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Combined Associations of a Polygenic Risk Score and Classical Risk Factors With Breast Cancer Risk

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Abstract

We evaluated the joint associations between a new 313-variant PRS (PRS_{313}) and questionnaire-based breast cancer risk factors for women of European ancestry, using 72 284 cases and 80 354 controls from the Breast Cancer Association Consortium. Interactions were evaluated using standard logistic regression and a newly developed case-only method for breast cancer risk overall and by estrogen receptor status. After accounting for multiple testing, we did not find evidence that per-standard deviation PRS_{313} odds ratio differed across strata defined by individual risk factors. Goodness-of-fit tests did not reject the assumption of a multiplicative model between PRS_{313} and each risk factor. Variation in projected absolute lifetime risk of breast cancer associated with classical risk factors was greater for women with higher genetic risk (PRS_{313} and family history) and, on average, 17.5% higher in the highest vs lowest deciles of genetic risk. These findings have implications for risk prevention for women at increased risk of breast cancer.

Precision prevention and early detection of cancer is a key aim of cancer research and uses tools such as risk prediction models for risk stratification (1,2). Many breast cancer risk prediction models are focused either on classical risk factors or on inherited mutations causing a moderate-to-high risk of cancer and do not include risk associated with common susceptibility variants (3). Modeling the joint associations of genetic and classical risk factors could result in substantial improvement in risk stratification and therefore improved prevention and screening modalities for breast cancer (4–7).

Combined associations of single nucleotide polymorphisms (SNPs) can be summarized by a polygenic risk score (PRS); women in the top 1% of the newly derived 313-SNP PRS (PRS_{313}) have a fourfold increased risk of breast cancer than women at population-average risk (8). Previous studies, which evaluated combined associations between classical risk factors and breast cancer PRS based on 77 SNPs (9) and 24 SNPs (10), found weak or no evidence of departure from the multiplicative risk assumption for overall breast cancer. In the current study, we extend these analyses to assess the combined associations of the PRS_{313} and classical risk factors using data from the Breast Cancer Association Consortium (BCAC). This new PRS has been validated by prospective studies and shown to be more predictive than the previously reported 77-SNP PRS (11) for risk of breast cancer overall as well as for estrogen receptor (ER) subtype-specific breast cancer (8). Additionally, this study found evidence of interaction for ER-positive disease between PRS_{313} and family history, indicating the need to consider the joint effects of these 2 factors (8).

Detailed information on study samples, genetic data, and risk factor data is provided in the Supplementary Materials (available online). Briefly, we performed analyses using data from women of European ancestry from 16 prospective cohorts, 14 population-based case-control studies, and 16 nonpopulation-based studies included in BCAC (Supplementary Table 1, available online). Samples were genotyped using 2 arrays: iCOGS (12) and OncoArray (13–15). Risk factor data were derived with respect to a reference age (date at diagnosis for cases and date at interview for controls). Development of the PRS is briefly explained in Supplementary Materials (available online) (8). We standardized the PRS to have unit standard deviation for the controls.

Departure from the assumption of multiplicative combined effects of standardized PRS_{313} and each risk factor was assessed using two methods: unconditional logistic regression model and likelihood ratio test, and a newly developed case-only method, which assumes independence between PRS and risk factors in the underlying population and has greater efficiency compared with logistic regression (16). Individual models were fitted for each PRS-risk factor combination for overall and ER-specific breast cancer. Models were adjusted for reference age, study, and corresponding 10 ancestry-informative principal components for each array. Array-specific results were meta-analyzed using a fixed-effect inverse-variance weighted method. To evaluate global goodness-of-fit of the multiplicative model between PRS_{313} and each risk factor, we performed the Hosmer-Lemeshow test using population-based studies. Moreover, we assessed goodness-of-fit at the extremes of the distribution (tails) using a tail-based test (17). Using the iCARE-BPC3 model (4), we projected absolute lifetime risk of breast cancer for 50-year-old white non-Hispanic US women up to aged 80 years. We assessed the distribution of risk because of classical (ie, menstrual and reproductive and lifestyle) and modifiable risk factors, respectively, within categories of risk defined by genetic factors (ie, breast cancer family history and PRS_{313}).

Associations between PRS_{313} and overall and ER-specific breast cancer risk are likely to be overestimated because there was substantial overlap between the SNP discovery samples and our dataset (Supplementary Figure 1, available online). The number of cases and controls varied for each risk factor, ranging from 61 617 cases and 74 698 controls for ever parous to 14 576 cases and 19 640 controls for pack-years smoked for overall breast cancer risk (Supplementary Table 2, available online). Based on the population-based case-control and prospective cohort studies, the associations of the risk factors with overall and ER subtype-specific breast cancer were of the expected magnitude and direction (Supplementary Table 3, available online).

After accounting for multiple testing using Bonferroni adjustment ($P_{int} < .05/16 = .003$), none of the interactions between PRS_{313} and any classical risk factor was statistically significant except for family history (Table 1). All statistical tests were 2-

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Table 1. Odds ratios and 95% confidence intervals for multiplicative interactions between the 313-SNP PRS (continuous) and classical risk factors of breast cancer, overall and by ER status

		Case-control logistic regression method[a,c]									Case-only linear regression method[a,b,c]					
		Overall breast cancer risk			ER-positive breast cancer risk			ER-negative breast cancer risk			Overall breast cancer risk		ER-positive breast cancer risk		ER-negative breast cancer risk	
Risk factors	Controls	Cases	OR_{int} (95% CI)	P_{int}	Cases	OR_{int} (95% CI)	P_{int}	Cases	OR_{int} (95% CI)	P_{int}	OR_{int} (95% CI)	P_{int}	OR_{int} (95% CI)	P_{int}	OR_{int} (95% CI)	P_{int}
Age at menarche (per 2 years)	64 087	52 170	1.01 (0.99 to 1.03)	.26	36 820	1.01 (0.99 to 1.03)	.29	8323	1.01 (0.98 to 1.04)	.55	1.01 (1.00 to 1.02)	.22	1.01 (0.99 to 1.02)	.37	1.02 (0.99 to 1.06)	.21
Ever parous (yes/no)	72 552	59 298	0.97 (0.93 to 1.00)	.07	41 858	0.98 (0.94 to 1.02)	.35	9273	0.98 (0.92 to 1.05)	.57	0.97 (0.94 to 1.00)	.08	0.99 (0.96 to 1.03)	.72	1.00 (0.92 to 1.09)	.97
Number of children (1, 2, 3, ≥4)[d]	61 654	48 786	1.00 (0.99 to 1.02)	.96	34 666	1.00 (0.99 to 1.02)	.73	7552	0.99 (0.96 to 1.02)	.53	1.01 (0.99 to 1.02)	.38	1.01 (1.00 to 1.03)	.11	1.00 (0.97 to 1.04)	.90
Age at FFTP (per 5 years)[d]	53 042	41 671	1.00 (0.99 to 1.02)	.82	29 601	1.00 (0.98 to 1.01)	.68	6517	0.99 (0.96 to 1.02)	.52	1.00 (0.98 to 1.01)	.39	0.99 (0.97 to 1.00)	.06	1.00 (0.97 to 1.03)	.92
Breastfeeding (yes/no)[d]	37 568	34 199	1.02 (0.98 to 1.06)	.44	24 273	1.01 (0.96 to 1.05)	.81	5548	1.01 (0.95 to 1.08)	.74	1.02 (0.99 to 1.05)	.17	1.02 (0.98 to 1.06)	.36	1.02 (0.95 to 1.11)	.55
Duration of breast feeding (per 12 mo)[d]	26 367	27 741	1.00 (0.98 to 1.02)	.71	19 329	1.00 (0.97 to 1.02)	.76	4669	0.99 (0.95 to 1.03)	.57	1.01 (0.99 to 1.03)	.32	1.01 (0.99 to 1.03)	.57	0.99 (0.96 to 1.03)	.77
Adult height (per 5 cm)	62 414	54 847	0.99 (0.98 to 1.00)	.07	38 730	0.99 (0.98 to 1.00)	.04	8682	1.00 (0.98 to 1.02)	.77	1.00 (0.99 to 1.01)	.92	0.99 (0.98 to 1.01)	.29	1.01 (0.99 to 1.03)	.48
Premenopausal BMI (per 5 kg/m^2)[e]	15 610	12 837	0.98 (0.95 to 1.00)	.08	8354	0.99 (0.96 to 1.02)	.48	2333	0.95 (0.91 to 1.00)	.04	0.97 (0.94 to 1.00)	.02	1.00 (0.96 to 1.03)	.77	0.95 (0.89 to 1.01)	.10
Postmenopausal BMI (per 5 kg/m^2)[f]	46 137	37 088	1.01 (0.99 to 1.02)	.49	27 305	1.01 (0.99 to 1.02)	.39	5260	1.01 (0.99 to 1.04)	.36	1.01 (1.00 to 1.02)	.29	1.01 (1.00 to 1.03)	.08	0.99 (0.96 to 1.02)	.45
Ever use of oral contraceptives (yes/no)	56 768	44 979	1.01 (0.98 to 1.04)	.63	31 640	1.02 (0.98 to 1.05)	.36	7061	1.02 (0.97 to 1.08)	.42	0.99 (0.97 to 1.02)	.45	1.00 (0.97 to 1.02)	.75	1.01 (0.95 to 1.08)	.73
Current use of EPT (yes/no)[f,g]	20 896	19 047	1.07 (1.01 to 1.14)	.02	14 465	1.06 (0.99 to 1.13)	.08	2761	1.05 (0.92 to 1.19)	.49	1.00 (0.96 to 1.04)	.93	0.98 (0.93 to 1.03)	.32	1.04 (0.91 to 1.18)	.59
Current use of ET (yes/no)[f,g]	20 716	18 716	0.97 (0.91 to 1.03)	.33	14 201	0.96 (0.90 to 1.03)	.28	2733	1.06 (0.94 to 1.20)	.37	0.96 (0.91 to 1.01)	.09	0.94 (0.89 to 0.99)	.03	1.08 (0.95 to 1.23)	.26
Alcohol consumption (per 10 g/day)	16 851	14 484	1.00 (0.97 to 1.02)	.75	10 253	0.98 (0.96 to 1.00)	.07	2259	1.06 (1.01 to 1.11)	.03	1.00 (0.99 to 1.02)	.71	0.99 (0.97 to 1.01)	.19	1.04 (1.00 to 1.08)	.06
Current smoking (yes/no)[h]	56 308	43 303	1.04 (1.00 to 1.08)	.07	30 486	1.05 (1.00 to 1.10)	.03	6813	1.05 (0.97 to 1.13)	.25	1.02 (0.98 to 1.05)	.42	1.02 (0.98 to 1.06)	.40	1.03 (0.95 to 1.11)	.52
Pack-years of smoking (per 10 pack-years)[i]	15 990	11 766	0.99 (0.98 to 1.01)	.43	8268	0.99 (0.97 to 1.01)	.19	1778	0.99 (0.96 to 1.02)	.67	1.00 (0.99 to 1.01)	.97	1.00 (0.99 to 1.01)	.99	1.00 (0.97 to 1.03)	.97
Family history in a first-degree relative (yes/no)[j]	50 955	42 024	0.93 (0.89 to 0.96)	3.00×10^{-5}	28 909	0.93 (0.90 to 0.97)	8.00×10^{-4}	6921	0.93 (0.87 to 0.99)	.03	—	—	—	—	—	—

[a]Number of cases are same for case-control and case-only method. PRS = polygenic risk score; SNP = single nucleotide polymorphisms; ORint = interaction odds ratio (per SD of PRS_{313}); CI = confidence intervals; FFTP = first full-term pregnancy; BMI = body mass index; EPT = estrogen-progesterone therapy; ET = estrogen-only therapy; ER = estrogen receptor; MHT = menopausal hormonal therapy.
[b]The case-only analyses do not provide additional evidence to case-control analyses.
[c]Models are adjusted for reference age, study, and 10 ancestry-informative principal components.
[d]Among parous women.
[e]Among premenopausal women.
[f]Among postmenopausal women.
[g]Models used to assess association with the use of MHT have been further adjusted for former use of MHT and use of any other type MHT preparations.
[h]Models used to assess association with current smoking have been further adjusted for former smoking.
[i]Among ever smoked.
[j]PRS and family history are not independent; therefore, case-only analyses were not conducted for family history.

sided. The observed interaction between PRS_{313} and family history for ER-positive breast disease is consistent with what has been previously published based on an overlapping dataset (8). Such an interaction was also found for overall and ER-negative breast cancer risk. There was no evidence for a clear dose-response in the estimated ORs associated with classical risk factors when stratified by PRS percentiles (Supplementary Figures 2–4, available online). Neither global nor tail-based goodness-of-fit tests supported departure from the multiplicative model for any risk factor for both overall and ER-positive breast cancer (Supplementary Table 4, available online). Goodness-of-fit tests were not performed for ER-negative breast cancer because of the relatively small sample size.

Lack of evidence for substantial departure from the multiplicative assumption between the PRS_{313} and risk factors using this large study implies that the absolute risk associated with each classical risk factor is greater for women with higher polygenic risk (5,18). This is illustrated by our projections, which show that the lifetime risk due to classical risk factors was higher with a wider variation across women who are at a higher risk due to genetic factors (PRS_{313} and family history) (Figure 1, a) and consistent with a recent study of body mass index combined with a measure of familial risk based on multigenerational family history (18). The predicted average lifetime risk due to all classical risk factors for women in the lowest and highest deciles of the genetic risk was 21.9% and 4.4%, respectively, so the difference in risk was 17.5%. The difference in risk between these 2 deciles associated with the subset of modifiable risk factors was 16.5% (Figure 1, b). However, the absolute risk projections shown in Figure 1 should be viewed with caution because they assume perfect model calibration. In addition, these absolute risk projections require validation.

Our analyses using the current PRS_{313} are based on a sample size 3 times larger than that used in previously published BCAC analyses (9), although the dataset for ER-negative breast cancer is still limited. Our previous work on the PRS_{313} development (8) and the current analyses is based on European ancestry and may not be generalizable to other populations, highlighting the need for more studies in populations of non-European or mixed ancestry.

Overall, the combined associations of the newly developed PRS_{313} and the classical risk factors on breast cancer risk are well explained by a multiplicative model, except for family history, and will inform the development of overall and ER-specific risk prediction models in the future. Most important, our findings suggest that preventive strategies aimed at modifying individual risk factors could have stronger impact on absolute risk reduction for women at higher genetic risk.

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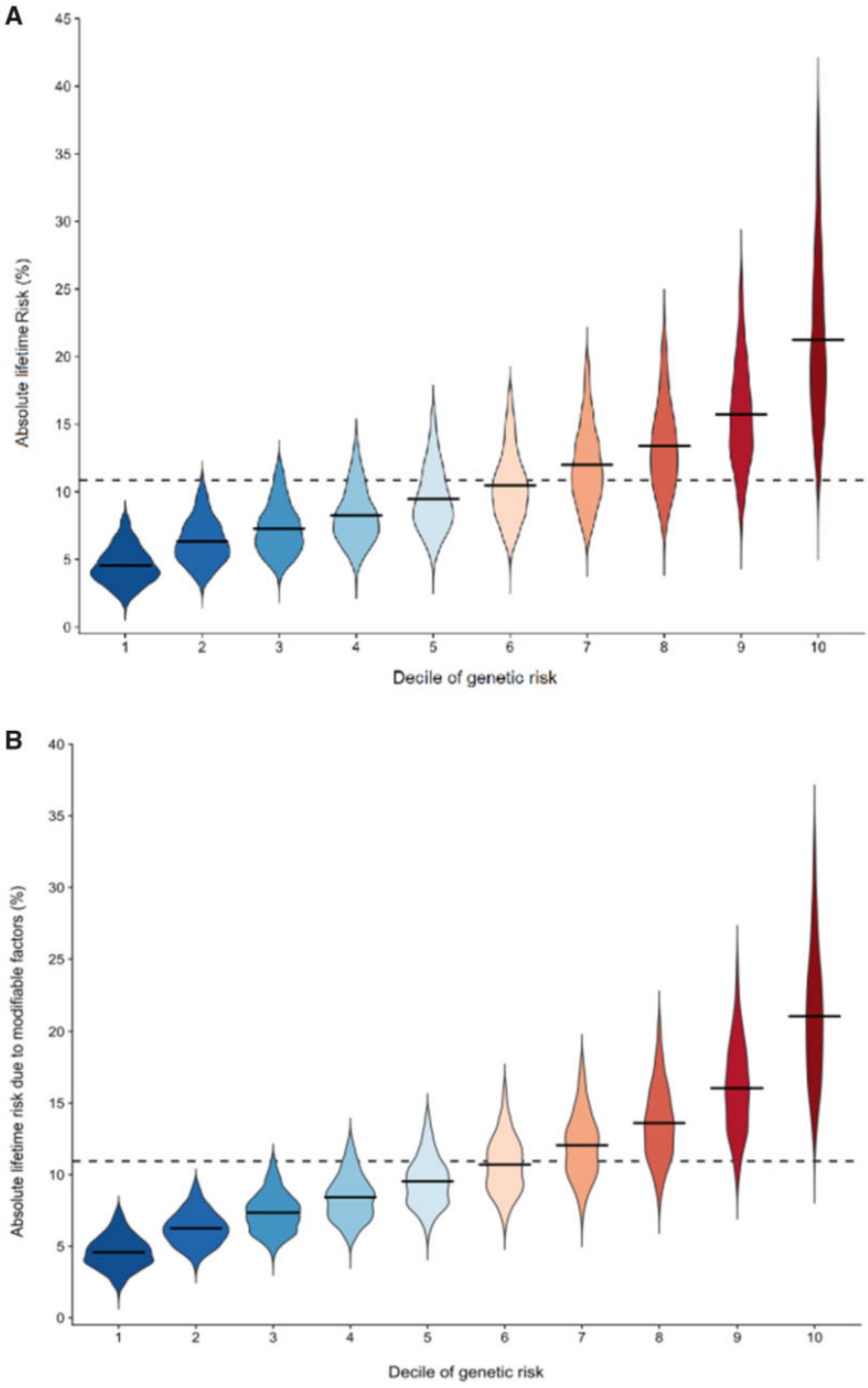

Figure 1. Distribution of absolute lifetime risk explained by **(a)** all classical risk factors and **(b)** modifiable classical risk factors within decile categories of genetic risk, due to 313-variant polygenic risk score (PRS) and family history, for 50-year-old white non-Hispanic women in the United States before aged 80 years. The **solid horizontal lines** represent the mean risk within each decile, and the **dashed horizontal line** across the plot represents the population lifetime mean risk (10.9%). Lifetime risk is estimated using the iCARE-BPC3 model and refers to absolute risk from aged 50 to 80 years. The genetic component includes the 313-variant PRS and breast cancer family history. The classical risk factor component includes the following risk factors: age at menarche, age at menopause, parity, age at first birth, height, body mass index (BMI), alcohol intake, smoking status, ever and current use of hormone replacement therapy (HRT), and HRT type among ever users. The modifiable classical risk factor component includes BMI, ever or current use of HRT, smoking status, and alcohol consumption. Outliers defined as points beyond 1.5 times the interquartile range below the first quartile or above the third quartile were excluded from the plot.

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