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Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in *BRCA1* and *BRCA2* Mutation Carriers

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Abstract

Background: Genome-wide association studies (GWAS) have identified 94 common single-nucleotide polymorphisms (SNPs) associated with breast cancer (BC) risk and 18 associated with ovarian cancer (OC) risk. Several of these are also associated with risk of BC or OC for women who carry a pathogenic mutation in the high-risk BC and OC genes BRCA1 or BRCA2. The combined effects of these variants on BC or OC risk for *BRCA1* and *BRCA2* mutation carriers have not yet been assessed while their clinical management could benefit from improved personalized risk estimates.
Methods: We constructed polygenic risk scores (PRS) using BC and OC susceptibility SNPs identified through population-based GWAS: for BC (overall, estrogen receptor [ER]–positive, and ER-negative) and for OC. Using data from 15 252 female *BRCA1* and 8211 *BRCA2* carriers, the association of each PRS with BC or OC risk was evaluated using a weighted cohort approach, with time to diagnosis as the outcome and estimation of the hazard ratios (HRs) per standard deviation increase in the PRS.
Results: The PRS for ER-negative BC displayed the strongest association with BC risk in *BRCA1* carriers (HR = 1.27, 95% confidence interval [CI] = 1.23 to 1.31, $P = 8.2\times10^{-53}$). In *BRCA2* carriers, the strongest association with BC risk was seen for the overall BC PRS (HR = 1.22, 95% CI = 1.17 to 1.28, $P = 7.2\times10^{-20}$). The OC PRS was strongly associated with OC risk for both *BRCA1* and *BRCA2* carriers. These translate to differences in absolute risks (more than 10% in each case) between the top and bottom

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deciles of the PRS distribution; for example, the OC risk was 6% by age 80 years for *BRCA2* carriers at the 10th percentile of the OC PRS compared with 19% risk for those at the 90th percentile of PRS.
Conclusions: BC and OC PRS are predictive of cancer risk in *BRCA1* and *BRCA2* carriers. Incorporation of the PRS into risk prediction models has promise to better inform decisions on cancer risk management.

Women who carry a pathogenic mutation in the BRCA1 or BRCA2 gene are at high risk of developing breast and ovarian cancers. The clinical management of healthy women with a *BRCA1* or *BRCA2* mutation involves a combination of frequent screening, risk-reducing surgeries, and chemoprevention (1). Important decisions include whether or not to undergo preventive mastectomy and the age at which to undergo risk-reducing salpingo-oophorectomy (RRSO). These choices are invasive, have substantial side effects, and are associated with adverse psychological effects (2–6). Improved personalized cancer risk estimates may help to identify women at particularly high risk or with high risk of disease at early ages who may benefit from early intervention as well as women at lower risk who may opt to delay surgery or chemoprevention (7). This could be achieved by incorporating risk-modifying factors into risk prediction.

Population-based genome-wide association studies have identified 94 common breast and 18 ovarian cancer susceptibility loci (8–10). While a smaller number of these loci were associated with risk in *BRCA1* and *BRCA2* mutation carriers at stringent statistical significance thresholds, the effect sizes in carriers are generally similar to those in the general population, once differences in the distributions of breast tumor estrogen receptor status in mutation carriers and noncarriers are taken into account (9,11). Individually the identified breast and ovarian cancer risk-modifying variants confer only small to modest increases in risk. However, their effects can be combined into polygenic risk scores (PRSs), which may be associated with much larger relative risks (12,13). Prior to the clinical implementation of these findings, it is important to assess the predictive utility of PRS in terms of discrimination, calibration, and potential for risk stratification (14).

Because women with *BRCA1* and *BRCA2* mutations are already at high risk of developing breast and ovarian cancers, the combined effects of risk-modifying variants could lead to much larger differences in the absolute risk of developing the disease as compared with the general population (12,13,15,16). Earlier studies investigating the effect of PRS on the absolute risks of breast and ovarian cancer risks of *BRCA1* and *BRCA2* mutation carriers demonstrated potential for risk stratification (13,17–19). However, these have been based on small numbers of single-nucleotide polymorphisms (SNPs; <15) and most were restricted to theoretical projections of the PRS association rather than empirical evaluations.

In this study, we developed different PRSs for breast and ovarian cancer as well as estrogen receptor (ER)–specific PRS based on reported susceptibility loci from population-based studies and evaluated their associations with risks for *BRCA1* and *BRCA2* carriers. We estimated absolute risks of developing breast and ovarian cancer for individuals with different values of the PRS in order to assess whether these PRS provide clinically useful risk stratification of mutation carriers.

Methods

Study Population

Eligible study subjects included in the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) are female carriers of a pathogenic mutation in either *BRCA1* or *BRCA2* who are age 18 years or older. Mutation carriers were recruited by 56 study centers in 26 countries. The majority were recruited through cancer genetics clinics, and enrolled into national or regional studies. We used data from 15 252 *BRCA1* (breast cancer = 7797, ovarian cancer = 2462) and 8211 *BRCA2* (breast cancer = 4330, ovarian cancer = 631) mutation carriers who were genotyped with the iCOGS array. Quality control has been described in detail elsewhere (11,13,18). Each of the host institutions recruited mutation carriers under protocols approved by local ethics review boards. Written informed consent was obtained from all subjects. Only samples of European ancestry were included in the present analysis.

Polygenic Risk Scores

The effects of cancer susceptibility variants on cancer risks for mutation carriers were combined into PRS. The PRS for individual i was defined as the sum of the number of risk alleles across k variants weighted by the effect size of each variant:

$$PRS_i = \beta_1 g_{1i} + \ldots + \beta_k g_{ki},$$

where g_{li} is the genotype of person *i* for variant l, expressed as the number of effect alleles (0, 1, or 2), and β_l is the per-allele log risk ratio (odds ratio [OR] or hazard ratio [HR]) (Supplementary Tables 1–6, available online) associated with the effect allele of SNP l.

The primary PRSs were based on SNPs found to be associated with breast or ovarian cancer through genome-wide association studies (GWASs) in the general population. For breast cancer, we used the published PRSs for overall breast cancer, ER-positive breast cancer, and ER-negative breast cancer (8,20). In addition, we created updated PRSs based on findings from population-based association and fine-mapping studies reported before April 2015 (Supplementary Table 1, available online) (8,10,21–28). More details on the variant selection are provided in the Supplementary Methods (available online).

We developed an ovarian cancer PRS by including the most strongly associated variant from each region associated at a genome-wide statistical significance level with ovarian cancer risk in population-based studies or studies that combined population data and data from mutation carriers (Supplementary Table 2, available online) (9,23).

We also constructed secondary *BRCA1*- and *BRCA2*-specific PRSs that were based on all variants showing evidence of association in *BRCA1* and *BRCA2* carriers, using the results and weights from the *BRCA1*- and *BRCA2*-specific GWASs (11–13) (Supplementary Tables 3–6 and Supplementary Methods, available online). However, the studies that led to the identification of these variants were based on the same data set as the present analysis. Therefore, these *BRCA1*- and *BRCA2*-specific PRSs cannot be independently validated in the present analysis. To reduce the bias from overfitting, we also constructed and evaluated unweighted versions of these PRSs.

For the SNPs included in each PRS, we assessed whether there was evidence for pairwise interactions (Supplementary Methods, available online).

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Table 1. Per-standard-deviation hazard ratios and 95% confidence intervals for the associations of polygenic risk scores with breast and ovarian cancer risk in *BRCA1* and *BRCA2* carriers*

PRS	No. of SNPs	*BRCA1* carriers		*BRCA2* carriers	
		HR (95% CI)	P†	HR (95% CI)	P†
Outcome: breast cancer					
Overall BC PRS	88	1.14 (1.11 to 1.17)	1.8×10^{-18}	1.22 (1.17 to 1.28)	7.2×10^{-20}
ER-positive BC PRS	87	1.11 (1.08 to 1.15)	3.5×10^{-13}	1.22 (1.16 to 1.27)	4.0×10^{-19}
ER-negative BC PRS	53	1.27 (1.23 to 1.31)	8.2×10^{-53}	1.15 (1.10 to 1.20)	6.8×10^{-10}
Outcome: ovarian cancer					
OC PRS	17	1.28 (1.22 to 1.34)	2.5×10^{-26}	1.49 (1.34 to 1.65)	8.5×10^{-14}

*The PRS created from the latest reported population-based study results were used. BC = breast cancer; CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; OC = ovarian cancer; PRS = polygenic risk score; SNP = single-nucleotide polymorphism.
†P value for a one-sided test using a weighted cohort Cox regression with time to breast or ovarian cancer diagnosis, respectively, as the outcome.

Statistical Analysis

To account for the nonrandom sampling of mutation carriers with respect to disease status, the association of each PRS with breast or ovarian cancer risk was analyzed using a weighted cohort Cox regression with time to breast or ovarian cancer diagnosis, respectively, as the outcome (Supplementary Methods, available online) (29). We evaluated the associations of the breast cancer PRS (ie, overall breast cancer PRS, ER-positive PRS, and ER-negative PRS) with the risk for overall breast cancer for *BRCA1* and *BRCA2* mutation carriers. The ovarian cancer PRS was assessed for association with the risk of developing overall ovarian cancer for *BRCA1* and *BRCA2* mutation carriers. For these analyses, subjects were categorized into PRS percentile groups. To provide easily interpretable associations, the association analyses were repeated using continuous PRS predictors standardized to have mean 0 and variance 1. We assessed whether the hazard ratio per unit of the PRS varied with age by including a term for the interaction of the standardized PRS with age. We also fitted a Cox regression that included separate PRS effects by age group.

To evaluate the ability of the PRS to discriminate between individuals developing breast or ovarian cancer at different ages, we computed the rank Harrell's c index (Supplementary Methods, available online) (30).

Absolute age-specific cumulative risks of developing breast or ovarian cancer at different percentiles of the standardized PRS were calculated according to the approach described previously (Supplementary Methods, available online) (15,31).

Analyses were carried out in R using GenABEL (32) and in STATA v13.1 (33). The associations of the continuous PRSs with breast or ovarian cancer risk were evaluated using one-sided statistical tests because we evaluated the directional hypothesis of increased cancer risk with a higher PRS. All other statistical tests were two-sided. Detailed methods are provided in the Supplementary Methods (available online).

Results

PRS Associations With Cancer Risks

Using data from 15 252 *BRCA1* and 8211 *BRCA2* carriers (Supplementary Table 7, available online), there was no evidence for interaction between any two variants involved in any of the PRSs after accounting for multiple testing (results not shown). All breast cancer PRSs derived from population-based study results (Supplementary Tables 1, available online) were statistically significantly associated with breast cancer risks for both *BRCA1* and *BRCA2* carriers (Table 1). Compared with the PRS developed by Mavaddat et al. (Supplementary Table 9, available online), the updated breast cancer PRS displayed slightly stronger associations in *BRCA1* carriers, but no improvements were seen in *BRCA2* carriers.

The PRS for ER-negative breast cancer displayed the strongest association with breast cancer risk in *BRCA1* carriers (per standard deviation HR = 1.27, 95% confidence interval [CI] = 1.23 to 1.31, $P = 8.2\times10^{-53}$) (Table 1). Smaller HR estimates in *BRCA1* breast cancer were seen for the PRS for overall breast cancer (HR = 1.14, 95% CI = 1.11 to 1.17, $P = 1.8\times10^{-18}$) and ER-positive breast cancer (HR = 1.11, 95% CI = 1.08 to 1.15, $P = 3.5\times10^{-13}$). In *BRCA2* carriers, the ER-negative breast cancer PRS displayed a smaller per SD HR for breast cancer risk (HR = 1.15, 95% CI = 1.10 to 1.20, $P = 6.8\times10^{-10}$) compared with *BRCA1* carriers, whereas the overall breast cancer PRS (HR = 1.22, 95% CI = 1.17 to 1.28, $P = 7.2\times10^{-20}$) and the ER-positive PRS (HR = 1.22, 95% CI = 1.16 to 1.27, $P = 4.0\times10^{-19}$) displayed stronger associations. The subsequent breast cancer analyses focus on the updated ER-negative breast cancer PRS for *BRCA1* carriers and the updated overall breast cancer PRS for *BRCA2* carriers.

Consistent with the above models, there were clear trends in risk by PRS for both *BRCA1* and *BRCA2* carriers when PRS was categorized by percentile (Table 2). The hazard ratio estimates were consistent with those predicted by the model, in which PRS was fitted as a continuous covariate (Figure 1).

We also investigated whether the associations for the most strongly associated PRS differ by mutation type, as defined by the mutation functional effect (Supplementary Methods, available online). There was marginal evidence of an interaction between the breast cancer risk PRS and class 2 mutations in *BRCA2* mutation carriers ($P = 0.03$, with a slightly higher HR estimate for the PRS for class 2 mutation carriers).

The population-based ovarian cancer PRS was strongly associated with ovarian cancer risk in *BRCA1* carriers with a per SD HR of 1.28 (95% CI = 1.22 to 1.34, $P = 2.5\times10^{-26}$) (Table 1). The hazard ratio estimate was larger for ovarian cancer risk in *BRCA2* carriers (HR = 1.49, 95% CI = 1.34 to 1.65, $P = 8.5\times10^{-14}$). When we compared the hazard ratio estimates against the hazard ratios predicted under a multiplicative polygenic model, only the hazard ratio estimate for *BRCA2* carriers for the 60% to 80% category was statistically significantly higher than the predicted value (Figure 1).

The unweighted *BRCA1*- and *BRCA2*-specific PRS for breast and ovarian cancer, constructed on the basis of association results in CIMBA, showed strong evidence of association with breast and ovarian cancer (Supplementary Table 10, available online).

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Table 2. Proportion of samples and number of events in percentile categories of polygenic risk scores and their associations with breast and ovarian cancer risks*

	BRCA1 carriers		*BRCA2* carriers	
Percentile category, %	No. of events (% samples in percentile category)	HR (95% CI)†	No. of events (% samples in percentile category)	HR (95% CI)†
Outcome: breast cancer				
0–5	222 (3.6)	0.76 (0.64 to 0.91)	138 (4.0)	0.80 (0.63 to 1.02)
5–10	250 (4.1)	0.70 (0.59 to 0.82)	142 (4.2)	0.68 (0.54 to 0.87)
10–20	551 (8.7)	0.77 (0.68 to 0.87)	340 (8.9)	0.92 (0.77 to 1.09)
20–40	1377 (18.7)	0.98 (0.89 to 1.07)	764 (18.8)	1.00 (0.87 to 1.15)
40–60	1534 (20.4)	1 (ref.)	793 (19.1)	1 (ref.)
60–80	1729 (21.0)	1.21 (1.11 to 1.33)	950 (21.2)	1.16 (1.02 to 1.32)
80–90	950 (11.0)	1.32 (1.19 to 1.47)	557 (11.4)	1.37 (1.17 to 1.60)
90–95	519 (5.8)	1.50 (1.31 to 1.72)	309 (5.8)	1.76 (1.43 to 2.17)
95–100	665 (6.7)	1.82 (1.61 to 2.07)	337 (6.7)	1.51 (1.25 to 1.82)
Outcome: ovarian cancer				
0–5	85 (4.7)	0.66 (0.51 to 0.86)	20 (4.8)	0.76 (0.39 to 1.47)
5–10	110 (5.3)	0.81 (0.64 to 1.02)	18 (5.3)	0.67 (0.34 to 1.32)
10–20	215 (10.5)	0.80 (0.66 to 0.96)	39 (10.4)	0.87 (0.54 to 1.39)
20–40	478 (20.9)	0.95 (0.82 to 1.10)	104 (20.4)	1.02 (0.71 to 1.46)
40–60	468 (19.9)	1 (ref.)	107 (20.4)	1 (ref.)
60–80	519 (19.5)	1.19 (1.03 to 1.38)	159 (19.5)	1.73 (1.25 to 2.40)
80–90	267 (9.3)	1.43 (1.20 to 1.70)	76 (9.1)	1.84 (1.24 to 2.72)
90–95	155 (4.9)	1.54 (1.24 to 1.91)	45 (4.8)	1.87 (1.16 to 3.02)
95–100	165 (5.1)	1.86 (1.51 to 2.29)	63 (5.4)	3.04 (2.00 to 4.61)

*The polygenic risk score (PRS) created from reported population-based study results were used. The percentile boundaries were derived assuming a normally distributed PRS. The estrogen receptor–negative breast cancer PRS was used for the associations with breast cancer risk in *BRCA1* carriers and overall breast cancer PRS in *BRCA2* carriers. CI = confidence interval; HR = hazard ratio.

†Hazard ratio from a weighted cohort Cox regression with time to breast or ovarian cancer diagnosis, respectively, as the outcome.

PRS x Age Interaction

There was evidence for a PRSxage interaction for the ER-negative breast cancer PRS for *BRCA1* carriers ($P = 3\times10^{-6}$) and for the overall breast cancer PRS for *BRCA2* carriers ($P = .01$) (Table 3). In the ovarian cancer analysis, a statistically significant interaction with age was seen for the ovarian cancer PRS for *BRCA1* carriers ($P = .003$). Each of these PRSs showed stronger associations in younger age groups.

Discrimination

The ER-negative PRS had the highest value of Harrell's (c = 0.58, 95% CI = 0.57 to 0.59) for breast cancer in *BRCA1* carriers (Table 4). For breast cancer in *BRCA2* carriers, the highest values for Harrell's c were achieved by the population-based overall and ER-positive breast cancer PRSs (c = 0.56, 95% CI = 0.55 to 0.58, in each case). For ovarian cancer, the OC-PRS had a c of 0.58 (95% CI = 0.56 to 0.60) for *BRCA1* carriers and a c of 0.63 (95% CI = 0.60 to 0.67) for *BRCA2* carriers.

Predicted Absolute Risks by PRS Percentile

We used the age-specific hazard ratio estimates to compute absolute cumulative breast and ovarian cancer risks for mutation carrier by PRS percentiles (Figure 2). We used the updated ER-negative PRS to predict breast cancer risk for *BRCA1* carriers and the updated overall breast cancer PRS to predict breast cancer risk for *BRCA2* carriers. *BRCA1* carriers at the 10th percentile of the PRS had a risk of 21% of developing breast cancer by age 50 years and a 56% risk by age 80 years. In contrast, the *BRCA1* carriers at the 90th percentile of the PRS had a 39% breast cancer risk by age 50 years and 75% by age 80 years. The ovarian cancer risk was 6% by age 80 years for *BRCA2* carriers at the 10th percentile of the ovarian cancer PRS compared with 19% risk for those at the 90th percentile of PRS.

Discussion

This is the first evaluation of the combined effects of all known common breast and ovarian cancer susceptibility loci on cancer risks for women who carry a *BRCA1* or *BRCA2* mutation. We found strong evidence of association with cancer risks for PRSs constructed using the results of population-based studies. These associations provide strong support for the hypothesis of a polygenic component for breast and ovarian cancer risks, respectively, that is largely shared between the general population and *BRCA1* and *BRCA2* mutation carriers. Moreover, the pattern of associations with the breast cancer subtype–specific PRS confirms the importance of tumor ER status (11). The PRS based on SNPs associated with ER-negative disease in the general population displayed a much stronger association with overall breast cancer risk for *BRCA1* carriers than the ER-positive PRS, consistent with the observation that the predominant tumor subtype in *BRCA1* carriers is ER negative (34,35). In contrast, the majority of tumors in *BRCA2* carriers tend to be ER positive. Consistent with this, the ER-positive PRS and the PRS for overall breast cancer constructed from general population data exhibited stronger associations than the ER-negative PRS in *BRCA2* carriers.

Using the overall, ER-positive, and ER-negative breast cancer PRSs developed by Mavaddat, the per SD hazard ratio estimates

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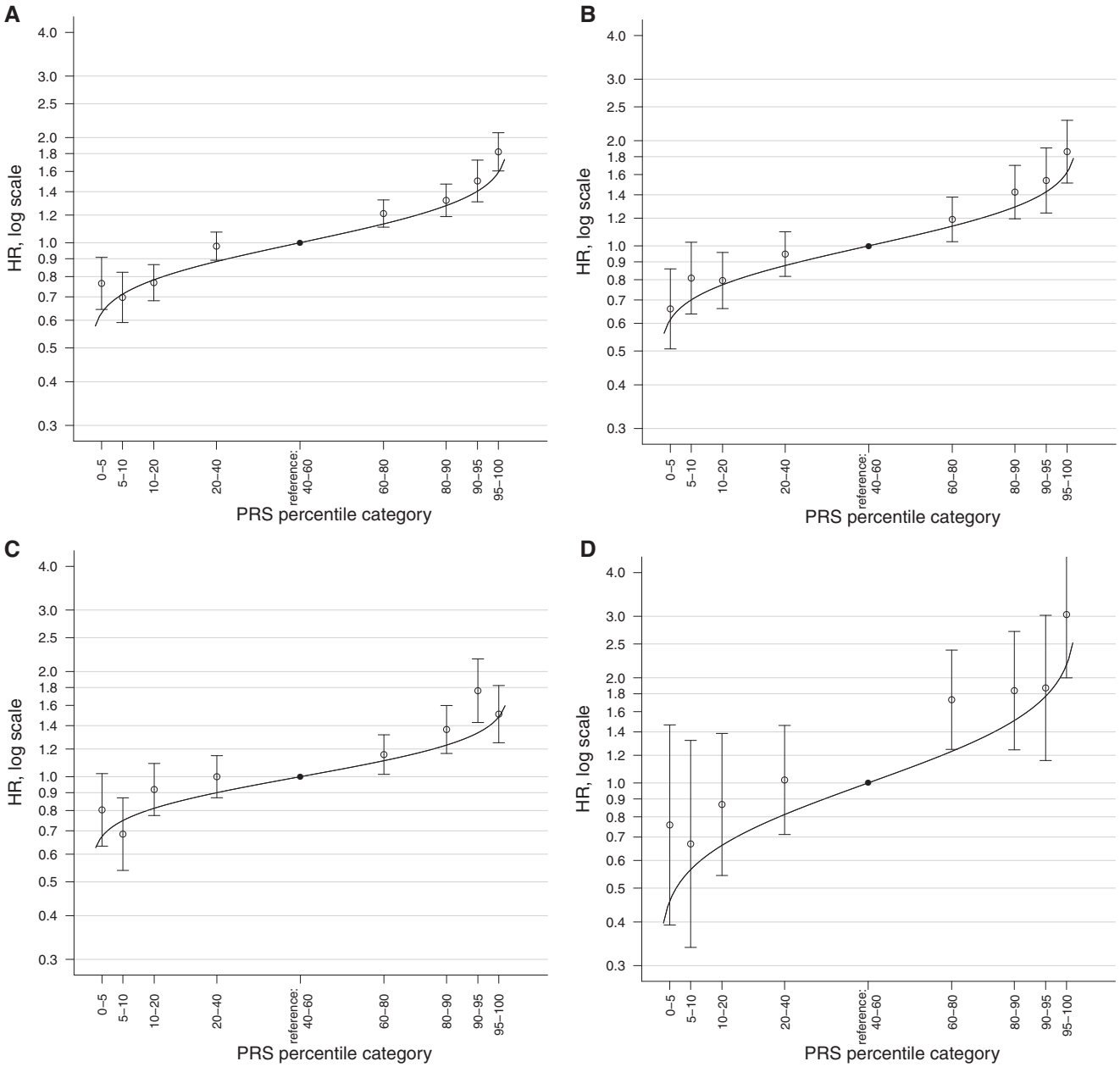


Figure 1. Hazard ratios (HRs) and 95% confidence intervals (**error bars**) for percentiles of the polygenic risk score (PRS) relative to the middle quintile. The estrogen receptor–negative breast cancer (BC) PRS **(A)** and the overall BC PRS **(C)** were used for breast cancer in *BRCA1* and *BRCA2* carriers, respectively, and the ovarian cancer (OC) PRS for the OC associations **(B, D)**. **Lines** denote the theoretical estimates under a multiplicative polygenic model with means and standard deviations of $\bar{x} = 0.10$ and SD = 0.41 for the ER-negative BC PRS, $\bar{x} = 0.41$ and SD = 0.50 for the overall BC PRS, $\bar{x} = 0.47$ and SD = 0.37 for the OC PRS.

in mutation carriers were smaller than the corresponding per SD odds ratio estimates for breast cancer in the population-based study (20). These observations suggest that the relative extent by which the SNPs modify breast cancer risks in *BRCA1* and *BRCA2* mutation carriers is somewhat smaller than that in the general population, perhaps because a subset of SNPs do not combine multiplicatively with mutation status. Alternatively, these observations may reflect a difference in the design: Under a simple proportional hazards model, the predicted odds ratio is larger than the corresponding rate ratio (HR), but this difference is usually small (36). Moreover, some overestimation cannot be ruled out entirely for the per SD odds ratio estimates from the population-based study because of a winner's curse effect. Interestingly, the hazard ratio estimate for the association of the ovarian cancer PRS with ovarian cancer risk was statistically significantly higher for *BRCA2* than for *BRCA1* mutation carriers. As a result, this PRS had also a higher discriminatory ability for ovarian cancer for *BRCA2* carriers compared with *BRCA1* mutation carriers.

Each of the most strongly associated PRSs displayed statistically significant interactions with age, with the exception of the ovarian cancer PRS in *BRCA2* carriers, such that the hazard ratio per unit PRS decreased with increasing age. One possible explanation for the observed interaction between age and the ER-negative breast cancer PRS in *BRCA1* mutation carriers could due to the use of the ER-negative breast cancer PRS from the general

Table 3. Age-specific hazard ratio estimates for the PRS associations and HR estimates for a PRS x age interaction*

	BRCA1 carriers			*BRCA2* carriers		
Age category, y	No. of events	HR per unit SD increase in the ER- PRS (95% CI)	P†	No. of events	HR per unit SD increase in the overall BC PRS (95% CI)	P†
Outcome: breast cancer						
18–39	4125	1.63 (1.52 to 1.74)	–	1731	1.65 (1.44 to 1.88)	–
40–49	2557	1.18 (1.13 to 1.23)	4.2×10^{-15}	1587	1.22 (1.14 to 1.31)	8.5×10^{-5}
50–59	846	1.14 (1.09 to 1.21)	.40	718	1.10 (1.02 to 1.19)	.05
≥60	269	1.20 (1.11 to 1.29)	.33	294	1.12 (1.03 to 1.23)	.75
Interaction HR		0.993 (0.990 to 0.996)	3.3×10^{-6}		0.995 (0.991 to 0.999)	.01
Main effect PRS		1.69 (1.50 to 1.91)			1.55 (1.29 to 1.87)	
Outcome: ovarian cancer						
18–49	1258	1.55 (1.42 to 1.69)		172	3.05 (2.35 to 3.97)	
50–59	808	1.11 (1.05 to 1.18)	1.1×10^{-9}	227	1.52 (1.26 to 1.84)	8.2×10^{-6}
≥60	396	1.14 (1.06 to 1.21)	.67	232	1.21 (1.12 to 1.30)	.03
Interaction HR		0.992 (0.988 to 0.998)	.003		0.991 (0.979 to 1.00)	.11
Main effect PRS		1.83 (1.43 to 2.34)			2.48 (1.34 to 4.58)	

*The population-derived polygenic risk score (PRS) for estrogen receptor–negative breast cancer was used for the associations with breast cancer in *BRCA1* carriers and the overall breast cancer PRS in *BRCA2* carriers. *P* values relate to the difference in PRS association between each age group from the preceding younger group and to the interaction term. CI = confidence interval; HR = hazard ratio; PRS = polygenic risk score.
†*P* value for a two-sided test using a weighted cohort Cox regression with time to breast or ovarian cancer diagnosis, respectively, as the outcome.

Table 4. Discrimination of population-derived polygenic risk scores for breast and ovarian cancer in *BRCA1* and *BRCA2* carriers*

	Harrell's c statistic (95% CI)	
PRS	*BRCA1* carriers	*BRCA2* carriers
Discrimination for breast cancer		
Overall BC PRS	0.541 (0.530 to 0.551)	0.566 (0.551 to 0.581)
ER-positive BC PRS	0.532 (0.522 to 0.543)	0.566 (0.551 to 0.581)
ER-negative BC PRS	0.581 (0.571 to 0.592)	0.538 (0.523 to 0.553)
Discrimination for ovarian cancer		
OC PRS	0.579 (0.559 to 0.600)	0.628 (0.592 to 0.665)

*BC = breast cancer; CI = confidence interval; ER = estrogen receptor; OC = ovarian cancer; PRS = polygenic risk score.

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population to predict the risk of overall breast cancer risk for *BRCA1* mutation carriers. Although the majority of breast cancers in *BRCA1* mutation carriers are ER negative, the proportion of ER-negative breast tumors decreases with increasing age at diagnosis (35). If the population-based ER-negative PRSs were also associated primarily with ER-negative breast cancers in *BRCA1* mutation carriers, the ER-negative PRS would be more predictive of breast cancer in *BRCA1* carriers at younger ages. In contrast, in *BRCA2* carriers the proportion of ER-positive disease was found to decrease with increasing age at diagnosis (35). Therefore, the overall PRS from the general population, which is associated primarily with ER-positive breast cancers, may be more predictive of breast cancer in *BRCA2* mutation carriers at younger ages. Alternatively, it is possible that genetic risk modification has a stronger effect on developing early-onset breast cancer.

A limitation of the present study is our inability to take family history into account because this information was not available for the majority of samples. Although the tests of association remain valid, it was therefore not possible to investigate how the associations vary by family cancer history.

Overall, the discrimination achieved by the PRS investigated in the current study was moderate. The highest discrimination was achieved by the ovarian cancer PRS in *BRCA2* carriers. We found the overall breast cancer PRS to have somewhat lower discriminatory ability in mutation carriers compared with the general population (20). However, given the different study designs, ER tumor specificity in mutation carriers, and different measures of relative risk, these model performance estimates may not be directly comparable.

One possible explanation for the differences in the relative risk of the PRS between the mutation carriers and the population-based study is that not all variants identified in population-based studies are actually associated with risk in mutation carriers, perhaps as a result of functional redundancy (9). Conversely, variants that specifically modify risk in mutation carriers, examples of which have already been reported (13,18), would not be included in PRSs derived from population-based studies, and such variants might improve discrimination. On the other hand, because of the large sample sizes available in population-based studies, the SNP selection and the logOR estimates used as weights for these PRSs are likely to be more reliable than for PRSs based on mutation carriers. We also derived *BRCA1*- and *BRCA2*-specific PRSs that include variants discovered by population-based studies but only those showing evidence of association in mutation carriers. This approach makes use of the discovery power of population-based studies while accounting for possible mutation carrier–specific differences in associations. However, the SNP selection and weights were based on results from the same data set as that used in the present analysis. For this reason, we investigated the associations of mutation carrier–specific PRSs without weights to reduce the possible overfitting. An analysis in an independent sample of mutation carriers will be required to assess whether these mutation-specific PRSs outperform population-based PRSs.

The present study demonstrates that there are large differences in the absolute cancer risks between *BRCA1* and *BRCA2* mutation carriers with higher vs lower values of the PRS. These

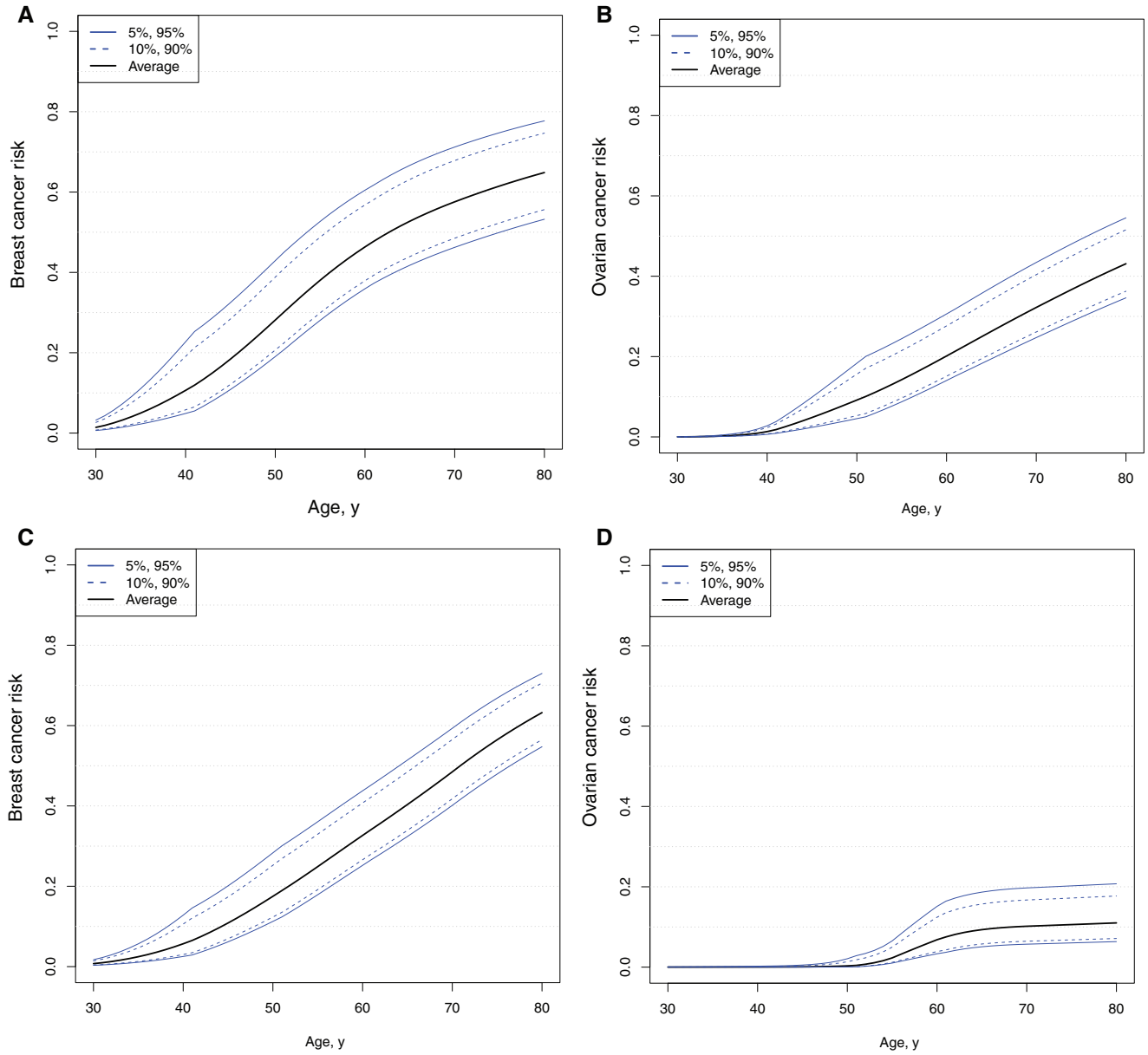


Figure 2. Predicted breast cancer risks by percentile of the polygenic risk scores (PRSs). The estrogen receptor–negative breast cancer PRS was used for *BRCA1* carriers **(A)** and the overall breast cancer PRS for *BRCA2* carriers **(C)**. Ovarian cancer risks are given by percentile of the ovarian cancer PRS in *BRCA1* **(B)** and *BRCA2* **(D)** carriers. Age-specific PRS associations were used to calculate these cumulative risks.

differences are much greater than those found in population-based studies (20,37) because the average risks conferred by *BRCA1* and *BRCA2* mutations are already high (17,18). The clinical management of healthy women with a *BRCA1* or *BRCA2* mutation involves a combination of frequent screening, risk-reducing surgery, and possibly chemoprevention (1), which can associated with substantial side effects. In particular, RRSO leads to premature menopause, is associated with increased morbidity, and has implications for family planning (38,39). Therefore, the timing of RRSO has to be carefully considered. There are no widely accepted risk thresholds for RRSO in mutation carriers: RRSO is recommended to all carriers on the basis of their average risk. The current National Comprehensive Cancer Network guidelines recommend RRSO for *BRCA1* carriers at age 35 to 40 years and *BRCA2* carriers at age 40 to 45 years (40). The average cumulative risk of ovarian cancer by age 40 years for *BRCA1* mutation carriers has been estimated as 2.8% (41). However, on the basis of our analyses, the cumulative risk of ovarian cancer for those at the lowest 1% of the PRS by age 40 years is predicted to be 0.7%, and 20% of *BRCA1* mutation carriers are predicted to have a risk of ovarian cancer of less than 1.3% by age 40 years. Therefore, the current results may be used to develop risk-based thresholds for RRSO recommendations. One possibility would be to assume that women with *BRCA1* mutations would not be offered RRSO until their cumulative risk of ovarian cancer approaches or exceeds 2.8%. A similar rule has recently been recommended for the counseling of women with mutations in moderate-risk genes (42). The ages at

which women with *BRCA1* mutations would reach a cumulative risk of ovarian cancer of 2.8% are 48 years for those at the 1st percentile of the PRS, and 46, 45, 44, and 43 years for those at the 5th, 10th, 20th, and 30th percentiles of the PRS, respectively. For these women, deferring oophorectomy to these ages as opposed to the recommended age of 35 to 40 years may be preferable for childbearing and to avoid very early menopause. Another option would be to use risk-based thresholds defined for the general population. For example, a 10% lifetime risk of ovarian cancer is often cited as a recommended threshold for RRSO (43). Based on our results, *BRCA2* carriers at the 10th percentile of the ovarian cancer PRS have an estimated 6% lifetime risk and approximately 38% of *BRCA2* mutation carriers have a lifetime risk of ovarian cancer that is less than 10%. Women at this lower end of the risk spectrum might opt to delay RRSO to near or after natural menopause in order to avoid the harmful longer-term adverse effects of a surgically induced premature menopause, and this also provides a longer period for childbearing. Therefore, the PRS may be informative in guiding women with *BRCA1* and *BRCA2* mutations on the optimal timing of RRSO and can identify women at lower risk who may opt for less intensive interventions, such as salpingectomy with delayed oophorectomy.

Decisions in relation to breast cancer prevention could also be influenced by refined risk estimates. For example, the *BRCA1* carriers at the 90th percentile of the ER-negative breast cancer PRS had an estimated breast cancer risk of 19% by age 40 years and 39% by age 50 years, compared with 5% by age 40 years and 21% by age 50 years for carriers at the 10th percentile of the PRS. As with RRSO, there are currently no widely accepted risk thresholds for offering risk-reducing bilateral mastectomy (RRBM) for women with *BRCA1* and *BRCA2* mutations. However, studies in nonmutation carriers have shown that the uptake and timing of RRBM is directly related to the magnitude of breast cancer risk (44), and similar arguments may be applicable to mutation carriers. To provide comprehensive risk prediction, the PRS should be combined with other risk factors, including family history. Such a model would form the foundation for the development of risk-based clinical management guidelines for mutation carriers. In parallel, it will be necessary to perform risk communication studies to assess the acceptability of risk stratification in women with *BRCA1* and *BRCA2* mutations.

In conclusion, the results demonstrate that these PRSs could be useful in risk prediction for mutation carriers. Incorporating these PRSs into risk prediction models for *BRCA1* and *BRCA2* mutation carriers, together with other risk modifiers, may allow for more personalized risks for *BRCA1* and *BRCA2* mutation carriers and ultimately facilitate better management of mutation carriers.

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