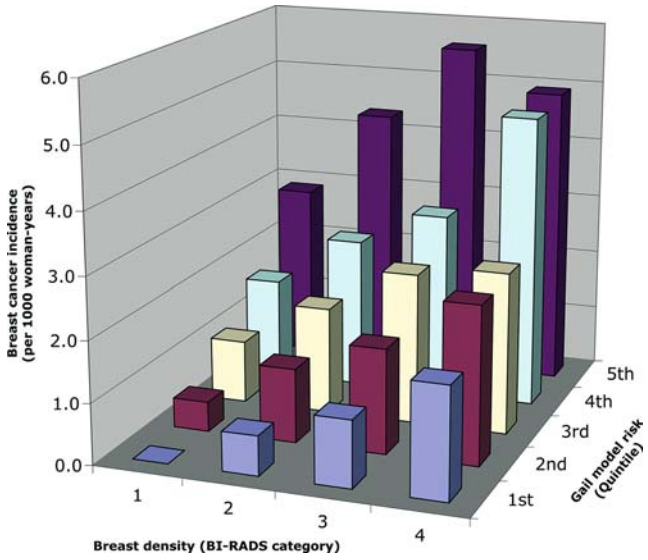

Figure 2. Breast cancer incidence by mammographic breast density within quintiles of Gail model risk.

The Gail model was originally developed with logistic regression using a nested case–control design limited to 5 years of follow-up [5]. Our cohort had variable length of follow-up and used proportional hazards modeling, but the results produced similar estimates for risk factor coefficients and the *c*-index. By recalculating the coefficients for the Gail model risk factors, we optimized the predictive ability of the Gail model in this data set. The fact that the *c*-index for the Gail model in this data set (0.67) was higher than that calculated for the Nurses Health Study [8] (0.58) suggests that there was no significant bias against the Gail model in our analyses. Because our model was developed and validated using the same data set, our estimates for the *c*-index are likely to be optimistic.

Some of the data used by the Gail model to calculate 5-year risk of invasive breast cancer were limited in this dataset. We relied on self-report of prior biopsies and did not know whether the pathology demonstrated atypical hyperplasia. However, we estimated that less than 1% of the cohort would have had a diagnosis of atypical hyperplasia. There was also a large amount of missing data. Most of the cohort was missing information on age at menarche and 13% were missing data on the number of first degree relatives with breast cancer. The missing data were coded according to the method used by the NCI Gail Risk Calculator, but the resulting misclassification may partly explain the relatively poor predictive accuracy of the Gail model. On the other hand, the *c*-index calculated for the Gail model in this cohort was substantially higher than that calculated for the Gail model in the Nurses Health Study [8], which suggests that this was not a significant limitation. Furthermore, limiting the analysis to participants with complete data did not change the results.

Rockhill et al. [33] recently evaluated the predictive accuracy of the most sophisticated log-incidence model developed by Graham and Colditz [34,35] based on ideas proposed by Pike et al. [36,37] using prospective data from the Nurses' Health Study. The complete model incorporated 18 risk factors including those of the Gail model, alcohol intake, use of hormone therapy, height, and body mass index. Even this complex and sophisticated model was only modestly accurate at identifying which women would be at highest risk of developing breast cancer (*c*-index 0.63). A common feature of all of the models proposed to date is the lack of biological markers of breast cancer risk. Proposed biomarkers such as nipple aspirate fluid cytology, breast

Table 3. Breast cancer incidence by quintile of predicted risk

Quintile	Gail model		Gail model plus breast density		Breast density alone	
	Breast cancer *n* (%)	Incidence per 1000 woman-years	Breast cancer *n* (%)	Incidence per 1000 woman-years	Breast cancer *n* (%)	Incidence per 1000 woman-years
1st	75 (8)	0.99	62 (6)	0.79	68 (7)	0.82
2nd	136 (14)	1.50	119 (12)	1.47	131 (14)	1.76
3rd	117 (12)	1.80	150 (16)	1.96	157 (16)	2.06
4th	241 (25)	2.80	221 (23)	2.75	265 (28)	2.75
5th	386 (40)	4.60	402 (42)	4.78	334 (35)	4.67
RR, 5th to 1st quintile (95% CI)	4.54 (3.55–5.82)		5.94 (4.56–7.75)		5.64 (4.35–7.32)	

density, bone mineral density, and hormone levels with relative risks of 3 to 5 may increase the predictive accuracy of risk models slightly, but modeling has demonstrated that combinations of risk factors with RR of 20 to 50 are needed in order to significantly improve predictive accuracy [38,39]. New biomarkers more strongly associated with breast cancer are needed to increase the predictive accuracy of breast cancer risk models significantly.

Our results support the hypothesis that a simple categorical estimation of mammographic breast density can predict risk of breast cancer about as well as the Gail model. More precise measures of breast density have the potential to improve prediction models of breast cancer incidence. If our results are confirmed, routine assessment and reporting of breast density on mammogram reports may be useful for patients and physicians in raising awareness of the risk of breast cancer and making decisions about approaches to prevention. New biomarkers for breast cancer are needed to significantly improve risk assessment models.

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