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Breast Cancer Risk Prediction Using a Clinical Risk Model and Polygenic Risk Score

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Abstract

Purpose—Breast cancer risk assessment can inform the use of screening and prevention modalities. We investigated the performance of the Breast Cancer Surveillance Consortium

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Conflict of interest: Dr. Jessica Leung receives consultation fees from Hologic, Inc. related to the development of contrast-enhanced mammography.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Specifically, each registry in the Breast Cancer Surveillance Consortium and the Statistical Coordinating Center (SCC) have received institutional review board approval for either active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act (HIPAA) compliant and all registries and the SCC have received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities who are subjects of this research.

Informed consent: Informed consent was obtained from all individual participants included in the study.

(BCSC) risk model in combination with a polygenic risk score (PRS) comprised of 83 single nucleotide polymorphisms identified from genome wide association studies.

Methods—We conducted a nested case-control study of 486 cases and 495 matched controls within a screening cohort. The PRS was calculated using a Bayesian approach. The contributions of the PRS and variables in the BCSC model to breast cancer risk were tested using conditional logistic regression. Discriminatory accuracy of the models was compared using the area under the receiver operating characteristic curve (AUROC).

Results—Increasing quartiles of the PRS were positively associated with breast cancer risk, with OR 2.54 (95% CI 1.69-3.82) for breast cancer in the highest versus lowest quartile. In a multivariable model, the PRS, family history, and breast density remained strong risk factors. The AUROC of the PRS was 0.60 (95% CI 0.57-0.64), and an Asian-specific PRS had AUROC 0.64 (95% CI 0.53-0.74). A combined model including the BCSC risk factors and PRS had better discrimination than the BCSC model (AUROC 0.65 versus 0.62, $p = 0.01$). The BCSC-PRS model classified 18% of cases as high-risk (5-year risk = 3%), compared with 7% using the BCSC model.

Conclusion—The PRS improved discrimination of the BCSC risk model and classified more cases as high-risk.

Impact—Further consideration of the PRS's role in decision-making around screening and prevention strategies is merited.

Keywords

Breast cancer; single nucleotide polymorphisms; risk assessment; cancer surveillance and screening

Introduction

Breast cancer risk varies based on mammographic breast density, family history, reproductive history, hormone exposure, genetic variants and other risk factors [1]. Risk prediction models are useful to identify high-risk women who may benefit from supplemental screening with MRI [2] or chemoprevention [1,3]. Risk prediction models may also be useful to guide the age at which screening begins, and the frequency of screening [4,5]. Improving the predictive power of risk models is an important step towards targeted screening and prevention.

Risk prediction models [1,6,7] have incorporated family history, demographic, reproductive, and hormonal risk factors. We developed the Breast Cancer Surveillance Consortium (BCSC) risk model to include mammographic breast density, a strong risk factor for breast cancer, in addition to age, race/ethnicity, first-degree relative with breast cancer, and history of breast biopsy [8,9]. The model has been validated in a multiethnic population and expanded to include history of benign breast disease [9].

Common genetic variants may also be useful in risk stratification. Genome-wide association studies (GWAS) have identified over 90 single nucleotide polymorphisms (SNPs) associated with breast cancer [10-20]. Although the individual effect sizes of each SNP are modest, together they account for 15-20% of familial breast cancer risk [20].

Polygenic risk scores (PRS) combine the effects of multiple SNPs and enhance breast cancer risk models. The Breast Cancer Association Consortium demonstrated that a 77-SNP PRS was a strong predictor of breast cancer in women with and without a positive family history [21]. Vachon and colleagues reported that adding a 76-SNP PRS to the BCSC risk model improved prediction [22]. Likewise, a 77-SNP PRS improved the discrimination of the Gail and Tyrer-Cuzick models [23]. Studies combining PRS and breast cancer risk factors have focused on Caucasian populations. We sought to replicate these findings in an independent population including non-Caucasian women. We used 83 SNPs to construct our PRS given the expanding number of validated SNPs in populations of different ethnicities.

Materials and Methods

Study population

We performed a nested case-control study within the California Pacific Medical Center (CPMC) Research Institute Cohort, which participates in the San Francisco Mammography Registry (SFMR). Participants were recruited from the Breast Health Center at CPMC, an imaging facility within the SFMR. All women presenting for mammography completed a questionnaire with demographic information and risk factor data. Questionnaire data were collected by the SFMR, as approved by the institutional review boards at CPMC and the University of California, San Francisco. From 2004-2011, women were also asked to provide blood samples for research and written informed consent to undergo genotyping. Samples were obtained from 19,276 women.

Cases ($n = 1,203$) had a first diagnosis of invasive breast cancer between 1998-2013. Diagnosis of breast cancer was ascertained by linkage to the California Cancer Registry (CCR), with last linkage on October 31, 2013; women without breast cancer at this time were considered controls. We randomly selected 500 cases for genotyping. Since blood sample collection could have occurred before or after first diagnosis of breast cancer, incident and prevalent cases were included. We also genotyped 500 controls matched by age at study mammogram, race/ethnicity, and mammography machine.

Of the 1,000 women genotyped, 19 were excluded from the analysis due to inability to retrieve the original mammography films for breast density measurement ($n = 14$), inability to calculate polygenic risk score due to failed genotyping ($n = 4$), and self-reported race for which BCSC risk could not be estimated ($n = 1$). Of the remaining 981 women, 495 were controls and 486 were cases.

Polygenic risk score

Genotyping was performed using an Illumina Oncoarray (Illumina, San Diego, CA, USA) at the Genomics Core of the University of Minnesota. For this analysis, we included SNPs reported as genome wide significant ($p < 5 \times 10^{-8}$) in studies of invasive breast cancer in Caucasian, Asian or Hispanic populations [11,12,15,16,24,17,18,25,10,14,19,26] which we identified by review of the GWAS catalogue [27]. If a SNP was not on the array, we sought a proxy SNP in strong linkage disequilibrium (LD), $r^2 > 0.9$. If multiple SNPs at a single locus were reported, we selected the SNP most strongly associated at that locus and dropped SNPs

in moderate to strong LD, $r^2 > 0.5$. We excluded SNPs associated with subtypes of breast cancer, but not breast cancer overall, and modifiers of BRCA1 and BRCA2 effect if they were not associated with breast cancer in non-BRCA1/2 carriers. The final list included 83 SNPs (**Table S1**).

We constructed two separate PRS, one with the allele frequencies and odds ratios (ORs) from Caucasian populations used in the main analysis, and another with allele frequencies and ORs from East Asian populations (**Table S2**) [15,16,18]. The Asian-specific PRS had 76 SNPs after the exclusion of SNPs that were non-polymorphic in Asian populations. For SNPs not validated in an Asian population, the Caucasian odds ratio and the published East Asian allele frequency from 1000 Genomes [28] were used.

We calculated the PRS as the composite likelihood ratio (LR) representing the individual effects of each SNP. For each locus with alleles A and a, the probability of genotypes given disease status can be given by the equations:

$$\begin{aligned} P(AA|D+) &= \frac{p^2\gamma^2}{p^2\gamma^2 + 2p(1-p)\gamma + (1-p)^2} \\ P(Aa|D+) &= \frac{2p(1-p)\gamma}{p^2\gamma^2 + 2p(1-p)\gamma + (1-p)^2} \\ P(aa|D+) &= \frac{(1-p)^2}{p^2\gamma^2 + 2p(1-p)\gamma + (1-p)^2} \end{aligned}$$

where p is the population frequency of the risk allele and γ is the per-allele relative risk of breast cancer (approximating the OR) [29]. The likelihood ratios for breast cancer can be given as $\frac{P(AA|D+)}{P(AA|D-)}$, $\frac{P(Aa|D+)}{P(Aa|D-)}$, and $\frac{P(aa|D+)}{P(aa|D-)}$, respectively. Assuming all of the SNPs are inherited independently and there are no interactions between them, the LR for each multi-SNP genotype, G_i , is the product of the likelihood ratios for the genotype, g_i , of each of the n SNPs.

$$LR_{G_i} = \prod_{i=1}^n \frac{P(g_i|D^+)}{P(g_i|D^-)}$$

Using a Bayesian approach, the 5-year risk of breast cancer for a person with LR_{G_i} is

$$P(D^+|G_i) = \frac{\frac{K_i}{1-K_i} LR_{G_i}}{\frac{K_i}{1-K_i} LR_{G_i} + 1}$$

where K_i is the 5-year risk probability projected by the BCSC model [29].

BCSC risk score

We used a fitted version of the BCSC model (fitted-BCSC) for multivariable analysis on the association of the PRS and other BCSC risk factors with breast cancer. Each variable was included as a separate regression term, including body mass index (BMI) given the confounding effect of BMI on the relationship between mammographic density and breast cancer risk [30]. We used version 2.0 of the BCSC model (BCSCv2) to generate absolute

risk estimates [8]. Version 2.0 is the most current version of the BCSC model and allows calculation of 5- and 10-year risk, but does not calculate risk for women over the age of 74 [31]. Mammographic breast density was classified according to the Breast Imaging Reporting and Data System (BI-RADS) scoring system [32]: almost entirely fatty (a), scattered areas of fibroglandular density (b), heterogeneously dense (c), and extremely dense (d). Category b was designated as the reference group.

Statistical analysis

We compared demographic data and risk factors between cases and controls using the chi-squared test for categorical measures and the t-test for continuous measures. All tests of statistical significance were two-sided, with $\alpha = .05$. Univariate and multivariable conditional logistic regression models to predict breast cancer were constructed with the polygenic risk score, the fitted BCSC model (fitted-BCSC), and the PRS combined with the fitted BCSC model (fitted-BCSC-PRS model). The PRS was analyzed as a continuous variable and as quartiles of the PRS in controls.

The area under the receiver operating characteristic curve (AUROC) was used to compare discrimination of the models. To account for the matched case-control design, the AUROC and confidence intervals were calculated using a stratified bootstrap algorithm ($n = 1000$ replications) with separate sampling from cases and controls. To evaluate for overfitting in the fitted-BCSC model, we performed split-sample validation. Two-thirds of the dataset ($n = 654$), with an equal number of cases and controls, was randomly sampled as the training set. The coefficients corresponding to the variables in the fitted-BCSC model were used for prediction in the validation set ($n = 327$). The AUROC of the fitted-BCSC model was compared between randomly generated discovery and validation sets across 1,000 replications.

To evaluate the effect of the PRS on the reclassification of risk, we calculated two 5-year risk estimates: one using the BCSCv2 estimate, and another using the BCSCv2 estimate modified by the PRS (BCSCv2-PRS model). Given that the BCSCv2 model does not calculate risk estimates for women over age 74, this analysis was limited to the 471 cases and 460 controls under the age of 74. We calculated the percentages of controls and cases whose risk estimates fell within 5- and 10-year risk strata according to the BCSCv2 and BCSCv2-PRS models. Calibration of the fitted-BCSC-PRS model was assessed using the Hosmer-Lemeshow test [33].

Primary statistical analysis was performed using STATA 14.1 (StataCorp, College Station, TX, USA). The PRS was generated using a script in R (R Foundation, Vienna, Austria). The BCSCv2 absolute risk calculations were done using SAS Version 9.3 (SAS Institute, Cary, NC, USA).

Results

Demographics and exposures

Eighty percent of participants were of self-reported Caucasian/White race, while women of self-reported East Asian descent were the most prevalent non-Caucasian subgroup,

comprising 11% of overall participants (**Table 1**). Cases were more likely to have a positive family history of breast cancer, prior biopsy, and dense breasts (BI-RADS c and d). Cases were also more likely to be at high or very high risk using the **BCSCv2** 5-year risk estimates. Three hundred three cases (62.3%) had incident cancers, and the remaining 183 cases (37.7%) had prevalent cancers.

An 83-SNP polygenic risk score was constructed based on SNPs with published genomewide associations with breast cancer (**Table S1**). We expanded on a previously described 76-SNP PRS [22] by including SNPs validated in Asian or Hispanic populations [11,15,10], with additional SNPs curated from published catalogues [12,27,13,17]. Our PRS had 71 SNPs in common with the previously described 76-SNP PRS [22]. Nine of the 83 SNPs were nominally associated with breast cancer ($p < 0.05$) (**Table S1**). The mean PRS was higher in cases than in controls, 1.20 (standard deviation 0.95) versus 0.97 (standard deviation 0.68).

Effect of polygenic risk score and other risk factors on breast cancer

There was a strong association between higher PRS and breast cancer, with the highest risk quartile having an OR of 2.54 (95% CI 1.69-3.82) compared with the lowest risk quartile (**Table 2**). Family history (OR 1.89, 95% CI 1.39-2.56), history of breast biopsy (OR 1.58, 95% CI 1.16-2.15), and breast density (OR 1.51, 95% CI 1.13-2.03 for BIRADS c and OR 1.95, 95% CI 1.24-3.07 for BIRADS d) were also associated with breast cancer in univariate analyses. In a multivariable model including PRS and family history, there was minimal change in the associations between the PRS quartiles and family history on breast cancer risk. In the fitted-BCSC model, which includes all risk factors in the BCSC risk model in addition to BMI, the point estimates for the PRS were minimally changed.

The fitted-BCSC model accounts for the effect of BMI on breast density as a predictor. Since obesity is associated with higher breast cancer risk but lower breast density [34], we suspected that BMI was a negative confounder of the association between density and breast cancer. Adjusting for BMI increased the magnitude of the effect of breast density (**Table S3**). Adding the PRS to this model minimally attenuated the association between each density category and breast cancer. Given that BMI was a significant risk factor for breast cancer, and changed the point estimates associated with each BIRADS category substantively (10%), we used the fitted-BCSC model in our primary analysis.

Split-sample validation showed evidence of overfitting with the fitted-BCSC model, although the effect on the AUROC point estimate was minimal. The AUROC was 0.62 (95% CI 0.59-0.66) in the discovery set and 0.61 (95% CI 0.54-0.68) in the validation set.

Discrimination of models

Receiver operating characteristic curve analysis was used to compare the discrimination of three models (**Fig. 1**): the PRS alone, the fitted-BCSC model, and the polygenic risk score plus fitted-BCSC model (fitted-BCSC-PRS). The AUROC of the fitted-BCSC model was 0.62 (95% CI 0.59-0.66), which was slightly higher than that of the PRS model, which was 0.60 (95% CI 0.57-0.64) (**Table 3**). The fitted-BCSC-PRS model had the highest

discrimination, with an AUROC of 0.65 (95% CI 0.61-0.68). Specifically, the difference between the AUROCs for the fitted-BCSC model with and without the PRS reached statistical significance ($p = 0.01$). When the analysis was restricted to incident cases only, the AUROCs were 0.01 higher for the PRS, fitted-BCSC and fitted-BCSC-PRS models (**Fig. S1**).

A 76-SNP PRS constructed using East Asian-specific allele frequencies and ORs (**Table S2**) was tested in the Asian subset of our study. Using the Asian-specific PRS, the mean PRS was 0.96 (SD 0.43) in Asian controls and 1.24 (SD 0.60) in Asian cases. In Asians, the discrimination of the Asian PRS was higher than that of the overall PRS, with AUROC of 0.64 (95% CI 0.53-0.74) versus AUROC 0.62 (95% CI 0.52-0.73), **Figs. 2A and 2B**. In contrast, the AUROC associated with the general PRS was 0.59 (95% CI 0.56-0.63) in Caucasians (**Fig. 2C**). When the Asian-specific PRS was combined with the fitted-BCSC model, the AUROC increased to 0.72 (95% CI 0.62-0.82). In Caucasians, the fitted-BCSC-PRS model AUROC was 0.63 (95% CI 0.59-0.67), **Fig. S2**.

We investigated how risk prediction for cases and controls differed when the PRS was used to modify the BCSC model absolute risk estimate. **Fig. 3** shows the percentages of cases and controls classified within 5-year risk strata according to estimates generated using the BCSCv2 and BCSCv2-PRS models. The BCSCv2-PRS model classified 49% of controls as having a 5-year risk $\geq 1\%$ (**Fig. 3A**), compared with 33% of controls according to the BCSCv2-PRS model (**Fig. 3B**). The 5-year risk threshold of $\geq 1\%$ is considered low-risk, given the 5-year risk of an average 50 year-old Caucasian woman is 1.3% [35]. Additionally, the BCSCv2-PRS model classified more cases as extremely high risk (5-year risk $\geq 3\%$, indicated by the dashed line in **Fig. 3**). The USPSTF currently recommends consideration of chemoprevention for women with a 5-year risk $\geq 3\%$. The BCSCv2-PRS model classified 18% of cases above this threshold, compared with 7% according to the BCSCv2 model. A similar effect was seen when comparing 10-year risk estimates generated by the unmodified BCSCv2 model and the BCSCv2 model modified by the PRS (**Fig. S3**).

Calibration of the models was assessed using the Hosmer-Lemeshow test with the study population split into 10 subgroups of identical risk. There was no significant deviation from expectation of the fitted-BCSC-PRS model (chi-squared = 975.7, $p = 0.42$), or the BCSCv2-PRS model (chi-squared = 937.0, $p = 0.41$).

Discussion

An 83-SNP polygenic risk score was a strong risk factor for breast cancer whose effect was not diminished by adjustment for family history, prior breast biopsy, or breast density. Adding the PRS to the BCSC model improved discrimination, suggesting the PRS plays a role in risk stratification, and exerts an effect distinct from clinical risk factors and breast density. The BCSCv2-PRS classified nearly three times as many cases into the high-risk ($\geq 3\%$) strata compared with the BCSCv2 model.

The results of our main analysis are mostly consistent with prior studies. The AUROC of our PRS alone, 0.60 (95% CI 0.57-0.64), is similar to the c-statistic of 0.62 (95% CI 0.62-0.63)

using a 77-locus PRS in a study of over 30,000 cases and controls [21]. The only other study on a combined PRS-BCSC model reported improved discrimination when a 76-SNP PRS was added to the BCSC model [22]. Our study replicated these results from Vachon, et al using an 83-SNP PRS that included 71 SNPs from that study. There were slight differences in the AUROC for the BCSC-PRS model in our study (0.65, 95% CI 0.61-0.68) compared with Vachon (0.69, 95% CI 0.64-0.73) [22]. The reported AUC from the latter study was based on a multiple sampling approach in the validation cohort, and did not account for BMI in the BCSC model.

The AUROC of 0.62 for the fitted-BCSC model was lower than previously reported values, which range from 0.65-0.66 [8,9,22]. Matching by age and race/ethnicity, two of the variables in the model, likely decreased its predictive power. Furthermore, prior studies incorporated solely incident cases while ours included both prevalent and incident cancers. When the analysis was restricted to incident cancers, the AUROC for the fitted-BCSC and fitted-BCSC-PRS models increased. On the other hand, overfitting may have led to overestimation of the AUROC of the fitted-BCSC and fitted-BCSC-PRS models. Our cross-validation analysis showed that the fitted-BCSC model had a higher AUROC in the discovery set, but the absolute difference was 0.01, justifying fitting a modified BCSC model to derive the predictive value of BMI-adjusted breast density.

One of the strengths of this study is the multi-ethnic makeup relative to prior investigations of the PRS. This allowed for exploration of the performance of a PRS tailored to East Asians, the largest non-Caucasian subgroup. Nearly all SNPs discovered in Caucasians have been validated in Asians, with similar ORs [18]. The PRS using ORs from Caucasian populations applied to Asian populations should perform well, as we observed. When Asian-specific allele frequencies and ORs were used, the discrimination improved, although we are unable to exclude the effect of chance due to the relatively wide confidence interval for the AUROC in Asians. To our knowledge, our study is the first to investigate the performance of a race or ethnicity-specific PRS. Additional studies in larger populations should help refine the PRS in East Asians and other populations.

Our study supports previously reported observations about polygenic risk. First, the modest attenuation in the effects of PRS and family history in joint models suggests that a small fraction of family history is attributed to these SNPs. This is consistent with prior studies [21,23,36]. Second, the association between breast density and breast cancer was slightly attenuated after adjustment for the PRS. Breast density is 60-70% heritable, and GWAS have identified 7 loci associated with percent dense area [37]. Our PRS includes at least two SNPs associated with density, rs10995190 (ZNF365) and rs3817198 (LSP1) and SNPs from ESR1, a locus that is associated with density [37,38]. Thus, our version of the PRS accounts for a small portion of the heritability of breast density, and inclusion of the PRS minimally affects the association between breast density and breast cancer.

We used a Bayesian approach to combine information on risk across SNPs [39]. Others have used an approach where the PRS is calculated as the sum of the product of the per-allele log-OR and the number of risk alleles for each SNP [21,22] which can be re-scaled so that it averages one [40]. Both approaches assume the independent effect of SNPs, a reasonable

assumption based on an evaluation of 2-way interactions for breast cancer in Caucasian women [41]. Our Bayesian approach reflects the traditional method for combining information from diagnostic tests [42,43]. In practice, we found that the Bayesian approach and the approach using ORs yield very similar results with these parameters.

Our results should be interpreted with caution since this was a single-center study with lower representation of black and Hispanic patients relative to the U.S. population. Women who perceived themselves as higher risk may have been more likely to consent to provide a blood sample, and it is possible that the baseline risk amongst study participants differs from that of the general population. Compared to previous descriptions of the BCSC cohort, controls were noted to have slightly higher breast density, and were more likely to have a family history of breast cancer [44].

In addition, future analyses should evaluate the performance of race/ethnicity-specific PRS in non-Caucasian populations. The association between the PRS and various breast cancer phenotypes should be validated. Case-case studies have found that higher PRS is positively associated with good prognosis cancers [45,46]. Our study was not adequately powered to explore subsets of breast cancer.

The USPSTF recommends the consideration of chemoprevention in women with 5-year risk $\geq 3\%$ [3]. The PRS reclassifies more women to this higher risk category when added to the BCSC model. One promising area of study involves using the PRS to identify women who would benefit from chemoprevention, since it is unknown whether a high PRS is predictive of benefit from tamoxifen. Although the PRS has been assessed in high-risk women enrolled in two large tamoxifen prevention trials [47], there are no comparative data on the PRS in women who received placebo, and the relative benefit of tamoxifen in women with high polygenic risk remains undetermined.

The PRS may also identify women who might benefit from intensive screening. The American Cancer Society recommends that women with $>20\text{-}25\%$ lifetime risk consider screening with MRI [2]. Our study did not project lifetime risk since the BCSC model has only been calibrated for 5- and 10-year risk, though women in the top percentile based on PRS alone have $>25\%$ lifetime risk and women in the top 5th percentile have $>20\%$ risk [21]. Prospective studies are needed to determine whether more intensive screening for high-risk women based on PRS and other risk factors prevents breast cancer morbidity and mortality.

One approach that is currently being studied involves using the combined BCSC-PRS risk estimate to guide screening strategies depending on whether an individual's 5-year risk exceeds certain thresholds. For instance, women aged 40-49 whose risk equals or exceeds that of an average 50 year-old may be recommended to begin screening immediately rather than defer to age 50. In those without known genetic mutations, polygenic risk may identify additional women whose genetic risk is comparable to that of moderate or high-penetrance mutation carriers. Adjunctive MRI screening may be considered for those at high polygenic risk, analogous to existing guidelines for mutation carriers [48]. A prospective trial on this approach is already underway [49].

In summary, the polygenic risk score is an independent predictor of breast cancer risk that may improve identification of high-risk women in both Caucasian and East Asians. The declining cost and increasing accessibility of genetic-based assays may make it possible to use the PRS with other models to risk-stratify women [48]. The PRS deserves further study on its role in guiding both screening and prevention efforts, and the screening trial currently underway should address its utility, both alone and in combination with other risk factors, to impact clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AUROC	area under the receiver operating characteristic curve
BCSC	Breast Cancer Surveillance Consortium
BIRADS	Breast Imaging Reporting and Data System
BMI	body mass index
CCR	California Cancer Registry
CPMC	California Pacific Medical Center
GWAS	genomewide association study
LR	likelihood ratio
OR	odds ratio
PRS	polygenic risk score
SFMR	San Francisco Mammography Registry
SNPs	single nucleotide polymorphisms

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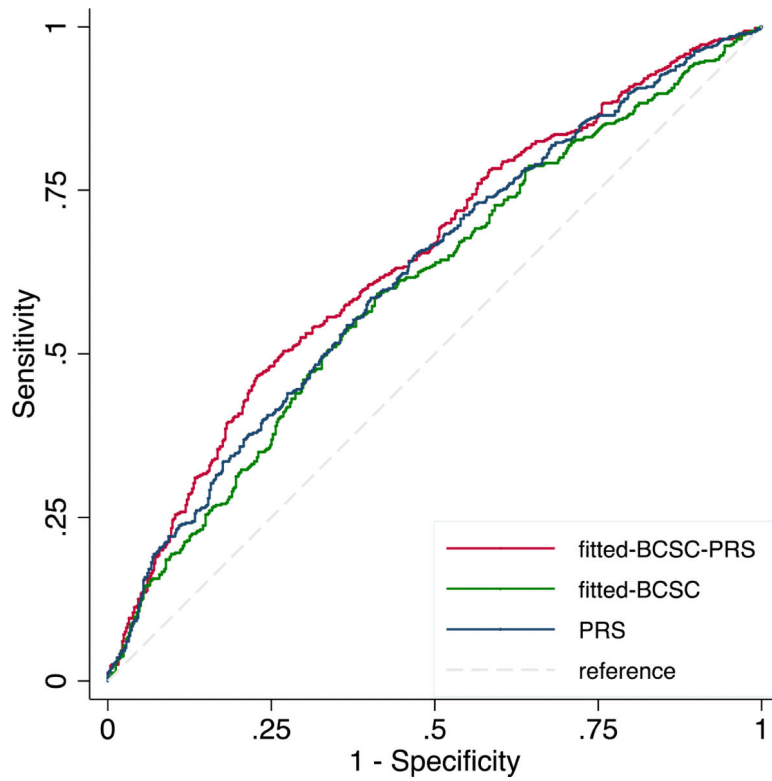


Fig. 1. The receiver operating characteristic curves for the polygenic risk score (PRS), fitted BCSC model (fitted-BCSC), and the fitted BCSC model plus polygenic risk score (fitted-BCSC-PRS) are shown. The p-value shown corresponds to the null hypothesis that the AUROCs between all models are equal

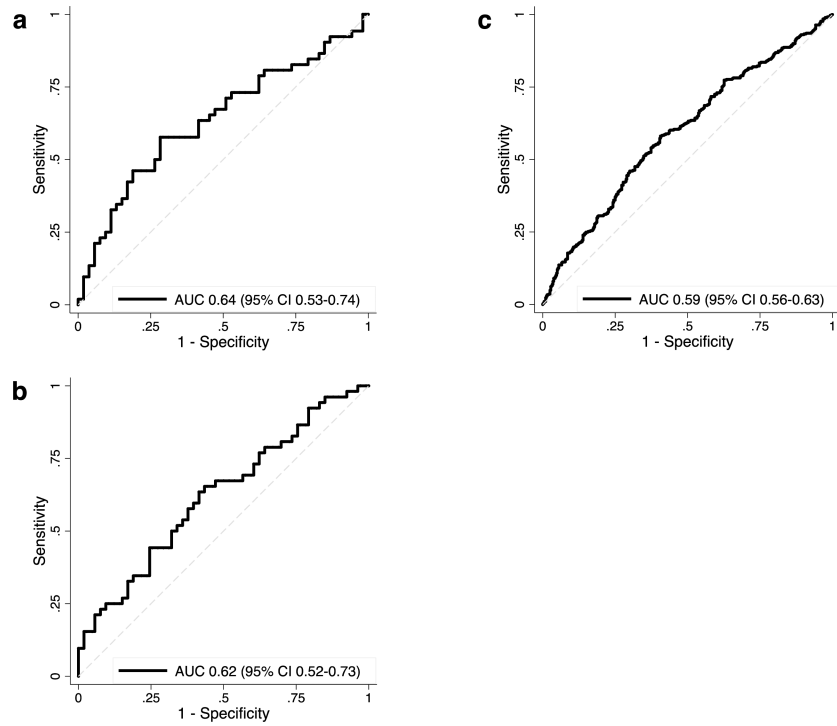


Fig. 2. The receiver operating characteristic curves and corresponding area under the curve (AUC) with 95% confidence interval are shown for (A) the Asian-specific, 76-SNP polygenic risk score in East Asians, (B) the general, 83-SNP polygenic risk score in East Asians, and (C) the general, 83-SNP polygenic risk score in Caucasians

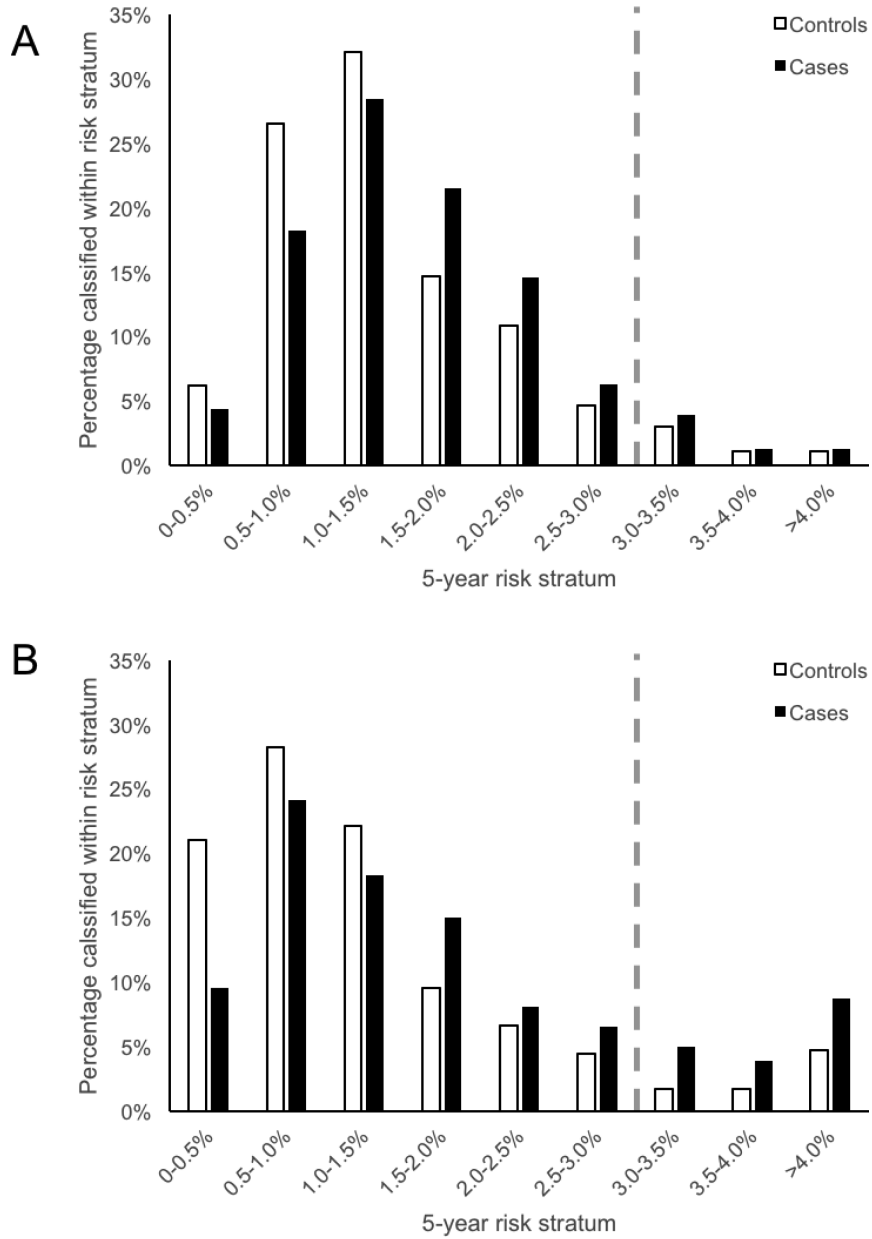


Fig. 3. The percentage of cases and controls within 5-year risk strata according to estimates from two models are shown: (A) the BCSCv2 model, and (B) the BCSCv2-PRS model. The USPSTF recommends consideration of chemoprevention in women with a 5-year risk $\geq 3\%$, represented by the dashed line

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Table 1

Baseline characteristics and demographic data

Characteristic	Controls	Cases	P
Matched variables			
Mean age (range) - years	56 (36-86)	56 (36-86)	
Race - no. (%)			
White	387 (80.3)	387 (80.3)	
Asian	51 (10.6)	51 (10.6)	
Hispanic	10 (2.1)	11 (2.1)	
Black	9 (1.9)	9 (1.9)	
Mixed	23 (4.8)	24 (5.0)	
Other (Non-Asian)	2 (0.4)	1 (0.2)	
Unmatched variables			
First-degree relative with breast cancer - no. (%)	81 (16.8)	137 (28.6)	<0.001
History of breast biopsy - no. (%)	91 (18.9)	129 (26.8)	0.004
Mean Body Mass Index (S.D.)*	24.4 (5.0)	25.1 (4.6)	0.041
Breast density, BIRADS - no. (%)			0.01
a, almost entirely fatty	38 (7.9)	27 (5.6)	
b, scattered areas of fibroglandular density	197 (40.9)	158 (32.8)	
c, heterogeneously dense	192 (39.8)	222 (46.1)	
d, extremely dense	55 (11.4)	75 (15.6)	
BCSC 5-year risk ^a - no. (%)			0.001
Low (0%-<1.00%)	<u>154 (32.7)</u>	<u>104 (22.6)</u>	
Average (1.00%-1.66%)	<u>185 (39.3)</u>	<u>171 (37.2)</u>	
Intermediate (1.67%-2.49%)	<u>86 (18.3)</u>	<u>126 (27.4)</u>	
High (2.50%-3.99%)	<u>41 (8.7)</u>	<u>53 (11.5)</u>	
Very high (4.00%)	<u>5 (1.1)</u>	<u>6 (1.3)</u>	
Mean polygenic risk score (S.D.)	0.97 (0.69)	1.20 (0.85)	<0.001

^aBCSC 5-year risk only calculated in the subset of women age 74 and under

Table 2
Unadjusted and adjusted logistic regression evaluating association of quartiles of polygenic risk score and invasive breast cancer

Characteristic	Unadjusted		Adjusted for family history		Fitted-BCSC model ^a	
	O.R. (95% CI)	P	O.R. (95% CI)	P	O.R. (95% CI)	P
Polygenic Risk Score Quartiles						
<0.57	referent		referent		referent	
0.57 - 0.84	1.34 (0.90 - 2.00)	0.15	1.45 (0.96 - 2.19)	0.074	1.41 (0.92 - 2.16)	0.12
0.84 - 1.26	1.76 (1.18 - 2.62)	0.005	1.89 (1.26 - 2.85)	0.002	1.86 (1.22 - 2.84)	0.004
>1.26	2.54 (1.69 - 3.82)	<0.001	2.67 (1.76 - 4.05)	<0.001	2.51 (1.63 - 3.86)	<0.001
First degree relative with breast cancer	1.89 (1.39 - 2.56)	<0.001	1.92 (1.40 - 2.64)	<0.001	1.71 (1.24 - 2.37)	0.001
History of breast biopsy	1.58 (1.16 - 2.15)	0.004	--	--	1.53 (1.09 - 2.15)	0.013
Breast density, BIRADS						
a, almost entirely fatty	0.88 (0.51 - 1.52)	0.64	--	--	0.80 (0.44 - 1.45)	0.46
b, scattered areas of fibroglandular density	referent				referent	
c, heterogeneously dense	1.51 (1.13 - 2.03)	0.006			1.57 (1.14 - 2.16)	0.006
d, extremely dense	1.95 (1.24 - 3.07)	0.004			2.42 (1.44 - 4.07)	0.001

^a adjusted for first degree relative with breast cancer, history of breast biopsy, body mass index, breast density

Table 3

Areas under the receiver operating characteristic curve for risk models

Model	AUROC*	95% CI
Polygenic risk score (PRS)	0.60	0.57 - 0.64
BCSC model (fitted-BCSC)	0.62	0.59 - 0.66
BCSC model + polygenic risk score (fitted-BCSC-PRS)	0.65	0.61 - 0.68

* p-value < 0.001 for difference across models

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