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BRIEF COMMUNICATION

The Contributions of Breast Density and Common Genetic Variation to Breast Cancer Risk

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Abstract

We evaluated whether a 76-locus polygenic risk score (PRS) and Breast Imaging Reporting and Data System (BI-RADS) breast density were independent risk factors within three studies (1643 case patients, 2397 control patients) using logistic regression models. We incorporated the PRS odds ratio (OR) into the Breast Cancer Surveillance Consortium (BCSC) risk-prediction model while accounting for its attributable risk and compared five-year absolute risk predictions between models using area under the curve (AUC) statistics. All statistical tests were two-sided. BI-RADS density and PRS were independent risk factors across all three studies ($P_{interaction}$ = .23). Relative to those with scattered fibroglandular densities and average PRS (2nd quartile), women with extreme density and highest quartile PRS had 2.7-fold (95% confidence interval [CI] = 1.74 to 4.12) increased risk, while those with low density and PRS had reduced risk (OR = 0.30, 95% CI = 0.18 to 0.51). PRS added independent information (P < .001) to the BCSC model and improved discriminatory accuracy from AUC = 0.66 to AUC = 0.69. Although the BCSC-PRS model was well calibrated in case-control data, independent cohort data are needed to test calibration in the general population.

Mammographic breast density is associated with decreased diagnostic accuracy of mammography (1,2) and increased breast cancer risk (3,4). Recent legislation, passed in nineteen states, mandates radiologists to communicate the importance of breast density information to patients undergoing mammography. Because 45% to 50% of women have heterogeneously

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or extremely dense breasts (5), this legislation will result in increased patient-provider discussions regarding breast screening frequency, supplemental screening strategies, and risk (6). Additional factors for further risk stratification, especially for women with dense breasts, are needed to inform these discussions (7).

To date, almost 80 confirmed breast cancer susceptibility loci have been identified (8–23) and explain approximately 14% of familial breast cancer risk (8). Coupled with established risk factors like breast density, these loci are likely to increase the utility and accuracy of clinical risk prediction.

We conducted two studies to evaluate the contribution of established breast cancer susceptibility loci to the Breast Imaging Reporting and Data System (BI-RADS) density and breast cancer association. First, we determined whether a polygenic risk score (PRS) composed of 76 single-nucleotide polymorphisms (SNPs) is a statistically significant risk factor independent of BI-RADS density in three epidemiologic studies. Second, we examined whether the addition of this PRS improves performance of the Breast Cancer Surveillance Consortium (BCSC) five-year risk-prediction model in a nested case-control study (24).

Studies included 456 case patients and 1166 age-matched control patients nested within the Mayo Mammography Health Study (MMHS) cohort (25,26) and two clinic-based case-control studies with 675 case patients and 864 frequency age-matched control patients (Mayo Clinic Breast Cancer Study [MCBCS]), and 512 case patients and 367 unmatched control patients (Bavarian Breast Cancer Cases and Control Study [BBCC]), for a total 1643 case patients and 2397 control patients (25,27,29) (Supplementary Table 1 and Methods, available online). All studies obtained informed consent, ethics, and institutional approvals.

BI-RADS breast density was categorized as defined in the BI-RADS lexicon (30) into one of four categories: 1) almost entirely fat, 2) scattered fibroglandular densities, 3) heterogeneously dense, 4) extremely dense, by expert radiologists on mammograms close to (MCBCS and BBCC) or years prior (MMHS) to diagnosis. Genotyping of the 76 SNPs (8–23) was conducted on a custom Illumina iSelect genotyping array (8) (Supplementary Methods, available online).

The PRS was formed using published per-minor-allele odds ratios (ORs) corresponding to the SNP associations with overall breast cancer (Supplementary Table 2, available online) (8–23). The log OR for each SNP was multiplied by the corresponding number of minor alleles, summed to generate a unique PRS for each person (31), and evaluated both as continuous (per standard deviation) and quartile measures. Logistic regression was used to examine the association of BI-RADS density, PRS, and their interaction with breast cancer risk, adjusting for age, 1/BMI (4,26), and study. ORs, area under the curve (AUC) (32,33), and 95% confidence intervals (CIs) were estimated. A likelihood ratio test (LRT) assessed statistical significance of associations between PRS and breast cancer while accounting for BI-RADS, age, and 1/BMI.

We formed the BCSC-PRS risk model by estimating the OR corresponding to a one-unit increase in the PRS with data from the BBCC and MCBCS studies only, and added this estimate directly into the original BCSC model (Supplementary Methods, available online) (24). We then estimated five-year risk of invasive cancer for the BCSC and BCSC-PRS models within the MMHS cohort (334 invasive case patients) using a resampling approach to obtain fifty sets of 334 genotyped control patients whose age distribution matched the full cohort. We compared the performance of the BCSC-PRS vs BCSC model using: 1) a LRT, 2) AUCs and corresponding 95% CIs, 3) change in AUC and 95% CIs based on standard errors estimated from 200 bootstrap samples. We assessed the calibration of BCSC and BCSC-PRS five-year risk by comparing observed and predicted numbers of cancers, adjusting for the case-control design (34), using the Hosmer-Lemeshow test (35) as done in other risk models using case-control data (31,36). All analyses were performed within the 50 resampled data sets, and results were combined across them using approaches developed for multiple imputation (37) (Supplementary Methods, available online). We evaluated the net reclassification of case patients (change in true-positive rate) and control patients (change in false-positive rate) for a five-year risk of 3% or greater (where there is greater absolute benefit of chemoprevention [38]) for the BCSC-PRS compared with the BCSC model. Estimates and corresponding 95% CIs were obtained using bootstrapping. All statistical tests were two-sided.

BI-RADS density, adjusted for age and 1/BMI, was a statistically significant risk factor for breast cancer within and across studies (Table 1; Supplementary Tables 3–5). The PRS was not strongly correlated with age, BMI, or density (all statistical correlations <.05). PRS was associated with breast cancer risk within and across the three studies and was a statistically significant risk factor independent of BI-RADS density ($P_{interaction}$ =.23) (Tables 1 and 2; Supplementary Tables 3–5, available online). PRS improved the fit of models with BI-RADS density, age, and 1/BMI (P_{LRT} < .001), resulting in an AUC of 0.69 (95% CI = 0.67 to 0.71) (Table 1, Supplementary Figure 1, available online).

Importantly, the PRS further stratified risk associated with extremely dense breasts, such that those with the lowest PRS had an odds ratio of 0.91 (95% CI = 0.53 to 1.56), while those in the highest PRS had a 2.7-fold (95% CI = 1.74 to 4.12) increased risk compared with women with scattered fibroglandular densities and average PRS (2nd quartile) (Table 2). Women with fatty breasts and in the lowest PRS quartile had the lowest risk (OR = 0.30, 95% CI = 0.18 to 0.51). Associations were similar across studies ($P_{interaction}$ = .24) and within menopausal subgroups ($P_{interaction}$ = .86) (Supplementary Table 6, available online).

We next incorporated the OR corresponding to a one-unit increase in the PRS estimated from the MCBCS and BBCC studies only (OR = 1.83, 95% CI = 1.59 to 2.11) into the BCSC model and evaluated the impact within the MMHS (Supplementary Table 7, available online). The BCSC and BCSC-PRS models were well calibrated when fit on the case-control sets sampled from MMHS (Supplementary Figure 2, available online). Addition of the PRS to the BCSC model provided a statistically significant improvement to the model fit (P_{LRT} < .001) and improved discrimination between case patients and control patients (AUC = 0.69, 95% CI = 0.64 to 0.73) compared with the BCSC model alone (AUC = 0.66, 95% CI = 0.61 to 0.70) (ΔAUC = 0.028, 95% CI = 0.007 to 0.049) (Supplementary Figure 3, available online). The BCSC-PRS model resulted in 36.8% of case patients exceeding the five-year risk threshold of 3% or greater where chemotherapy should be discussed, compared with 25.7% of cases using the BCSC model, for a net reclassification of 11% (95% CI = 7% to 15%) of cases. In control patients, these numbers were 13.0% and 10.7% for BCSC-PRS and BCSC, respectively, for a net 2% (95% CI = -1% to 5%) reclassification of control patients to a risk of 3% or greater, although not statistically significant (Supplementary Table 8, available online). The increase in number of cases with the BCSC-PRS at or above the 3% threshold may represent improved

Table 1. Contribution of continuous and quartile polygenic risk score measures to the Breast Imaging Reporting and Data System breast density and breast cancer association

	Odds ratios (95% CIs) corresponding to BI-RADS breast density and PRS measures in 4 models*			
Category	BI-RADS alone No PRS	Quartiles PRS alone No BI-RADS	BI-RADS+ Quartiles of PRS †	BI-RADS+ Continuous PRS†‡
BI-RADS density				
Almost entirely fat	0.55 (0.45 to 0.68)	–§	0.57 (0.46 to 0.70)	0.56 (0.45 to 0.70)
Scattered fibroglandular densities	1.00 (Ref.)		1.00 (Ref.)	1.00 (Ref.)
Heterogeneously dense	1.25 (1.07 to 1.46)		1.24 (1.06 to 1.45)	1.24 (1.06 to 1.45)
Extremely dense	1.77 (1.38 to 2.26)		1.75 (1.36 to 2.24)	1.73 (1.35 to 2.23)
PRS quartiles				
<0.50	–§	0.63 (0.52 to 0.78)	0.62 (0.51 to 0.77)	–§
0.50–0.86		1.00 (Ref.)	1.00 (Ref.)	
0.87–1.27		1.52 (1.26 to 1.83)	1.48 (1.23 to 1.79)	
1.28+		1.79 (1.50 to 2.14)	1.74 (1.45 to 2.09)	
PRS continuous‡	–§	–§	–§	1.48 (1.38 to 1.58)
AUC	0.66 (0.64 to 0.68)	0.68 (0.66 to 0.69)	0.69 (0.67 to 0.70)	0.69 (0.67 to 0.71)

* All three studies combined (n = 1643 case patients, 2397 control patients). Models adjusted for age, 1/BMI, study. AUC = area under the curve; BI-RADS = Breast Imaging Reporting and Data System; CI = confidence interval; PRS = polygenic risk score.
† Likelihood Ratio Test $P_{LRT} < .001$ for models with PRS and BI-RADS density compared with model with BI-RADS alone. All statistical tests were two-sided.
‡ Continuous PRS measure evaluated as per 1 standard deviation. Model with PRS continuous measure alone had OR = 1.49 (95% CI = 1.39 to 1.59) and AUC = 0.68 (95% CI = 0.66 to 0.69).
§ Variable not evaluated in this model.

Table 2. Association (odds ratios and 95% confidence intervals) of Breast Imaging Reporting and Data System breast density and polygenic risk score with breast cancer*

	Odds ratios (95% CI) corresponding to categories of BI-RADS density and PRS quartiles				
PRS quartiles	Almost entirely fat	Scattered fibroglandular densities	Heterogeneously dense	Extremely dense	$P_{interaction}$†
<0.50	0.30 (0.18 to 0.51)	0.65 (0.48 to 0.89)	0.80 (0.57 to 1.14)	0.91 (0.53 to 1.56)	
0.50–0.86	0.44 (0.28 to 0.68)	1.00 (Ref.)	1.40 (1.02 to 1.92)	1.56 (0.94 to 2.59)	
0.87–1.27	0.93 (0.62 to 1.40)	1.32 (0.99 to 1.76)	1.81 (1.34 to 2.46)	3.59 (2.26 to 5.70)	
1.28+	1.20 (0.81 to 1.78)	1.84 (1.40 to 2.42)	1.91 (1.42 to 2.57)	2.68 (1.74 to 4.12)	
					.23

* All three studies combined (n = 1643 case patients, 2397 control patients). Models adjusted for age, 1/BMI and study. BI-RADS = Breast Imaging Reporting and Data System; CI = confidence interval; OR = odds ratio; PRS = polygenic risk score.
† $P_{interaction}$ from logistic regression model including all three studies.

discrimination, but might also reflect poor model calibration in the upper tails, to some degree, especially as control patients were also upwardly reclassified.

Our findings that the PRS and BI-RADS density were independent risk factors and that incorporating the PRS into the BCSC risk model improved model fit and net reclassification for case patients suggest that both breast density and common genetic variation are important for risk prediction. Risk models with good discrimination and accuracy for predicting breast cancer are important for targeted screening and prevention (39). Tamoxifen, raloxifene, and aromatase inhibitors have been shown to be effective for primary prevention but are rarely used in practice (40) because of side effects and low interest of moderate-risk women in taking prevention medication for breast cancer (41,42). The highest-risk women may be more motivated to take preventive therapies and accept their potential complications (38). Our results demonstrate that the set of 76 SNPs improves the identification of women at the highest risk. Along with the increase seen in AUC, the net-reclassification of 11% of case patients (95% CI = 7% to 15%) to a risk level where women are more likely to benefit from chemoprevention suggests that SNPs could be useful clinically.

The main limitation of this study was lack of independent cohort data to check the calibration of the new BCSC-PRS model in the general population. Further, our studies consisted of primarily white women, and the translation of these findings to other racial and ethnic groups is unknown. A strength of our work was independent confirmation in three data sets that PRS adds discriminatory accuracy to BI-RADS breast density.

In summary, we found that BI-RADS breast density and a PRS composed of 76 SNPs are both important risk factors for breast cancer that can be incorporated into breast cancer risk models. If these models are used to estimate population risk, refining the high- and low-risk risk groups could result in more appropriate tailoring of screening and prevention interventions.

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Notes

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