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ORIGINAL REPORT

Prediction of Breast and Prostate Cancer Risks in Male *BRCA1* and *BRCA2* Mutation Carriers Using Polygenic Risk Scores

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See accompanying Editorial on page 2224

Data Supplement

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A B S T R A C T

Purpose

BRCA1/2 mutations increase the risk of breast and prostate cancer in men. Common genetic variants modify cancer risks for female carriers of *BRCA1/2* mutations. We investigated—for the first time to our knowledge—associations of common genetic variants with breast and prostate cancer risks for male carriers of *BRCA1/2* mutations and implications for cancer risk prediction.

Materials and Methods

We genotyped 1,802 male carriers of *BRCA1/2* mutations from the Consortium of Investigators of Modifiers of *BRCA1/2* by using the custom Illumina OncoArray. We investigated the combined effects of established breast and prostate cancer susceptibility variants on cancer risks for male carriers of *BRCA1/2* mutations by constructing weighted polygenic risk scores (PRSs) using published effect estimates as weights.

Results

In male carriers of *BRCA1/2* mutations, PRS that was based on 88 female breast cancer susceptibility variants was associated with breast cancer risk (odds ratio per standard deviation of PRS, 1.36; 95% CI, 1.19 to 1.56; $P = 8.6 \times 10^{-6}$). Similarly, PRS that was based on 103 prostate cancer susceptibility variants was associated with prostate cancer risk (odds ratio per SD of PRS, 1.56; 95% CI, 1.35 to 1.81; $P = 3.2 \times 10^{-9}$). Large differences in absolute cancer risks were observed at the extremes of the PRS distribution. For example, prostate cancer risk by age 80 years at the 5th and 95th percentiles of the PRS varies from 7% to 26% for carriers of *BRCA1* mutations and from 19% to 61% for carriers of *BRCA2* mutations, respectively.

Conclusion

PRSs may provide informative cancer risk stratification for male carriers of *BRCA1/2* mutations that might enable these men and their physicians to make informed decisions on the type and timing of breast and prostate cancer risk management.

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INTRODUCTION

Germline mutations in *BRCA1* and, predominantly, *BRCA2* are associated with increased risks in men of developing breast and prostate cancers.[1,2] *BRCA1/2* mutations account for approximately 10% of male breast cancer and 2% of prostate cancer cases.[3-5] Breast cancer in men is rare and accounts for less than 1% of all male tumors. By contrast, prostate cancer is the most common cancer in men, accounting for approximately 25% of male tumors.[6] The lifetime risk of male breast cancer in mutation carriers has been estimated to be 5% to 10% and 1% to 5% for carriers of *BRCA2* and *BRCA1* mutations, respectively, whereas estimates of lifetime prostate cancer risk are approximately 20% and 40% for carriers of *BRCA1* and *BRCA2* mutations, respectively.[3,7-10]

More than 100 common genetic variants (single nucleotide polymorphisms [SNPs]) that are associated with prostate cancer and female breast cancer have been identified via genome-wide association studies (GWAS) in the general population,[11,12] and their combined effects have been shown to have significant implications for risk stratification and targeted prevention.[13-15] By contrast, only two male breast cancer susceptibility SNPs have been identified to date,[16] but there is some evidence that suggests that common variants that are associated with female breast cancer may influence male breast cancer risk.[17-19]

Studies by the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) have shown that common SNPs modify the risk of breast and ovarian cancers for female *BRCA1* and *BRCA2* mutation carriers[20-22]; however, no study to date has investigated the associations of common SNPs with breast or prostate cancer risk for men with *BRCA1/2* mutations and their implications for cancer risk prediction.

In this study, we performed the first GWAS for breast and prostate cancers in male *BRCA1*/2 mutation carriers enrolled in CIMBA using the custom Illumina OncoArray. Furthermore, we evaluated the combined effects of known common breast and prostate cancer susceptibility variants on cancer risks for male carriers of *BRCA1/2* mutations and estimated absolute age-specific cumulative risks of developing breast and prostate cancers on the basis of combined SNP distributions. We demonstrate—to our knowledge for the first time—that combined SNP effects have important implications for risk profiling of male carriers of *BRCA1/2* mutations.

MATERIALS AND METHODS

Samples

CIMBA collects data on men with *BRCA1* or *BRCA2* clearly pathogenic variants—commonly termed mutations—who are older than 18 years, with the majority recruited via cancer genetics clinics.[23] Pathogenic variants were defined as previously described.[24] All participating studies have been approved by local ethical review committees.

To select samples for genotyping, we used a case-control study design, selecting all available male carriers of *BRCA1/2* mutations who were affected with breast and/or prostate cancer (cases) and matching them with up to three unaffected mutation carriers (controls). Cases and controls were matched for study group or country of residence, year of birth, and gene (*BRCA1* or *BRCA2*). A total of 1,989 male carriers were selected for genotyping: 265 with breast cancer, 212 with prostate cancer, 43 with both diseases, and 1,469 unaffected.

Genotyping and Quality Control

Genotyping was performed by using the Illumina OncoArray beadchip (approximately 570,000 SNPs with genome-wide coverage). Genotyping and quality control were performed as described in the Data Supplement. Of 1,989 samples, 1,802 passed the quality control step. We imputed genotypes using the 1000 Genomes Project as the reference panel (Data Supplement).

Statistical Methods

Association Analyses. We evaluated associations of SNPs with risks of breast and prostate cancer simultaneously using multinomial logistic regression. The control group in this analysis was defined as the set of samples without a breast or prostate cancer diagnosis. Breast and prostate cancer cases were defined on the basis of age at diagnosis, whichever occurred first. If breast and prostate cancer occurred at the same time, individuals were treated as patients with breast cancer. Thus, of 1,802 samples, 277 were defined as patients with breast cancer, 212 as patients with prostate cancer, and 1,313 as controls. Analyses were adjusted for the first three principal components, age at breast or prostate cancer for patient-cases and age at interview for controls, and gene (*BRCA1* or *BRCA2*). A robust variance approach—clustering of family membership—was used to adjust for related individuals. Additional logistic regression analyses were carried out to assess associations separately with breast or prostate cancer risk (Data Supplement). We also performed a set of sensitivity analyses by considering patient cases with both breast and prostate cancer as a separate group in a multinomial logistic regression model (Data Supplement). Analysis was performed in R (version 3.2.3; R Foundation, Vienna, Austria) and STATA software (version 13.1; STATA, College Station, TX; Computing Resource Center, Santa Monica, CA).

Polygenic Risk Scores. Assuming a log-additive model for the joint effects of SNPs, we constructed polygenic risk scores (PRSs) by summing the number of alleles across SNPs that were weighted by their estimated per-allele log-odds ratios (ORs) in published studies[11,12,22,25-32] (Data Supplement).

PRSs were standardized to have mean 0 and variance 1 (Data Supplement). We evaluated associations with quartiles of PRS on the basis of the PRS distribution in controls. Absolute age-specific cumulative risks of developing breast or prostate cancer at different percentiles of PRS were calculated using published methods[33] (Data Supplement).

Selection of SNPs Included in PRSs and Weights. **Breast Cancer PRSs.** We investigated three main PRSs using SNPs that were known to be associated with overall risk of breast cancer or risk of estrogen receptor (ER)–positive or –negative breast cancer from published studies that were performed in females from the general population. To construct each PRS and to avoid over-fitting, we used external log-OR estimates—for their association with risk for overall breast cancer or ER-positive or ER-negative breast cancer—from the largest association studies of the Breast Cancer Association Consortium.[12,22,28-31,34] No data from the current study were used to construct any of the PRSs. The three PRSs were defined as follows:

1. The overall PRS includes SNPs that were associated with breast cancer risk from population-based association studies. This PRS included 88 (77 genotyped, 11 imputed) SNPs.
2. The ER-positive PRS includes SNPs that were associated with ER-positive breast cancer. This PRS included 87 (76 genotyped, 11 imputed) SNPs. Weights for each SNP were based on published log-OR estimates for ER-positive breast cancer.
3. The ER-negative PRS includes SNPs associated with ER-negative disease. This PRS included 53 (47 genotyped, six imputed) SNPs. Weights for each SNP were based on log-OR estimates for ER-negative breast cancer.

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A list of SNPs and weights used in each PRS is shown in the Data Supplement. To identify the most strongly associated PRS, we have evaluated the associations of all three PRSs in the set of *BRCA1* and *BRCA2* samples combined and separately.

We also investigated two PRSs by using SNPs that were associated with breast cancer risk for female *BRCA1/2* mutation carriers (Data Supplement).

Prostate Cancer PRS. Prostate cancer PRS included variants that were associated with prostate cancer at genome-wide significant level in studies of the PRACTICAL consortium.[11,14,32,35-38] Log-OR estimates from published population-based studies were used according to the approach above.[11,32] This PRS included 103 (71 genotyped, 32 imputed) SNPs (Data Supplement).

RESULTS

We evaluated associations for a total of 9,530,887 SNPs in 1,802 male carriers of *BRCA1/2* mutations, including 277 patients with breast cancer, 212 patients with prostate cancer, and 1,313 controls. We investigated associations in the combined sample of *BRCA1/2* mutation carriers and separately in *BRCA2* mutation carriers. The number of *BRCA1* mutation carriers was too small to allow for separate analyses. Across the two analyses, no associations at $P < 10^{-8}$ were identified. A total of 577 SNPs exhibited associations at $P < 10^{-5}$. GWAS results are reported in the Data Supplement.

Breast Cancer PRSs

Of 102 SNPs included in the breast cancer PRSs, 68 SNPs (67%) yielded OR estimates in the same direction as those that have been previously reported for females in the general population. Eleven SNPs were associated with breast cancer risk at $P < .05$ (Data Supplement). After accounting for multiple testing, there was no evidence of pairwise interactions between any two variants in the PRSs.

The three main breast cancer PRSs that were constructed on the basis of associations with female breast cancer risk were strongly associated with male breast cancer risk for both *BRCA1* and *BRCA2* mutation carriers (Table 1). The OR estimate for male breast cancer per standard deviation (SD) increase in overall PRS was estimated to be 1.36 (95% CI, 1.19 to 1.56; $P = 8.6 \times 10^{-6}$) in combined *BRCA1/2* carriers. Associations remained significant when *BRCA1* and *BRCA2* carriers were analyzed separately (*BRCA1*: OR, 1.49; 95% CI, 1.07 to 2.07; $P = .019$; *BRCA2*: OR, 1.36; 95% CI, 1.17 to 1.58; $P = 7.2 \times 10^{-5}$). Men in the 3rd and 4th quartiles were at significantly increased risk of breast cancer compared with men in the bottom quartile of the PRS (Table 1), but the numbers of carriers in individual quartiles in the *BRCA1* only analyses were too small to draw definitive conclusions.

The magnitude and strength of associations were similar for the PRS that was constructed on the basis of SNPs associated with ER-positive breast cancer in females (Table 1). The ER-negative PRS showed a weaker association with breast cancer risk for male carriers of *BRCA1/2* mutations. Results were similar when the associations were evaluated using logistic regression (Data Supplement) and when considering the patients with both breast and prostate cancer as a separate group in a multinomial logistic regression model (Data Supplement).

Prostate Cancer PRS

Of 103 SNPs that were included in the prostate cancer PRS, 74 SNPs (71%) had estimated ORs in the same direction as those previously reported in population-based studies. Eight SNPs were associated at $P < .05$ (Data Supplement).

There was a highly significant association between the prostate cancer PRS and prostate cancer risk for male carriers of *BRCA1/2* mutations (OR for prostate cancer per SD increase, 1.56; 95% CI, 1.35 to 1.81; $P = 3.2 \times 10^{-9}$; Table 2). Associations remained significant when analyses were performed separately for carriers of *BRCA1* and *BRCA2* mutations (*BRCA1*: OR, 1.72; 95% CI, 1.30 to 2.29; $P = 1.8 \times 10^{-4}$; *BRCA2*: OR, 1.49; 95% CI, 1.26 to 1.77; $P = 4.9 \times 10^{-6}$). There was an increasing risk of prostate cancer with increasing PRS quartiles. When compared with the 1st quartile, OR for prostate cancer for men in the 2nd quartile was 1.82 (95% CI, 1.07 to 3.08; $P = .026$), for men in the 3rd quartile, 2.23 (95% CI, 1.32 to 3.76; $P = .003$), and for men in the 4th quartile, 3.36 (95% CI, 2.05 to 5.52; $P = 1.7 \times 10^{-6}$).

We observed significant associations between prostate cancer PRS with both low (< 7) and high (≥ 7) Gleason score prostate cancers (Table 2). There was no evidence of interaction between age at diagnosis and/or observation and any breast or prostate cancer PRSs (Data Supplement).

Discriminatory Ability

The overall breast cancer and ER-positive PRSs had an area under the curve (AUC) of 0.59 (95% CI, 0.55 to 0.63). ER-negative PRS had the lowest AUC at 0.55 (95% CI, 0.51 to 0.59). The AUC for prostate cancer PRS was estimated to be 0.62 (95% CI, 0.58 to 0.66).

Predicted Risks of Male Breast and Prostate Cancer by PRS Percentile

We used the estimated OR for the breast cancer overall PRS and the prostate cancer PRS from the combined analysis of *BRCA1/2* samples to calculate male breast and prostate cancer risks at the 5th, 10th, 50th, 90th, and 95th percentiles of PRS distributions (Figs 1, 2, and 3 and Data Supplement). There were large differences in absolute risks between percentile groups. For *BRCA2* carriers, the risk of breast cancer by age 80 years is 5% for men at the 5th percentile of the PRS and 14% for men at the 95th percentile; the risk of prostate cancer by age 80 years is 19% for men at the 5th percentile of the PRS and 61% for men at the 95th percentile. For carriers of *BRCA1* mutations, men at the 5th percentile of the prostate cancer PRS have a 7% risk of developing prostate cancer by age 80, and men at the 95th percentile of the PRS distribution have a prostate cancer risk of 26%.

DISCUSSION

We performed the first GWAS, to our knowledge, in male carriers of *BRCA1/2* mutations to identify common variants that modify the risks of breast and prostate cancer in these men. Although we analyzed the largest series of male mutation carriers available, this study is underpowered to detect associations with individual low-risk SNPs.

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Table 1. Associations Between Overall PRS, ER-Positive PRS, and ER-Negative PRS With Male Breast Cancer Risk for Carriers of *BRCA1* and *BRCA2* Mutations

	All Samples					*BRCA1* Samples					*BRCA2* Samples				
Quartile	No. of Controls	No. of Breast Cancer Cases	OR	95% CI	*P*	No. of Controls	No. of Breast Cancer Cases	OR	95% CI	*P*	No. of Controls	No. of Breast Cancer Cases	OR	95% CI	*P*
Overall PRS															
1st	329	43	1.00	—	—	106	3	1.00	—	—	223	40	1.00	—	—
2nd	328	56	1.28	0.83 to 1.99	.265	92	12	4.78	1.30 to 17.6	.018	236	44	1.04	0.64 to 1.68	.873
3rd	327	76	1.72	1.14 to 2.60	.01	82	5	2.24	0.52 to 9.70	.28	245	71	1.68	1.08 to 2.61	.022
4th	329	102	2.35	1.57 to 3.51	3.1×10^{-5}	100	13	4.85	1.35 to 17.4	.015	229	89	2.18	1.41 to 3.37	4.7×10^{-4}
Trend	1,313	277	1.36*	1.19 to 1.56	8.6×10^{-6}	380	33	1.49*	1.07 to 2.07	.019	933	244	1.36*	1.17 to 1.58	7.2×10^{-5}
ER-positive PRS															
1st	328	41	1.00	—	—	103	2	1.00	—	—	225	39	1.00	—	—
2nd	329	56	1.36	0.87 to 2.11	.173	91	12	6.96	1.49 to 32.4	.014	238	44	1.07	0.66 to 1.73	.786
3rd	328	82	1.95	1.28 to 2.96	.002	87	7	4.34	0.86 to 22.0	.076	241	75	1.84	1.18 to 2.87	.007
4th	328	98	2.37	1.57 to 3.56	3.8×10^{-5}	99	12	6.58	1.41 to 30.7	.017	229	86	2.18	1.40 to 3.38	.001
Trend	1,313	277	1.36*	1.19 to 1.56	5.4×10^{-6}	380	33	1.59*	1.15 to 2.20	5.0×10^{-3}	933	244	1.35*	1.16 to 1.56	8.9×10^{-5}
ER-negative PRS															
1st	329	52	1.00	—	—	85	5	1.00	—	—	244	47	1.00	—	—
2nd	327	67	1.39	0.93 to 2.08	.108	103	10	1.74	0.56 to 4.43	.34	224	57	1.41	0.91 to 2.19	.123
3rd	329	78	1.61	1.10 to 2.38	.015	102	11	1.93	0.64 to 5.83	.245	227	67	1.61	1.06 to 2.46	.027
4th	328	80	1.60	1.08 to 2.37	.018	90	7	1.28	0.39 to 4.26	.686	238	73	1.73	1.13 to 2.64	.011
Trend	1,313	277	1.19*	1.05 to 1.35	6.0×10^{-3}	380	33	1.14*	0.81 to 1.60	.467	933	244	1.22*	1.06 to 1.40	6.0×10^{-3}

Abbreviations: ER, estrogen receptor; OR, odds ratio; PRS, polygenic risk score.
*OR for male breast cancer per standard deviation increase in the standardized PRS.

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Table 2. Associations of Population-Based Prostate Cancer PRS With Prostate Cancer Risk, Overall and by Tumor Gleason Grade, for Male Carriers of *BRCA1* and *BRCA2* Mutations

	All Samples					*BRCA1* Samples					*BRCA2* Samples				
PRS Group	No. of Controls	No. of Prostate Cancer Cases	OR	95% CI	*P*	No. of Controls	No. of Prostate Cancer Cases	OR	95% CI	*P*	No. of Controls	No. of Prostate Cancer Cases	OR	95% CI	*P*
Prostate cancer PRS, quartile															
1st	328	26	1.00	—	—	88	9	1.00	—	—	240	17	1.00	—	—
2nd	329	47	1.82	1.07 to 3.08	.026	94	14	1.45	0.59 to 3.58	.418	235	33	2.01	1.05 to 3.86	.035
3rd	328	55	2.23	1.32 to 3.76	.003	106	15	1.45	0.59 to 3.58	.416	222	40	2.69	1.41 to 5.12	.003
4th	328	84	3.36	2.05 to 5.52	1.7×10^{-6}	92	33	3.45	1.50 to 7.97	.004	236	51	3.26	1.75 to 6.06	1.8×10^{-4}
Trend	1,313	212	1.56†	1.35 to 1.81	3.2×10^{-9}	380	71	1.72†	1.30 to 2.29	1.8×10^{-4}	933	141	1.49†	1.26 to 1.77	4.9×10^{-6}
Association between prostate PRS and prostate cancer by Gleason score															
Controls	1,313	—	—	—	—	380	—	—	—	—	933	—	–	—	—
Gleason score < 7	—	53	1.44†	1.10 to 1.87	.008	—	26	1.26†	0.81 to 1.94	.306	—	27	1.64†	1.17 to 2.31	.004
Gleason score ≥ 7	—	102	1.67†	1.37 to 2.04	4.7×10^{-7}	—	21	2.01†	1.23 to 3.29	.005	—	81	1.59†	1.29 to 1.97	2.0×10^{-5}
Gleason score missing	—	57	1.49†	1.13 to 1.97	.004	—	24	2.09†	1.37 to 3.17	.001	—	33	1.18†	0.82 to 1.68	.370
Case only analysis: Gleason score ≥ 7 *v* < 7			1.19†	0.81 to 1.75	.372			1.60†	0.89 to 2.90	.118			0.99†	0.59 to 1.66	.960

Abbreviations: OR, odds ratio; PRS, polygenic risk score.
†OR for prostate cancer per standard deviation increase in the standardized PRS.

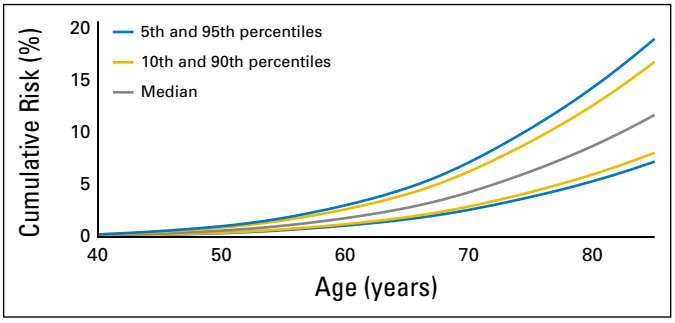


Fig 1. Predicted breast cancer cumulative risk for male carriers of *BRCA2* mutations by percentile of overall polygenic risk score that was constructed by using results from population-based studies.

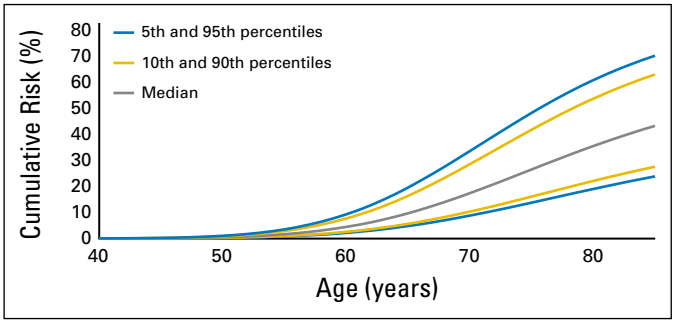


Fig 3. Predicted prostate cancer cumulative risk for male carriers of *BRCA2* mutations by percentiles of prostate cancer polygenic risk score that was constructed by using results from population-based studies.

We have demonstrated that the combined effects of known breast cancer susceptibility SNPs modify breast cancer risk for male mutation carriers and, separately, that the combined effects of known prostate cancer susceptibility SNPs modify prostate cancer risk for male mutation carriers.

PRSs that were constructed with SNPs for female breast cancer and prostate cancer in the general population are highly predictive of risk in male carriers of *BRCA1/2* mutations. These results provide the first direct evidence of overlap in the genetic susceptibility to female breast and prostate cancers in the general population as well as the modification of risks of male breast and prostate cancer in men with *BRCA1/2* mutations.

We estimated an OR for breast cancer of 1.36 per SD increase in the overall breast cancer PRS. No study in the general population has assessed this exact PRS yet, but Mavaddat et al[15] estimated an OR for female breast cancer of 1.55 for a PRS based on a subset of SNPs in females. Although the present estimate in males is not significantly different from that observed in females, it is somewhat lower. A lower OR may be a result of certain breast cancer SNPs that were included in the PRS that are not associated with male breast cancer risk, or individual SNPs may have smaller ORs for male breast cancer than female breast cancer. Alternatively, the estimate of Mavaddat et al[15] may be susceptible to some level of winner's curse bias.

The prostate cancer PRS was associated with prostate cancer risk in male carriers of *BRCA1/2* mutations, with an OR of 1.56 per SD increase in PRS. A previous study on prostate cancer PRS in the general population estimated an OR of 1.74.[14]

Overall, our results indicate that population-based breast and prostate cancer PRSs are predictive of cancer risk for male mutation carriers, which suggests a general model of susceptibility under which *BRCA1/2* mutations and other common cancer susceptibility variants interact multiplicatively on the risk of developing breast and prostate cancers.

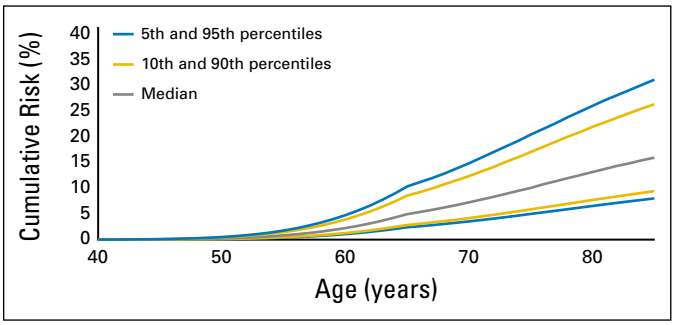


Fig 2. Predicted prostate cancer cumulative risk for male carriers of *BRCA1* mutations by percentiles of prostate cancer polygenic risk score that was constructed by using results from population-based studies.

To calculate PRSs we have used SNPs and corresponding log-OR estimates from external, population-based studies; therefore, the present analysis represents an independent validation of those externally derived PRSs and indicates that they are independently predictive of cancer risks for male carriers of *BRCA1/2* mutations. Although the present analysis was based on a case-control study design, information on SNPs is not subject to the usual biases that are associated with retrospective studies (eg, recall biases); therefore, the reported associations between the PRSs investigated and cancer risks are unlikely to be influenced by the study design.

The ER-positive PRS had a stronger association with male breast cancer in *BRCA1/2* mutation carriers than did the ER-negative PRS, which was in line with the observation that the majority of male patients with breast cancer among *BRCA1/2* mutation carriers are ER positive.[23]

We observed large differences in absolute risk between men in the bottom and the top of the PRS distribution. In particular, prostate cancer risk by age 80 years for male carriers of *BRCA1* mutations ranges from 7% for those at the bottom 5% of the risk distribution to 26% for those at the top 5% of the PRS distribution. By age 80 years, male carriers of *BRCA2* mutations are predicted to have a risk of prostate cancer that ranges from 19% for those at the bottom 5% of the risk distribution to 61% for those at the top 5% of the distribution, and a breast cancer risk that ranges from 5% to 14%.

In these calculations, we assumed conservative average prostate cancer risks for both *BRCA1* and *BRCA2* mutations; however, higher estimates for the effect of *BRCA1/2* mutations have been reported in the literature.[4,9] Prospective studies of male mutation carriers will be useful for assessing the calibration of absolute cancer risks by PRS percentiles; however, such studies are not currently available with sufficiently large numbers of incident male breast and prostate cancer cases.

Although there are no established screening or intervention strategies for male carriers of *BRCA1/2* mutations, few clinical management recommendations include education, clinical breast examination, and prostate cancer screening.[39] The present findings may inform the development of clinical recommendations on the basis of polygenic risk stratification of male mutation carriers to personalize management recommendations. For example, the current

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United Kingdom NICE guidelines recommend enhanced surveillance for women with a lifetime risk greater than 17% of developing breast cancer, regardless of their *BRCA1/2* status.[40] Similar approaches may be developed for male carriers of *BRCA1/2* mutations for whom management would differ on the basis of their individual lifetime risk. For example, on the basis of the prostate cancer PRS, 43% of men with *BRCA1* mutations are predicted to have a prostate cancer risk of greater than 17% and may benefit from enhanced screening, whereas those at lower risk may opt for more limited surveillance.

Our data provide a strong impetus for new prospective screening studies in high-risk cohorts, such as the IMPACT trial,[41] to include genetic risk assessment by PRSs in study protocols to assess the impact of cancer risk stratification in male mutation carriers. Recently, it has been suggested that polygenic risk-stratified screening can reduce overdiagnosis in the general population.[42-44] Similar arguments may apply to male mutation carriers in whom polygenic risk prediction may further improve the effectiveness of screening.

A potential limitation of the current study is that family history information was not readily available for mutation carriers; therefore it was not possible to assess how the prostate and breast cancer risks in male carriers that are associated with PRSs vary by family history. Although this would not invalidate the association results, considering the effect of family history will be important in the context of genetic counseling.

Men with *BRCA1/2* mutations represent a small but unique patient group in terms of clinical management. Our results suggest that risk profiling on the basis of PRSs may identify male carriers of *BRCA1/2* mutations at both sufficiently reduced or increased risk of breast or prostate cancer, with implications for their clinical management. To facilitate this, it will be important to incorporate such PRSs into breast or prostate cancer risk prediction algorithms.[45]

As an accurate risk assessment is the basis of cancer prevention and screening strategies, the PRSs presented here may be used to provide male carriers of *BRCA1/2* mutations and their physicians with more detailed information on their breast and prostate cancer risks to aid prevention and screening decisions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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