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Incremental impact of breast cancer SNP panel on risk classification in a screening population of white and African American women

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Abstract

Breast cancer risk prediction remains imperfect, particularly among non-white populations. This study examines the impact of including single nucleotide polymorphism (SNP) alleles in risk prediction for white and African American women undergoing screening mammogram. Using a prospective cohort study, standard risk information and buccal swabs were collected at the time of screening mammography. A 12 SNP panel was performed by deCODE Genetics. Five-year and lifetime risks incorporating SNPs were calculated by multiplying estimated Breast Cancer Risk Assessment Tool (BCRAT) risk by the total genetic risk ratio. Concordance between the BCRAT and the Combined Model (BCRAT + SNPs) in identifying high-risk women was measured using the kappa statistic. SNP data were available for 813 women (39% African American, 55% white). The mean BCRAT 5-year risk was 1.70% for whites and 1.19% for African Americans. Mean genetic risk ratios were 1.10 in whites and 1.29 in African Americans. Among whites, three SNPs had higher frequencies, and among African Americans, seven SNPs had higher and four had lower high-risk allele frequencies than previously reported. Agreement between the BCRAT and the Combined Model was relatively low for identifying high-risk women (5-year κ=0.53, lifetime κ=0.37). Addition of SNPs had the greatest effect among African Americans, with 13% identified as having high 5-year risk by BCRAT, but 33% by the Combined Model. A greater proportion of African Americans were reclassified as having high 5-year risk than whites using the Combined Model (21% vs. 10%). The addition of SNPs to the BCRAT reclassifies the high-risk status of some women undergoing screening mammography, particularly African Americans. Further research is needed to determine the clinical validity and utility of the SNP panel for use in breast cancer risk prediction, particularly among African Americans for whom these risk alleles have generally not been validated.

Keywords

breast cancer; SNPs; risk prediction; African American; race

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Introduction

Accurate risk assessment has the potential to decrease morbidity and mortality from breast cancer by facilitating individualized prevention strategies. Genome-wide association studies (GWAS) have identified several single-nucleotide polymorphisms (SNPs) that increase the risk of breast cancer,[1–12] and panels of SNP markers are now commercially marketed as a way to improve breast cancer risk assessment. SNP panel risk estimates can be combined with existing risk models such as the Breast Cancer Risk Assessment Tool (BCRAT, also known as the Gail model), which uses individual risk factors such as age, family history, reproductive history, and history of breast biopsy or atypical hyperplasia to estimate a woman's absolute risk of breast cancer.[13] The combination of SNP panels with the BCRAT has been shown to at most modestly improve risk prediction.[14–18] SNP panels reclassify some women across risk categories, which may potentially change clinical management.

The BCRAT was originally developed using data from white women, but was subsequently updated and validated for use in African American women. However, the discriminatory accuracy among African American women is lower than among white women.[19] Thus, improving risk prediction among African-American women is a particularly important goal. Although SNP panel markers were identified and validated primarily in white European populations, it is likely that the distribution of risk alleles will vary across populations and lead to differential contributions of SNP risk prediction by race or ethnicity.

In this study we evaluated how the combination of the BCRAT with the 12 SNP panel changed risk stratification in both white and African American women undergoing screening mammography. Although studies attempting to validate these risk variants in women of African descent have yielded mixed results,[20–26] there is insufficient data to estimate race specific effects. Thus, we applied the population level effects for the SNP panel results from published data to both African American and white women to assess the potential reclassification from the current use of SNP panels.

Methods

Participants

Between January 2010 and January 2011, consecutive women aged 40 and older undergoing screening mammography at the Hospital of the University of Pennsylvania were invited to participate in the study. Women with a prior personal history of breast or ovarian cancer, mantle radiation, with a known BRCA 1/2 mutation or with a family member with a BRCA 1/2 mutation were excluded. Approximately 1738 women were invited to participate, of whom 1324 were eligible and 823 women were enrolled. The study was approved by the University of Pennsylvania Institutional Review Board (810985) and written informed consent was obtained from each study participant.

Procedures

Women completed a personal and family health questionnaire as part of screening mammography, including information on race, age at menarche, age at first live birth, number of biopsies, presence of atypical hyperplasia, and family history of breast and ovarian cancer. This information was abstracted from the questionnaires and used to calculate risk of developing breast cancer using the BCRAT. The results of the screening event at which participants were recruited were included in the calculation of the BCRAT risk (for example, if a biopsy resulted from the screening study performed at the time of enrollment, this biopsy and its results were incorporated into the BCRAT). Women completed buccal swabs for DNA collection, which were sent to deCODE Health for analysis using Illumina Infinium II whole-genome genotyping. The deCODE SNP assay included 12 loci which have consistently been associated with breast cancer risk: 2q35 (rs13387042), MRPS30 (rs4415084), FGFR2 (rs1219648), TNRC9/TOX3 (rs3803662), 8q24 (rs13281615), LSP1 (rs3817198), 5q11 (rs889312), NEK10 (rs4973768), 1p11 (rs11249433), RAD51L1 (rs999737), COX11 (rs6504950), CASP8 (rs1045485).[1–6,11,12]

Analysis

Three women with insufficient data to calculate BCRAT risk and seven women with incomplete SNP data were excluded from analysis, leaving a study population of 813. Body mass index was calculated from self-reported weight and height. Two sample t-tests and Chi squared tests were used to compare baseline characteristics for white and African American women. Individual risk alleles for each patient as well as a final risk score were provided by deCODE which used published odds ratios for high-risk variants along with the population frequencies to calculate a single risk ratio summarizing all 12 SNPs. Each SNP was tested for deviations from Hardy-Weinberg equilibrium in the total population and by race. Using one-sample t-tests, we compared the frequency of each high-risk allele to the expected frequency from deCODE. Adjusted 5-year and lifetime absolute risks were then calculated by multiplying the BCRAT risk by the total genetic risk ratio from the SNP panel, which has been shown to be an appropriate alternative to adjusting the BCRAT model for SNP relative risks, particularly when calculating 5-year risk estimates.[18] However, this multiplication method overestimates the lifetime risk at high risk levels. Two sample t-tests were used to compare the mean risk scores by race. Elevated risk was defined as a 5-year risk greater than or equal to 1.7% or a lifetime risk greater than or equal to 20%. Finally, Cohen’s Kappa was used to assess agreement between the BCRAT risk alone and the BCRAT risk combined with the SNP panel. All statistical tests were performed using R software (version 12.0).

Results

The descriptive characteristics of the study population are shown in Table 1. Overall, the mean age of study participants was 52 years. Approximately 28% of participants reported a prior biopsy, but only 6 women reported atypical hyperplasia on the biopsy. Fifty-five percent of women were white, 39% were African American, 1% was Hispanic, 1% was Asian, and 5% identified as other race/ethnicity. With the exception of first degree relatives with breast cancer, all baseline characteristics differed significantly between whites and African Americans. The majority of women had mammograms that were BIRADS 1 or 2

(89%). Very few women had results of BIRADS 3 or greater (<1%). Ten percent of women had BIRADS 0 mammograms, requiring additional imaging, and 22 women (3%) had a biopsy. One woman was diagnosed with atypical hyperplasia, three were diagnosed with intraductal carcinoma, and three were diagnosed with invasive breast cancer. Mammogram results did not differ significantly by race.

Each of the 12 SNPs was tested for Hardy-Weinberg Equilibrium, and there were no significant deviations for the total population or by race (data not shown). We compared the frequencies of high-risk alleles for our study population to the deCODE expected frequencies (Table 2). In white women, 3 SNPs had significantly higher than expected frequencies of high-risk alleles (rs13281615, rs3803662, rs4973768). In African American women, seven high-risk alleles had significantly higher than expected frequencies (rs1045485, rs1219648, rs13387042, rs3803662, rs4415084, rs889312, rs999737), and four had significantly lower than expected frequencies (rs11249433, rs3817198, rs4973768, rs6504950).

Table 3 displays the average relative risk from the SNP panel, the average absolute risk from the BCRAT, and average absolute risk from the combined BCRAT model and SNP panel (Combined Model). Based on the SNP panel, the average relative risk of breast cancer in the study population was 1.17, meaning a 17% increased risk based on genetic profile. Using the BCRAT, the average 5-year breast cancer risk was 1.47% and the average lifetime risk was 10.56%. When the BCRAT and SNP panel risk estimates were combined, the average 5-year risk of breast cancer increased to 1.72% and the lifetime risk increased to 12.31%. Risk estimates differed significantly by race ($p<0.001$). White women had higher average risk estimates from the BCRAT model, while African American women had a higher average relative risk from the SNP panel. In the Combined Model, white women had higher average risk than African American women.

Elevated risk of breast cancer was defined as a 5-year risk greater than or equal to 1.7% or a lifetime risk greater than or equal to 20%. Among white women, the proportion with elevated 5-year risk was similar using the BCRAT and the Combined Model (Table 4, 41.5% vs. 41.3%). Among African American women, the percentage with elevated 5-year risk increased from 12.7% using the BRCAT to 32.9% using the Combined Model. For both white and African American women the lifetime risk estimates were higher using the Combined Model than the BCRAT alone. Six percent of white women had elevated lifetime risk using the BCRAT model, compared with 12.5% using the Combined Model. Only one African American woman was classified as having elevated lifetime risk using the BCRAT, compared with 5.7% using the Combined Model. Twenty-one percent of African American women were reclassified as having elevated 5-year risk of breast cancer with the Combined Model compared to only 10% of white women ($p<0.001$). There was no difference in the percent of women reclassified as having high lifetime breast cancer risk between African American and white women (5.4% vs. 7.8%, $p=0.195$)

In the total study population, there was fair agreement between the BCRAT and the Combined Model for 5-year risk ($\kappa=0.543$) and poorer agreement for lifetime risk ($\kappa=0.372$), and in both cases the Combined Model was more likely to classify individuals as

having elevated risk than the BCRAT alone ($p<0.001$). Among whites there was fair agreement for both 5-year ($\kappa=0.582$) and lifetime risk ($\kappa=0.462$), and the Combined Model was more likely to classify individuals as having elevated lifetime risk than the BCRAT alone ($p<0.001$). Among African Americans, there was fair agreement between the models for elevated 5-year risk ($\kappa=0.432$) but poor agreement for lifetime risk ($\kappa=0.010$). For both 5-year and lifetime risk, the Combined Model was significantly more likely to classify individuals as having elevated risk compared with the BCRAT alone ($p<0.001$). The results were similar in sensitivity analyses excluding women age 60 and older. We also calculated percent positive agreement, due to concern about small cell sizes[27], however the interpretations were similar to those using Kappa.

Discussion

Our results highlight that the addition of SNP information to the BCRAT reclassifies the risk status of some women in a screening mammography population. In particular, a significantly larger percentage of African American women were re-classified as high-risk when the 12 SNP panel was combined with the BCRAT. For 11 of the 12 SNPs in the panel, allelic frequencies for African American women were significantly different than the reported frequencies in white women. These results suggest that SNP panels have the potential to play a more important role in risk prediction among African American than white women and highlight the pressing need for studies of breast cancer SNP panels in minority populations to determine if this reclassification is clinically valid.

Though the BCRAT is widely used to estimate individual breast cancer risk, its discriminatory accuracy is limited, particularly in African American women. When the BCRAT was recalibrated for African Americans, the relative risk estimates for most risk factors were lower for African American than for white women.[19] In other words, the risk factors explained a smaller proportion of the cancer burden in African American women than white women. The average age-specific AUC, or probability that a randomly selected case had a higher predicted risk than a randomly selected control, was 0.555 for African American women, which was lower than the discriminatory accuracy of the original BCRAT model (0.596)[19], and highlights significant room for improvement in breast cancer risk prediction, particularly for African American women.

Our results suggest that the use of SNP panels may increase the proportion of African American women classified as high-risk of breast cancer compared to the BCRAT alone, but future validation is needed to determine whether this re-classification is correct. Validation studies of the 12 SNP panel in African American women are ongoing, but several studies have examined the associations of individual SNPs with breast cancer risk, with mixed results.[20,22–24,26,28–30] Relative risk estimates for rs13387042 (2q35) in African American women were similar to relative risk estimates used for the SNP panel in two studies.[21,22] An additional two studies found rs1219648 (FGFR2) to be significantly associated with increased breast cancer risk in African American women, with higher relative risk estimates than the SNP panel.[20,22] The association of rs4415084 (5p12, FGF10) with increased breast cancer risk was of borderline significance overall, but strongly associated with ER positive breast cancer in African American women.[28] If these higher relative risks represent the true

association in African American women, risk stratification for African American women from the SNP panel would be underestimated. The T allele of rs3803662 (16q12, TOX3) was significantly associated with a decreased breast cancer risk in African American women, while this allele has been associated with increased risk in white women[23]. If this association were true, then our risk stratification from the 12 SNP panel may be overestimated. Several studies have failed to detect significant associations with rs13387042[20,23,26], rs1219648 [23,24,26], rs3803662[20,21,26,29], and rs4415084[21,26]. The eight remaining SNPs in the panel have not been replicated as significantly associated with breast cancer risk in any studies of African American populations (rs1045485[20], rs11249433[21,23,26], rs13281615[20–23,26], rs3817198[20,21,23,26], rs4973768[21,23,26], rs6504950[23,26], rs889312[20,21,23,24,26], rs999737[21,26]). A recent study examining 19 loci in women of African ancestry failed to validate any high-risk SNPs from previous GWAS.[26]

Several challenges to genetic susceptibility studies in African American women complicate the validation of the 12 SNP panel. First, given that the 12 SNPs in the panel have modest effect sizes, a large sample size of minority women is needed to have sufficient statistical power to detect associations. Second, the SNPs in the panel may be causal variants or they may be in linkage disequilibrium with causal variants. When SNP analysis is shifted to an African American population, the tagging relationship between the genotyped SNP and the risk variant may be disrupted, as a result of differing patterns of linkage disequilibrium between ancestral populations. Third, disease heterogeneity likely complicates both risk prediction and SNP validation. African American women are more likely than white women to develop triple negative cancers, which are believed to be etiologically different from hormone receptor positive cancers.

Population stratification and admixture are additional challenges when attempting to validate breast cancer risk variants in African Americans. We used self-reported race/ethnicity in our study, which may not sufficiently capture an individual's ancestral background. For example, the degree of West African versus European ancestry varies across individuals and across subpopulations of African Americans[31], and such population stratification can bias associations between SNPs and disease outcomes.[32] Ancestral informative makers (AIMs) can be used to identify individual ancestry and can be controlled for in studies of disease susceptibility SNPs.[33] Most of the studies referenced above adjusted for AIMs in the analysis. It is unclear whether the inclusion of AIMs improves prediction of breast cancer risk amongst African Americans.

For all of these reasons, future research is needed to clarify the clinical validity and utility of breast cancer associated SNPs in African American women, and SNP panels predictive of breast cancer risk in African American women should be explored.

A strength of our study is the inclusion of large number of African American participants. In addition, we obtained detailed information on breast cancer risk factors allowing us to calculate risk estimates using the BCRAT for each participant. Several limitations of our study should be noted. First, we used a simple multiplication of the BCRAT absolute risk and the total genetic relative risk ratio, which has been shown to be valid for 5-year risk, but may overestimate lifetime risk estimates at high risk levels.{Mealiffe, 2010 #51} Therefore

the lifetime risk estimates and proportions of individuals with high lifetime risk may be slightly elevated, and this may partly explain the poorer agreement between lifetime BCRAT and Combined models as compared to 5-year risks. Few African American women were classified as high-risk by either the BCRAT or Combined Models, and therefore our estimates of agreement are based on small numbers. In addition, because this study cohort was recently enrolled, we do not yet have information on long term cancer outcomes and therefore cannot validate the SNP panel. We plan to continue prospective follow-up of this cohort in order to evaluate and develop better risk stratification tools.

Identifying women with elevated risk for breast cancer can facilitate tailored preventive interventions[34–38], and the use of novel genetic markers has the potential to improve such risk stratification. Given the gaps in knowledge about breast cancer associated SNPs among African Americans and the burden of disease in this population, validation and identification of breast cancer associated SNP panels in African Americans should be a priority. This will require large pooled analyses of multiple GWAS studies in order to achieve sample sizes large enough to detect SNPs with moderate to small relative risks.

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Table 1

Characteristics of the Study Population, N=813

	Total (N=813)		White (N=448)		African American (N=316)		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P-value***
Age (years)	52.0	7.4	52.8	7.3	51.4	7.5	0.014
BMI (kg/m^2)	28.2	7.0	25.9	6.0	31.9	7.0	<0.001
	N	**%**	**N**	**%**	**N**	**%**	
Ashkenazi Jewish	63	7.8	62	13.8	0	0	---
Previous Biopsies							
0	574	70.6	295	65.9	236	74.7	0.012
1	154	18.9	91	20.3	58	18.4	
2 or more	77	9.5	57	12.7	19	6.0	
Unknown	8	1.0	5	1.1	3	1.0	
1° Relatives with Breast Cancer							
0	675	83.0	365	81.5	268	84.8	0.412
1	127	15.6	75	16.7	46	14.6	
2 or more	11	1.3	8	1.8	2	0.6	
2° Relatives with Breast Cancer							
0	634	78.0	333	74.4	260	82.3	0.019
1	136	16.7	91	20.3	38	12.0	
2 or more	42	5.2	24	5.3	17	5.4	
Unknown	1	0.1	0	0	1	0.3	
HRT use							
Never	658	80.9	330	73.7	283	89.6	<0.001
Past	98	12.1	68	15.2	27	8.5	
Current	47	5.8	43	9.6	3	1.0	
Unknown	10	1.2	7	1.6	3	1.0	
Age at Menarche							

	Total (N=813)		White (N=448)		African American (N=316)		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P-value***
<12	131	16.1	59	13.2	59	18.7	<0.001
12	207	25.5	132	29.5	67	21.2	
13	182	22.4	113	25.2	61	19.3	
14 or older	152	18.7	85	19.0	59	18.7	
Unknown	141	17.3	59	13.2	70	22.2	
Results of Mammogram							
BIRADS 0	83	10.2	44	9.8	35	11.1	0.645
BIRADS 1	606	74.5	336	75.0	233	73.7	
BIRADS 2	120	14.8	65	14.5	48	15.2	
BIRADS 3	2	0.25	2	0.5	0	0.0	
BIRADS 4	2	0.25	1	0.2	0	0.0	
Biopsy	22	2.7	8	1.8	10	3.2	0.459
Final Results of Screening							
BIRADS 1	633	77.9	350	78.1	245	77.5	0.403
BIRADS 2	140	17.2	78	17.4	55	17.4	
BIRADS 3	16	2.0	12	2.7	4	1.3	
Benign	15	1.9	6	1.3	6	1.9	
Atypical Hyperplasia	1	0.1	0	0.0	1	0.3	
Intraductal Carcinoma	3	0.4	0	0.0	2	0.6	
Invasive Carcinoma	3	0.4	1	0.2	2	0.6	
Lost to follow-up (BIRADS 0)	2	0.3	1	0.4	1	0.3	

* p-value comparing White to African American women

Table 2

Expected and Observed Allele frequencies

SNP	Risk Allele	Homozygote Relative Risk	Expected Allele Frequency	Total N=814	White N=449	White *p-value**	African American N=316	African American *p-value**
rs1045485 (CASP8)	G	1.03	0.870	0.899	0.872	0.888	0.937 ↑	<0.001
rs11249433 (1p11.2)	C	1.18	0.390	0.298	0.412	0.183	0.144 ↓	<0.001
rs1219648 (10q26, FGFR2)	G	1.31	0.380	0.402	0.396	0.317	0.421 ↑	0.030
rs13281615 (8q24.21)	G	1.10	0.400	0.446	0.462 ↑	<0.001	0.418	0.364
rs13387042 (2q35)	A	1.19	0.497	0.592	0.525	0.113	0.703 ↑	<0.001
rs3803662 (16q12, TOX3)	T	1.42	0.269	0.402	0.313 ↑	0.006	0.535 ↑	<0.001
rs3817198 (11p15, LSP1)	C	1.10	0.300	0.258	0.321	0.172	0.161 ↓	<0.001
rs4415084 (5p12, FGF10)	T	1.19	0.396	0.487	0.398	0.881	0.604 ↑	<0.001
rs4973768 (3p24, SLC4A7)	T	1.12	0.460	0.464	0.532 ↑	<0.001	0.369 ↓	<0.001
rs6504950 (17q23.2, STXBP4)	G	1.03	0.720	0.717	0.742	0.126	0.671 ↓	0.013
rs889312 (5q11.2, MAP3K1)	C	1.19	0.280	0.324	0.305	0.101	0.340 ↑	0.001
rs999737 (14q24.1, RAD51B)	C	1.06	0.760	0.853	0.778	0.204	0.957 ↑	<0.001

* p-value from one-sample t-test comparing observed to expected frequency

Table 3

Risk estimates from SNP panel, Breast Cancer Risk Assessment Tool (BCRAT), and combined estimates

	Total (N=813)		White (N=448)		African American (N=316)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
SNP Panel RR	1.17	0.42	1.10	0.40	1.29	0.42
BCRAT 5-year risk	1.47%	0.82	1.70%	0.94	1.19%	0.50
BCRAT 5-year + SNPs	1.72%	1.28	1.90%	1.54	1.52%	0.79
BCRAT lifetime risk	10.56%	4.31	12.03%	4.69	8.45%	2.61
BCRAT lifetime + SNPs	12.31%	7.19	13.29%	8.19	10.94%	5.30

* Significant differences between White and African American for all models, $p<0.001$

Table 4

Elevated 5-year and lifetime risk estimates by race from the Breast Cancer Risk Assessment Tool (BCRAT), and from BCRAT Combined with SNP panel risk estimate

	BCRAT			Combined BCRAT + SNP panel		
	White N (%)	African American N (%)	p-value	White N (%)	African American N (%)	p-value
5-year risk ≥1.7%	186 (41.5%)	40 (12.7%)	<0.001	185 (41.3%)	104 (32.9%)	0.019
Lifetime risk ≥20%	27 (6.0%)	1 (0.3%)	<0.001	56 (12.5%)	18 (5.7%)	0.002

Table 5

Comparisons of risk estimates from the Breast Cancer Risk Assessment Tool (BCRAT) and from the Combined BCRAT + SNP Panel

All Participants (N=813)

Elevated 5-year Risk		BCRAT + SNP Panel	
		No	Yes
BCRAT	No	458	117
	Yes	51	187

Kappa = 0.534; McNemar's p-value <0.001

Percent reclassified as high-risk: 14.4%

Elevated Lifetime Risk		BCRAT + SNP Panel	
		No	Yes
BCRAT	No	726	59
	Yes	6	22

Kappa = 0.372; McNemar's p-value <0.001

Percent reclassified as high-risk: 7.3%

White (N=448)

Elevated 5-year Risk		BCRAT + SNP Panel	
		No	Yes
BCRAT	No	217	45
	Yes	46	140

Kappa = 0.581; McNemar's p-value = 0.917

Percent reclassified as high-risk: 10.0%

Elevated Lifetime Risk		BCRAT + SNP Panel	
		No	Yes
BCRAT	No	386	35
	Yes	6	21

Kappa = 0.462; McNemar's p-value <0.001

Percent reclassified as high-risk:7.8%

African American (N=316)

Elevated 5-year Risk		BCRAT + SNP Panel	
		No	Yes
BCRAT	No	210	66
	Yes	2	38

Kappa = 0.422; McNemar's p-value <0.001

Percent reclassified high-risk: 20.9%

Elevated Lifetime Risk		BCRAT + SNP Panel	
		No	Yes
BCRAT	No	298	17
	Yes	0	1

Kappa = 0.100; McNemar's p-value <0.001

Percent reclassified as high-risk: 5.4%