Mammographic Breast Density and Breast Cancer: Evidence of a Shared Genetic Basis

Jajini S. Varghese¹, Deborah J. Thompson¹, Kyriaki Michailidou¹, Sara Lindström², Clare Turnbull⁶, Judith Brown¹, Jean Leyland¹, Ruth M.L. Warren², Robert N. Loos³, Nicholas J. Wareham³, Johanna Rommens³, Andrew D. Paterson⁷,⁸, Lisa J. Martin⁹, Celine M. Vachon¹⁰, Christopher G. Scott¹⁰, Elizabeth J. Atkinson¹⁰, Fergus J. Couch¹¹, Carmel Apicella¹², Melissa C. Southey¹³, Jennifer Stone¹², Rulla M. Tamimi⁴,⁵ for the MODE Consortium, Nazneen Rahman⁶, and Douglas F. Easton¹

Abstract
Percent mammographic breast density (PMD) is a strong heritable risk factor for breast cancer. However, the pathways through which this risk is mediated are still unclear. To explore whether PMD and breast cancer have a shared genetic basis, we identified genetic variants most strongly associated with PMD in a published meta-analysis of five genome-wide association studies (GWAS) and used these to construct risk scores for 3,628 breast cancer cases and 5,190 controls from the UK2 GWAS of breast cancer. The signed per-allele effect estimates of single-nucleotide polymorphisms (SNP) were multiplied with the respective allele counts in the individual and summed over all SNPs to derive the risk score for an individual. These scores were included as the exposure variable in a logistic regression model with breast cancer case–control status as the outcome. This analysis was repeated using 10 different cutoff points for the most significant density SNPs (1%–10% representing 5,222–50,899 SNPs). Permutation analysis was also conducted across all 10 cutoff points. The association between risk score and breast cancer was significant for all cutoff points from 3% to 10% of top density SNPs, being most significant for the 6% (2-sided P = 0.002) to 10% (P = 0.001) cutoff points (overall permutation P = 0.003). Women in the top 10% of the risk score distribution had a 31% increased risk of breast cancer [OR = 1.31; 95% confidence interval (CI) 1.08–1.59] compared with women in the bottom 10%. Together, our results show that PMD and breast cancer have a shared genetic basis that is mediated through a large number of common variants. Cancer Res; 72(6); 1–7. ©2012 AACR.

Introduction
Percent mammographic breast density (PMD) is defined as the proportion of a mammographic image occupied by radiodense tissue (largely stromal and epithelial tissues, appearing as white regions on the mammogram) as opposed to nondense, fatty tissue (the darker regions of the image). PMD is one of the strongest known risk factors for breast cancer. Women with dense tissue in more than 75% of the breast have been shown to be at a 4- to 5-fold increased risk of breast cancer compared with women who have mostly fatty breasts (1). The pathways through which the strong association between mammographic density and breast cancer is mediated are still unclear. Breast cancer has an estimated familial relative risk to first degree relatives of approximately 2 (2), and the heritability estimates for PMD range between 63% and 67% (3), hence it is plausible that these 2 traits share a common genetic basis.

A recent meta-analysis of 5 genome-wide association studies (GWAS) identified variants within intron 4 of the ZNF365 gene that are associated with PMD, adjusted for age and body mass index (BMI; ref. 4). One of the ZNF365 variants, rs10995190, had previously been shown in a GWAS to be associated with breast cancer in the same direction as the corresponding PMD
of more than 97%. We eliminated cryptic duplicates and Brie
posterior probability more than 0.95. Quality controls steps
using the Illuminus algorithm; we used genotypes with a
Institute, Cambridge, United Kingdom. Genotypes were called
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Sporadic versus Hereditary (POSH) breast cancer study. Cases
United Kingdom through the Prospective study of Outcomes in
Breast Cancer Study (FBCS) and from oncology clinics in the
and colleagues (5). The cases were recruited from 23 clinical
UK2 GWAS, as previously described in the work of Turnbull
Methods
Breast cancer case–control study population
The present analysis was based on genotype data from the
UK2 GWAS, as previously described in the work of Turnbull
and colleagues (5). The cases were recruited from 23 clinical
genetics centres in the United Kingdom through the Familial
Breast Cancer Study (FBCS) and from oncology clinics in the
United Kingdom through the Prospective study of Outcomes in
Sporadic versus Hereditary (POSH) breast cancer study. Cases
were preferentially selected to have at least 2 affected first-
or second-degree relatives, and had been screened to exclude
BRCA1 or BRCA2 mutations. The controls used in this study
were genotyped as part of the Wellcome Trust Case Control
Consortium (WTCCC) study and were drawn from the 1958
Birth Cohort (a population-based study in the United Kingdom
of individuals born in 1 week in 1958) and from the U.K.
National Blood Service (9). After quality control exclusions,
the analysis was based on data from 3,628 cases and 5,190
controls. The constituent studies were all approved by their
appropriate ethics committees.

Breast cancer case–control genotyping
Genotypes for cases were generated by a custom Illumina
Infinium 670k array, and controls were genotyped using an
Illumina Infinium 1.2M array at the Wellcome Trust Sanger
Institute, Cambridge, United Kingdom. Genotypes were called
using the Illuminus algorithm; we used genotypes with a
posterior probability more than 0.95. Quality controls steps
are as described in the work of Turnbull and colleagues (5).
Briefly, the analyses were based on individuals with a call rate
of more than 97%. We eliminated cryptic duplicates and first-
degree relative pairs based on identity-by-state (IBS) proba-
bilities, and individuals with non-European ancestry based on
comparison with genotypes in HapMap ancestry based on
Mammographic density measurements and genotyping
Associations between SNPs and density were based on the
meta-analysis of 5 GWAS (totaling 4,887 individuals) previ-
sely reported by the MODE consortium (4). The 5 studies
varied in their proportions of premenopausal women (0%–
46%) and in their proportions of women using hormone
replacement therapy at the time of their mammogram
(9%–46%). All studies estimated density with the CUMULUS
program (11). Percent density (dense area expressed as a
proportion of total breast area), adjusted for age, BMI, and
population stratification (using principal components analy-
sis), was taken as the phenotype. All women were of self-
described European descent and the majority (89%) were
postmenopausal at the time of mammogram. Each study used
multivariate adjustments on square root or natural logarithm
transformed percent density before using appropriate regres-
sion methods to generate estimates of per-allele effects.
Imputation was then used to generate statistics for approx-
imately 2.6M SNPs, based on HapMap II CEU as a reference. One
of the studies selected samples based on the upper and
lower extremes of the density distribution, treated density as
a binary trait and estimated per-allele ORs using logistic
regression, whereas the remaining studies used samples
unselected for density and analyzed density as a continuous
trait using linear regression. Because the effect size estimates
for the different studies were not directly comparable, the
meta-analysis was conducted by deriving signed Z scores for
each SNP for each study and deriving a test statistic by
summing the Z scores weighted by the square root of the
sample size (4).

Written informed consent was given by all participants. The
individual studies were approved by The Committee on the Use
of Human Subjects in Research at Brigham and Women’s
Hospital (Boston, MA); The Norfolk and Norwich Hospital
Ethics Committee (Norwich, Norfolk, UK); the Ethical Review
Board at Karolinska Institutet (Stockholm, Sweden); the Mayo
Clinic Institutional Review Board (Rochester, MN); and the
University Health Network (Toronto, ON, Canada),
respectively.
The Sisters in Breast Screening study

The Sisters in Breast Screening (SIBS) study of mammographic breast density was not included in the MODE meta-analysis of 5 GWAS (although it was included as a replication set for the most significant SNP in that study; ref. 4), and so it was possible to test the association of the polygenic risk score (PRS) with percent breast density using this set of women. The SIBS study is described in the work of Kataoka and colleagues (12). Briefly, families were identified through the National Health Service breast screening program in the United Kingdom. Eligibility was restricted to families in which 2 or more female blood relatives (sisters, half-sisters, first cousins, or aunt–niece) had had mammographic screening. The study was approved by the local research ethical committee. Study recruitment commenced in October 2002. The current analysis was limited to families whose data including mammographic density measurements were completed by July 2007.

For each participant, all available mammograms were retrieved from the local screening unit and were digitized. The mammograms were scanned using the Array 2905 Laser Film Digitizer and the program DicomScan Pro Plus Version 1.3E (Array Corporation), with 50-μm pixel resolution and 12-bit digitization, and an absorbance of 4.7. For each individual, we aimed to collect the earliest and most recently available mammograms. Mammographic density was measured with the CUMULUS program (11). Mammograms were analyzed in a random order, and the reader was blinded to the sequence of the mammograms and to the visual density evaluation that had been done by another reader.

This analysis was based on 1,145 women from 563 families who had been genotyped as part of an ongoing GWAS. Samples were genotyped by Illumina using the Illumina HumanCytoSNP-12 platform. Of 1,160 genotyped women, 6 were excluded on the basis of non-European ethnicity, and the twin with the lower call rate was excluded for each of the 9 pairs of monozygotic twins. The quality control steps were as for the UK2 GWAS; after exclusions genotypes were available for 184,838 SNPs. Genotype imputation was carried out in the same way as for the UK2 GWAS.

Statistical methods

All analyses were done within R and used the GenABEL package (13) implemented in R. A list of the most significant 10% of imputed SNPs (236,090 SNPs) from the density meta-analysis was intersected with the complete list of SNPs genotyped in the UK2 GWAS (531,158 SNPs). The 50,899 SNPs found on both lists were used in the analyses. The same exercise was carried out for other cutoff points of density SNPs between 1% and 10%. As a sensitivity analysis, we repeated the analyses of the 1% to 5% cutoff points using the intersection of the imputed density SNPs with the imputed SNPs in the UK2 GWAS.

To derive an overall test statistic, we assumed that each SNP associated with density would confer an approximately proportional effect on breast cancer risk (as would be expected if density were an intermediate phenotype). Specifically, we assumed that the per-allele log-relative risk of breast cancer conferred by each SNP would be (approximately) proportional to the per-allele mean density difference. The aim was to create a more informative score than would be obtained by simply summing the number of unweighted risk alleles. We further assumed that the combined effect of SNPs was additive for density and log additive for breast cancer risk (as has been observed for susceptibility SNPs identified to date).

Under this model, the log-odds of breast cancer for individual i would be related to the density SNPs using a PRS of the form:

$$\text{PRS}_i = \sum_{k=1}^{N} \beta_k G_{ik}$$

where $\beta_k$ is the per-allele change in mean density for SNP k and $G_{ik}$ is the genotype for SNP k in individual i (0, 1, or 2) in the breast cancer GWAS. However, because the meta-analysis was done by combining P values, the effect sizes were only available as signed Z scores ($Z_k$) rather than parameter estimates ($\beta_k$). Although the above test statistic could be based on the Z scores rather than the $\beta_k$, this would be inefficient because for a given P value, a rarer SNP (lower MAF) would have had a higher effect estimate compared with a more common SNP (higher MAF), and hence a higher predicted relative risk of breast cancer.

For a standard linear regression analysis of density against SNP k, the standard error of $\beta_k$ is given approximately by:

$$\text{SE}(\beta_k) \approx \sigma / \sqrt{2nq_k(1-q_k)}$$

where n is the sample size, $q_k$ and $1-q_k$ are the allele frequencies, and $\sigma$ is the (residual) trait variance in the density study. For simplicity, we approximated the allele frequencies $q_k$ from the density studies by the allele frequencies $p_k$ in the breast cancer study. Hence:

$$Z_k = \beta_k / \text{SE}(\beta_k) \approx \beta_k \sqrt{2np_k(1-p_k)}/\sigma$$

so that for a given sample size, as here, $\beta_k$ is proportional to $Z_k / \sqrt{p_k(1-p_k)}$. (The ranked density SNPs were based on a meta-analysis of imputations carried out by each group to the same reference panel, and so we would expect n to be the same for all SNPs, except in the case of SNPs that were poorly imputed in one or more studies.)

The PRS that we used for each individual was, therefore, of the form:

$$\text{PRS}_i = \sum_{k=1}^{N} Z_k G_{ik} / \sqrt{p_k(1-p_k)}$$

In computing the score, missing genotypes were replaced with the value 0, equivalent to assuming that the individual has a common homozygote genotype at that SNP (individuals with $\geq 3\%$ of genotypes missing had been excluded).

In practice, only a subset of the SNPs will be associated with density (the remainder being false positives) and the effect sizes will often be overestimated. Nevertheless, provided that some of the associated SNPs are also associated with risk, the composite score, PRS, should be associated with breast cancer risk. To test this hypothesis, PRS was included as the exposure variable in a logistic regression model with
breast cancer case–control status as the outcome. This analysis was repeated for different cutoff points of the top density SNPs (1%–10%). For the sensitivity analysis using imputed SNPs in the breast cancer GWAS (rather than just the observed SNPs) the genotypes $G_{ik}$ were replaced by the estimated allele doses.

To evaluate the probability of obtaining a significant association at any cutoff point by chance, a permutation $P$ value was obtained by randomly permuting the case–control status 5,000 times and repeating the association tests with the PRS calculated for each cutoff point. The number of permutations for which the $P$ value was less than or equal to the smallest actual $P$ value were counted to estimate an empirical $P$ value. The use of a permutation approach should make the test robust to the nonindependence of SNPs within the same linkage disequilibrium block.

To quantify the predictive value of the risk score, we calculated ORs by percentiles of PRS, using logistic regression.

To assess the association of the PRS with breast density, we intersected the SNPs used to calculate the PRS in the case–control study (50,899 SNPs) with the list of SNPs successfully imputed in the SIBS study. Thus, the PRS for the SIBS women were calculated using 49,912 SNPs. Percent densities for up to 4 mammograms per woman (both breasts and 2 time points) were adjusted for age at mammogram and BMI, and the mean over the 4 values (or over all available images, if less than 4) was used. Linear regression was carried out to assess the association between the PRS and adjusted percent density, allowing for the nonindependence of relatives.

Statistical analyses were conducted using R and Stata version 10.0. All $P$ values are 2 sided.

**Results**

This study examined the association between breast cancer risk in 3,628 cases and 5,190 controls and a PRS based on a woman’s genotypes at the top approximately 5,000 to 50,000 ranked SNPs from a genome-wide meta-analysis of mammographic breast density. The PRS based on the top 10% of density SNPs ranged between $-5.274$ and $6.982$ (mean $= 355$, SD $= 1,594$). The mean 10% PRS was $421$ (SD $= 1,582$) among the cases and $310$ (SD $= 1,600$) in the controls ($P = 0.0012$; Student $t$ test). A one-point increase in the PRS was associated with an increase in percent breast density of $6.9 \times 10^{-3}$ percentage points ($P = 0.014$) in the SIBS study.

The significance of the association between PRS and breast cancer risk for different cutoff points of significant density SNPs are shown in Fig. 1. The PRS based on the top 1% of density SNPs (5,222 SNPs) was not significantly associated with breast cancer ($P = 0.33$) but the association was significant at the 5% level for all cutoff points from 3% to 10%, being most significant for cutoff points between 6% and 10% ($P = 0.002$ for the 6% cutoff point; $P = 0.001$ for the 10% cutoff point; Fig. 1). For example, an increase of 1,000 PRS points (for the 10% cutoff point) was associated with a 4.5% increase in breast cancer risk [95% confidence interval (CI), 1.7%–7.3%]. Permutation analysis done across all 10 cutoff points (5,000 permutations) gave an overall empirical $P$ value of 0.003.

![Figure 1](image_url)

Figure 1. Significance of the mammographic breast density PRS for the prediction of breast cancer risk, according to percent cutoff point of SNPs used in the PRS. Significance levels were obtained using unconditional logistic regression.

The analysis was also repeated using the imputed genotype dosages for the top 1% to 5% of density SNPs. The results followed a similar pattern as seen with genotyped SNPs. The score based on the top 5% of imputed SNPs was significantly associated with breast cancer risk at $P = 0.01$ (Supplementary Fig. S1). Having established that the use of imputed SNPs did not change the broad pattern of the results, we did not extend the imputed analysis beyond the top 5% of SNPs for computational reasons.

We next categorized individuals by their risk score based on the top 10% of genotyped density SNPs (50,899 SNPs). We chose to use the scores based on the 10% cutoff point for convenience, although we note that the 10% scores are only slightly better than those obtained using the top 6% of SNPs. Women in the lowest decile of the PRS distribution were at a significantly lower risk of breast cancer than women with higher scores, with women in the top decile of PRS having an estimated OR $= 1.31$ (95% CI, 1.08–1.58) compared with the bottom decile (Table 1). There does not appear to be a steady gradient in risk, with women between the 10th and 25th percentiles, the 25th and 75th percentiles, and the 75th and 95th percentiles of the PRS distribution all having an approximately 19% higher risk than the lowest 10% of women. The group of SIBS women with the highest adjusted breast density were actually those between the 75th and 90th percentiles of PRS distribution ($P = 0.014$ versus the lowest decile), but the SDs are large, given the relatively small numbers (Table 1).

**Discussion**

In this study, we tested the hypothesis that common genetic factors contribute to the association between mammographic density and breast cancer. We calculated a PRS based on the signed $Z$ scores for the set of SNPs showing the strongest...
association with density in a meta-analysis of 5 breast density GWAS and examined whether this risk score was predictive of breast cancer status. We found that a risk score based on the top 10% of SNPs was significantly associated with breast cancer risk, whereas the risk score based on the top 1% was not. Consistent with this result women whose SNP profile is such as to give them a risk score in the top decile of the PRS distribution had a 31% increased risk of breast cancer compared with women in the lowest decile ($P = 0.0058$), although the effect on breast cancer risk appears only to be detectable at either extreme of the polygenic allele distribution.

The aim was not to identify the specific SNPs that are associated with both traits; we note that we observed only 2 SNPs that were associated with both PMD and breast cancer with $P$ values less than $10^{-4}$, one of which has been previously described (rs10995190; refs. 4, 5) and the other SNP (rs10509168) is also in the ZNF365 gene (the 2 are not strongly correlated, $r^2 = 0.13$). Our results suggest that more such SNPs should be reliably identifiable through larger meta-analyses of GWAS. Exclusion of SNPs rs10995190 and rs10509168 in ZNF365 and all correlated SNPs ($r^2 > 0.2$) made no material difference to the results (data not shown).

This study is the first to provide direct evidence from genotyping that mammographic breast density has a polygenic mode of inheritance, in line with other quantitative human traits, such as height and BMI (14). Using a Mendelian Randomization approach (15) with the PRS as the instrumental variable, we predicted that a 1,000-point increase in the PRS would be associated with an approximately 1.4% increase in breast cancer risk, which in turn could have inflated the observed effect of the density PRS on breast cancer risk. We were not able to reanalyze the meta-GWAS adjusting for case–control status, but the original report noted that for the most significant SNP (rs10995190) neither adjusting for case–control status nor excluding the cases changed the significance, suggesting that confounding was not present, at least for this SNP (4). We should also bear in mind that the set of cases included in this study were preferentially selected for an early age at breast cancer diagnosis and/or a positive family history of breast cancer, both of which may have upwardly biased the magnitude of the observed association (5).

One might have anticipated that the PRS based on the top 1% of density SNPs would show the most significant association with breast cancer risk. In fact, however, the significance of the association increased as further SNPs were added to the score, until about the 6% cutoff point, beyond which there was little improvement (a pattern broadly similar to that seen in the Multiple Sclerosis polygenic score study ref. 18). This suggests the existence of large numbers of SNPs associated with both traits, and that these are not limited to those variants showing the strongest associations with density. The flattening out of the graph beyond the 6% cutoff point may indicate a lack of power to detect variants with smaller shared effects, rather than an absence of such variants. Although one of the strengths of this study is the large number of samples in the density meta-GWAS from which the SNP rankings were obtained, the lower significance seen for the top 1% of SNPs may nevertheless point to a lack of power in the density study, resulting in imprecision in the ranking: an ongoing meta-analysis incorporating additional individual density studies may improve the precision.
with which SNPs are ranked. It should also be noted that this study only considered SNPs associated with PMD. It is possible that the absolute volume of dense tissue in the breast is more relevant for breast cancer risk, and hence that a PRS based on SNPs associated with absolute dense area (as a hypothesized better surrogate for volume) would show stronger evidence of a shared genetic basis with breast cancer risk.

To the best of our knowledge, this is the first such study to use SNPs ranked on the basis of their association with a quantitative trait to predict risk of a related disease. Other groups have used similar approaches to obtain disease-risk information from SNPs that are not individually significant, with mixed results. For example, using WTCCC data, Evans and colleagues (8) found that disease-specific polygenic scores gave only limited discrimination between cases and controls of the same disease for bipolar disorder, coronary heart disease, hypertension, Crohn’s disease, rheumatoid arthritis, and type II diabetes and that the discriminatory ability of the type I diabetes score was markedly reduced after the exclusion of SNPs in and around the MHC (a region known to be associated with type I diabetes). However, separate studies of multiple sclerosis and schizophrenia both found significant associations between disease risk and scores based on multiple SNPs, with the schizophrenia-derived polygenic score also predicting the risk of bipolar disease, but not of the 6 nonpsychiatric diseases in the WTCCC study described earlier (7, 18). Our results are in contrast to those of Machiela and colleagues (19) who, using a related approach, found no association between an unweighted PRS constructed using ranked SNPs from a breast cancer GWAS with breast cancer risk, after excluding 13 established breast cancer SNPs. Witte and Hoffmann also found that a similar polygenic model did not significantly predict breast cancer status (20). This presumably reflects the low power of both studies due to small training and testing sets (<1,200 cases and controls in total for each) and shows the need for large studies when considering variants with small effects. The power of our study was, in addition, boosted by the enrichment of the set of breast cancer cases for a positive family history of the disease.

Theoretically, the association we observed could result from population stratification, if there were strata with higher density and higher breast cancer risk. However, this is unlikely as the GWAS for density were not significantly different among cases and controls (5). A recent study reported no significant difference in their results with or without substitution of missing genotypes (21).

This analysis shows directly that a suitably chosen set of SNPs that do not reach genome-wide significance levels individually for one trait can nevertheless predict a genetically related trait when used in combination. This method could be used to look for shared genetic influences between other risk factors and breast cancer, or indeed between any pair of correlated heritable traits.

The recent identification of common SNPs associated with breast cancer risk indicate that susceptibility to breast cancer is at least partly polygenic (22). Our results suggest that a much larger number of common variants are involved, and, moreover that there is at least some overlap between the set of genetic variants involved in breast density and those involved in breast cancer risk. This observation in turn confirms that the well-established correlation between the 2 traits is genuine, and not the result of uncorrected confounding. It is not possible at this stage to determine whether the observed effect is attributable to variants which increase cancer risk via the creation of a dense breast, or to variants which act pleiotropically to affect both traits, or to a mixture of both types of variants. The identification of the relevant variants should help to elucidate the biologic mechanisms underlying breast density and the reasons for its association with breast cancer.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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