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

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ABSTRACT

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 BRCA1/2mutations from the Consortium of Investigators of Modifiers of BRCA1/2by 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 BRCA1/2mutations by constructing weighted polygenic risk scores (PRSs) using published effect estimates as weights.

Results

In male carriers of BRCA1/2mutations, 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; = 3.2). 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; = 10.5). Larger 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 61% for carriers of BRCA1/2mutations, respectively.

Conclusion

PRSs may provide informative cancer risk stratification for male carriers of BRCA1/2mutations 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 \textit{BRCA1} and, predominantly, \textit{BRCA2} are associated with increased risks in men of developing breast and prostate cancers.\textsuperscript{1,2} \textit{BRCA1}/2 mutations account for approximately 10\% of male breast cancer and 2\% of prostate cancer cases.\textsuperscript{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.\textsuperscript{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 \textit{BRCA2} and \textit{BRCA1} mutations, respectively, whereas estimates of lifetime prostate cancer risk are approximately 20\% and 40\% for carriers of \textit{BRCA1} and \textit{BRCA2} mutations, respectively.\textsuperscript{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,\textsuperscript{11,12} and their combined effects have been shown to have significant implications for risk stratification and targeted prevention.\textsuperscript{13-15} By contrast, only two male breast cancer susceptibility SNPs have been identified to date,\textsuperscript{16} but there is some evidence that suggests that common variants that are associated with female breast cancer may influence male breast cancer risk.\textsuperscript{17-19}

Studies by the Consortium of Investigators of Modifiers of \textit{BRCA1}/2 (CIMBA) have shown that common SNPs modify the risk of breast and ovarian cancers for female \textit{BRCA1} and \textit{BRCA2} mutation carriers.\textsuperscript{20-22} However, no study to date has investigated the associations of common SNPs with breast or prostate cancer risk for men with \textit{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 \textit{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 \textit{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 \textit{BRCA1}/2 mutations.

MATERIALS AND METHODS

Samples

CIMBA collects data on men with \textit{BRCA1} or \textit{BRCA2} clearly pathogenic variants—commonly termed mutations—who are older than 18 years, with the majority recruited via cancer genetics clinics.\textsuperscript{23} Pathogenic variants were defined as previously described.\textsuperscript{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 \textit{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 (\textit{BRCA1} or \textit{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 (\textit{BRCA1} or \textit{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\textsuperscript{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\textsuperscript{23} (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.\textsuperscript{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.
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. Log-OR estimates from published population-based studies were used according to the approach above. 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 $P < 0.05$ (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 $1.56$; $P = 8.6 \times 10^{-5}$) 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 $2.07$; $P = 0.019$; 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 $P < 0.05$ (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 $1.81$; $P = 3.2 \times 10^{-5}$; 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 $3.08$; $P = 0.026$), for men in the 3rd quartile, $2.23$ (95% CI, $1.32$ to $3.76$; $P = 0.003$), and for men in the 4th quartile, $3.36$ (95% CI, $2.05$ to $5.52$; $P = 1.7 \times 10^{-5}$).

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 ORS 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.
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

| Quartile | All Samples | BRCA1 Samples | BRCA2 Samples |
|----------|-------------|---------------|---------------|
|          | 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 | 1.06 to 2.61 | .022 |
| 4th | 329 | 102 | 2.35 | 1.57 to 3.51 | 3.1 × 10⁻⁶ | 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 | 3.36* | 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 × 10⁻⁶ |
| ER-positive PRS | | | | | | | | | | | | | | |
| 1st | 328 | 41 | 1.00 | — | — | 103 | 2 | 1.00 | — | — | 223 | 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 × 10⁻⁶ | 99 | 12 | 6.56 | 1.41 to 30.7 | .017 | 229 | 86 | 2.18 | 1.40 to 3.38 | .001 |
| Trend | 1,313 | 277 | 3.36* | 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 × 10⁻⁶ |
| 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 | 1.85* | 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.
| PRS Group | No. of Controls | No. of Prostate Cancer Cases | OR 95% CI | P   |
|-----------|----------------|-----------------------------|---------|----|
| Prostate cancer PRS, quartile | | | | |
| 1st       | 328            | 26                          | 1.00    | —  |
| 2nd       | 329            | 47                          | 1.62    | 1.07 to 3.08 | .026 |
| 3rd       | 328            | 56                          | 2.23    | 1.32 to 3.76 | .003 |
| 4th       | 328            | 84                          | 3.36    | 2.05 to 5.52 | 1.7 x 10^-6 |
| Trend     | 1,313          | 212                         | 1.56†   | 1.35 to 1.81 | 3.2 x 10^-6 |

**Association between prostate PRS and prostate cancer by Gleason score**

| Controls | No. of Cases | OR 95% CI | P   |
|----------|--------------|-----------|----|
| Gleason score < 7 | —            | 1.44† | 1.10 to 1.87 | .008 |
| Gleason score ≥ 7 | —            | 1.67† | 1.37 to 2.04 | 4.7 x 10^-7 |

**Case only analysis:**

| Case only analysis | No. of Cases | OR 95% CI | P   |
|--------------------|--------------|-----------|----|
| Gleason score ≥ 7 | —            | 1.49† | 1.13 to 1.97 | .004 |

Abbreviations: OR, odds ratio; PRS, polygenic risk score.
†OR for prostate cancer per standard deviation increase in the standardized PRS.
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 al15 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 significant 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 al15 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.

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.30 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...
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 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.

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Final approval of manuscript: All authors

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Support

Supported by the Italian Association for Cancer Research [AIRC, IG16933; for genotyping of the OncoArray in male mutation carriers]; genotyping of the OncoArray in CIMBA was supported by the Ministère de l’Économie, Innovation et Exportation du Québec Grant No. PSR-SIIRI-701 and the Government of Canada through Genome Canada and the Canadian Institutes of Health Research (GPH-129344), the Ministère de l’Économie, de la Science et de l’Innovation du Québec through Genome Québec, the Quebec Breast Cancer.

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Oncology Institute–Porto Breast Cancer Study) was supported by Liga Portuguesa Contra o Cancro. kConFab (Kathleen Cuningham Consortium for Research into Familial Breast Cancer) was supported by a grant from the National Breast Cancer Foundation, and previously by the National Health and Medical Research Council (NHMRC), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania, and South Australia, and the Cancer Foundation of Western Australia. The Clinical Follow Up Study received funding from the NHMRC, the National Breast Cancer Foundation, Cancer Australia, and the US NIH. A.B.S. is supported by an NHMRC senior research Fellowship (APP1061779). Curation of CIMBA variant nomenclature and classification in the Spurdle laboratory was supported by funding from the Cancer Council Queensland (APP1086286). KOHBRA (Korean Hereditary Breast Cancer Study) was supported by a grant from the National R&D Program for Cancer Control, Ministry for Health, Welfare and Family Affairs, Republic of Korea (1020350). KUMC (University of Kansas Medical Center) was supported by the University of Kansas Cancer Center (Grant No. P30-CA168524). MAYO (Mayo Clinic) was supported by NIH Grants No. CA116167, CA128978, and CA176785, a National Cancer Institute Specialized Program of Research Excellence (SPORE) in Breast Cancer (Grant No. CA116201), a grant from the Breast Cancer Research Foundation, and a generous gift from the David F. and Margaret T. Grohne Family Foundation. McGill University was supported by Jewish General Hospital Weekend to End Breast Cancer, Quebec Ministry of Economic Development, Innovation and Export Trade. Memorial Sloan Kettering Cancer Center was supported by grants from the Breast Cancer Research Foundation, the Robert and Kate Niehaus Clinical Cancer Genetics Initiative, and the Andrew Sabin Research Fund. NCI research of M.H.G. and J.T.L was supported by the Intramural Research Program of the US National Cancer Institute, and by support services contracts NO2-CP-11019-50 and NO2-CP-65504 with Westat, Rockville, MD. OSUCCG (The Ohio State University Comprehensive Cancer Center) was supported by the Ohio State University Comprehensive Cancer Center. SEABASS (South East Asian Breast Cancer Association Study) was supported by the Ministry of Science, Technology and Innovation, Ministry of Higher Education (UM.C/HIR/MOHE/06) and Cancer Research Initiatives Foundation. The Malaysian Breast Cancer Genetic Study is funded by research grants from the Malaysian Ministry of Science, Technology, and Innovation, Ministry of Higher Education (UM.C/HIR/MOHE/06), and charitable funding from Cancer Research Initiatives Foundation. SWE-BRCA (Swedish Breast Cancer Study) collaborators are supported by the Swedish Cancer Society. University of Chicago was supported by National Cancer Institute Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA125183), Grants No. R01-CA142996 and 1U01-CA161032, and by the Ralph and Marion Falk Medical Research Trust, the Entertainment Industry Fund National Women’s Cancer Research Alliance, and the Breast Cancer Research Foundation. University of Pennsylvania was supported by Breast Cancer Research Foundation; Susan G. Komen Foundation for the cure, Bassers Research Center for BRCA. University of Pittsburgh Magee-Women’s Hospital was supported by Frieda G. and Saul F. Shapira BRCA-Associated Cancer Research Program; Hackers for Hope Pittsburgh. Victorian Familial Cancer Trials Group (VFCTG) was supported by Victorian Cancer Agency, Cancer Australia, National Breast Cancer Foundation.

Prior Presentation

Presented at the 2015 Annual Meeting of the American Society of Human Genetics, October 6-10, 2015, Baltimore, MD.
# Authors' Disclosures of Potential Conflicts of Interest

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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to [www.asco.org/rwc](http://www.asco.org/rwc) or [ascopubs.org/jco/site/ifc](http://ascopubs.org/jco/site/ifc).

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Research Funding: Deciphera Pharmaceuticals (Inst)

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Dieter Niederacher  
No relationship to disclose

Doris Steinemann  
No relationship to disclose

Eric Hahnen  
Consulting or Advisory Role: AstraZeneca

Jan Hauke  
No relationship to disclose

Kerstin Rhiem  
Consulting or Advisory Role: AstraZeneca

Karin Kast  
Honoraria: Astra Zeneca

Consulting or Advisory Role: Roche

Travel, Accommodations, Expenses: Celgene, Roche

Norbert Arnold  
Honoraria: AstraZeneca

Consulting or Advisory Role: AstraZeneca

Nina Ditsch  
No relationship to disclose

Shan Wang-Gohrke  
No relationship to disclose

Barbara Wappenschmidt  
No relationship to disclose

Dorothea Wand  
No relationship to disclose

Christine Lasset  
No relationship to disclose

Dominique Stoppa-Lyonnet  
Consulting or Advisory Role: AstraZeneca

Research Funding: AstraZeneca (Inst)

Muriel Belotti  
No relationship to disclose

Francesca Daniola  
No relationship to disclose

Laure Barjhoux  
No relationship to disclose

Sylvie Mazoyer  
No relationship to disclose

Mattias Van Heetvelde  
No relationship to disclose

Bruce Poppe  
No relationship to disclose

Kim De Leeneer  
No relationship to disclose

Kathleen B.M. Claes  
No relationship to disclose

Miguel de la Hoya  
No relationship to disclose

Vanessa Garcia-Barberan  
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Pedro Perez Segura  
No relationship to disclose

Johanna I. Kiiski  
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Kristiina Aittomäki  
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Sofia Khan  
No relationship to disclose

Heli Nevanlinna  
No relationship to disclose
Polygenic Risk Scores in Male \textit{BRCA1} and \textit{BRCA2} Mutation Carriers
We thank Sue Healey for her contribution to CIMBA, in particular, for taking on the task of mutation classification with Olga Sinilnikova.

BCFR Australia: We acknowledge Maggie Angelakos, Judi Maskiell, Gillian Dite, Helen Tsimiklis.

BCFR Ontario: We thank members and participants in the Ontario Familial Breast Cancer Registry for their contributions to the study. BFBOCC-LT (Baltic Familial Breast Ovarian Cancer Consortium Lithuanian section): We acknowledge Vilius Rudaitis and Laimonas Griskevičius.

CIMBA (Copenhagen Breast Cancer Study, Rigshospitalet): We thank Bent Ejlersen Ejlersen and Anne-Marie Gerdes for the recruitment and genetic counseling of participants.

CNIO (Spanish National Cancer Centre): We thank Alicia Barroso, Rosario Alonso, and Guillermo Pita for their assistance.

COH-CGGCRN (City of Hope Clinical Cancer Genomics Community Research Network): Patients were recruited for study from the City of Hope Clinical Cancer Genomics Community Research Network. CONSIT TEAM: We acknowledge Daniela Zaffaroni of the Fondazione IRCCS Istituto Nazionale Tumori (INT), Milan, Italy; Brunella Pilato of the Istituto Nazionale Tumori “Giovanni Paolo II”, Bari, Italy; and the personnel of the Cogentech Cancer Genetic Test Laboratory, Milan, Italy. FCCC (Fox Chase Cancer Center): We thank Jo Ellen Weaver and Betsy Bove, MD, for their technical support.

GEMO (Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers): We pay a tribute to Olga M. Sinilnikova, who with Dominique Stoppa-Lyonnet, initiated and coordinated GEMO until she died on June 30, 2014, and we thank all the GEMO collaborating groups for their contribution to this study. GEMO Collaborating Centers are: Coordinating Centers, Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Hospices Civils de Lyon—Léon Bérard, Equipe Génétique du cancer du sein, Centre de Recherche Cancérologie de Lyon: Olga Sinilnikova (deceased), Sylvie Mazoyer, Francesca Damiali, Laure Barjhoux, Carole Verny-Pierre, Mélanie Léone, Nadia Bouteyr-Kryza, Alain Calender, Sophie Giraud; and Service de Génétique Oncologique, Institut Curie, Paris: Dominique Stoppa-Lyonnet, Marion Gauthier-Villars, Bruno Bieuch, Claude Houdayer, Etienne Rouleau, Lisa Golimard, Agnès Collet, Virginie Moncoutier, Muriel Belotti, Antoine de Pauw, Camille Elan, Catherine Nogues, Emmanuelle Fournie, Anne-Marie Birot; Institut Gustave Roussy, Villejuif: Brigitte Bressac-de-Pailleters, Olivier Caron, Marine Guillaud-Bataille; Centre Jean Perrin, Clermont-Ferrand: Yves-Jean Bignon, Nancy Uhrhammer; Centre Léon Bérard, Lyon: Christine Lasset, Valérie Bonadona, Sandrine Handallou; Centre François Baclesse, Caen: Agnès Hardouin, Pascaline Berthet, Dominique Varu, Laurent Castera; Institut Paoli Calmettes, Marseille: Hagay Sobol, Violaine Bourdon, Tetsuro Noguchi, Audrey Remenieras, François Eisinger; CHU Arnaud-de-Villeneuve, Montpellier: Isabelle Coupier, Pascal Pujol; Centre Oscar Lambret, Lille: Jean-Philippe Peyrat, Joëlle Fournier, Castera; Institut Paoli Calmettes, Marseille: Hagay Sobol, Violaine Bourdon, Tetsuro Noguchi, Audrey Remenieras, François Eisinger; CHU Arnaud-de-Villeneuve, Montpellier: Isabelle Coupier, Pascal Pujol; Centre Oscar Lambret, Lille: Jean-Philippe Peyrat, Joëlle Fournier, Françoise Révillion, Philippe Vennin (deceased), Claude Adenis; Centre Paul Strauss, Strasbourg: Danielle Muller, Jean-Pierre Fricker; Institut Bergonie, Bordeaux: Emmanuelle Barouk-Simonet, Françoise Bonnet, Virginie Bubien, Nicolas Sevenet, Michel Longy; Institut Claudius Regaud, Toulouse; Clermont-Ferrand: Yves-Jean Bignon, Nancy Uhrhammer; Centre Grenoble: Dominique Leroux, Hélène Dreyfus, Christine Rebischung, Magalie Peysselon; CHU Dijon: Fanny Coron, Laurence Faivre; CHU St-Etienne: Fabienne Prieur, Marine Lebrun, Caroline Kientz; Hôtel-Dieu Centre Hospitalier, Chambéry: Sandra Fert Ferrer; Centre Antoine Lacassagne, Nice: Marc Fréna; CHU Limoges: Laurence Vénat-Bouvet; CHU Nantes: Capucine Delnatte; CHU Bretonneau, Tours: Isabelle Mortemousse; Groupe Hospitalier Pitié-Salpêtrière, Paris: Florence Coulet, Cristelle Colas, Florent Soubrier, Mathilde Warcoin; CHU Vandoeuvre-les-Nancy: Johanna Sokolowska, Myriam Bronner; CHU Besançon: Marie-Agnès Collonge-Rame, Alexandre Damette; Creighton University, Omaha, NE: Henry T. Lynch, Carrie L. Snyder; G-FAST (Ghent University Hospital): B.P. is a senior clinical investigator of FWO. We acknowledge the technical support of Ilse Coeneen Brecht Crombez.

The personnel of the Cogentech Cancer Genetic Test Laboratory, Milan, Italy.

The Netherlands Comprehensive Cancer Organization (IKNL): L.I.H. Overbeek. HEBON thanks the registration teams of IKNL and PALGA for part of the data collection.

OLGC (Ovarian Cancer Research Group Netherlands (HEBON)): L.I.H. Overbeek. HEBON thanks the registration teams of IKNL and PALGA for part of the data collection.

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Acknowledgment
Breast Cancer Study): We thank Catarina Santos, MD, for her skillful contribution to the study. kConFab (Kathleen Cuningham Consortium for Research into Familial Breast Cancer): We thank Heather Thorne, Eveline Niedermayr, all the kConFab research nurses and staff, the heads and staff of the Family Cancer Clinics, and the Clinical Follow Up Study for their contributions to this resource, and the many families who contribute to kConFab. Memorial Sloan Kettering Cancer Center: We acknowledge Lauren Jacobs, MD. OCGN (Ontario Cancer Genetics Network): We thank members and participants in the Ontario Cancer Genetics Network for their contributions to the study. OSUCCG (The Ohio State University Comprehensive Cancer Center): Kevin Sweet, Caroline Craven, Julia Cooper, Leigha Senter, and Michelle O’Conor were instrumental in accrual of study participants, ascertainment of medical records, and database management. SEABASS (South East Asian Breast Cancer Association Study): We thank Yip Cheng Har, Nur Aishah Mohd Taib, Phuah Sze Yee, Norhashimah Hassan, and all the research nurses, research assistants, and doctors involved in the MyBrCa Study for assistance in patient recruitment, data collection, and sample preparation. In addition, we thank Philip Iau, Sng Jen-Hwei, and Sharifah Nor Akmal for contributing samples from the Singapore Breast Cancer Study and the HUKM-HKL Study, respectively. SWE-BRCA (Swedish Breast Cancer Study): Swedish scientists participating as SWE-BRCA collaborators are: from Lund University and University Hospital: Åke Borg, Håkan Olsson, Helena Jernström, Karin Henriksson, Katja Harbst, Maria Soller, Ulf Kristoffersson; from Gothenburg Sahlgrenska University Hospital: Anna Öfverholm, Margareta Nordling, Per Karlsson, Zakaria Einbeigi; from Stockholm and Karolinska University Hospital: Anna von Wachenfeldt, Annelie Liljegren, Annika Lindblom, Brita Arver, Gisela Barbany Bustinza, Johanna Rantala; from Umeå University Hospital: Beatrice Melin, Christina Edwinsdotter Ardnor, Monica Emanuelsson; from Uppsala University: Hans Ehrencrona, Maritta Hellström Pigg, Richard Rosenquist; from Linköping University Hospital: Marie Stenmark-Askmalm, Sigrun Liedgren. University of Chicago: O.I.O. is an ACS Clinical Research Professor. We thank Cecilia Zvocec, Qun Niu, physicians, genetic counsellors, research nurses, and staff of the Cancer Risk Clinic for their contributions to this resource, and the many families who contribute to our program. VFCTG (Victorian Familial Cancer Trials Group): We acknowledge Geoffrey Lindeman, Marion Harris, Martin Delatycki of the Victorian Familial Cancer Trials Group. We thank Sarah Sawyer and Rebecca Driessen for assembling these data and Ella Thompson for performing all DNA amplification.