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

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<td>Published Version</td>
<td>doi:10.1200/JCO.2016.69.4935</td>
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Prediction of Breast and Prostate Cancer Risks in Male BRCA1 and BRCA2 Mutation Carriers Using Polygenic Risk Scores


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 OncArray. 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, $P = 8.6 \times 10^{-15}$). 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, $P = 3.2 \times 10^{-10}$). 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 BRCA1/2 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.
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 multimonial 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 studies11,12,22,25-32 (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 methods25 (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.
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 genotypic, 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; \( P = 8.6 \times 10^{-5} \)) 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; \( P = .019 \); 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; \( P = 3.2 \times 10^{-3} \); 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; \( P = 1.7 \times 10^{-3} \)).

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.
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

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Overall PRS</th>
<th>BRCA1 Samples</th>
<th>BRCA2 Samples</th>
</tr>
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<tr>
<td></td>
<td>No. of Controls</td>
<td>No. of Breast Cancer Cases</td>
<td>OR</td>
</tr>
<tr>
<td>All Samples</td>
<td>329</td>
<td>43</td>
<td>1.00</td>
</tr>
<tr>
<td>1st 328</td>
<td>56</td>
<td>1.28</td>
<td>0.83 to 1.99</td>
</tr>
<tr>
<td>2nd 327</td>
<td>76</td>
<td>1.72</td>
<td>1.14 to 2.60</td>
</tr>
<tr>
<td>3rd 328</td>
<td>102</td>
<td>2.35</td>
<td>1.57 to 3.51</td>
</tr>
<tr>
<td>4th 329</td>
<td>102</td>
<td>2.35</td>
<td>1.57 to 3.51</td>
</tr>
<tr>
<td>Trend 1,313</td>
<td>277</td>
<td>1.36*</td>
<td>1.19 to 1.56</td>
</tr>
<tr>
<td>ER-positive PRS</td>
<td>1st 329</td>
<td>52</td>
<td>1.00</td>
</tr>
<tr>
<td>2nd 329</td>
<td>56</td>
<td>1.39</td>
<td>0.93 to 2.08</td>
</tr>
<tr>
<td>3rd 329</td>
<td>78</td>
<td>1.61</td>
<td>1.10 to 2.38</td>
</tr>
<tr>
<td>4th 328</td>
<td>80</td>
<td>1.60</td>
<td>1.08 to 2.37</td>
</tr>
<tr>
<td>Trend 1,313</td>
<td>277</td>
<td>1.19*</td>
<td>1.05 to 1.35</td>
</tr>
</tbody>
</table>

| ER-negative 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 328 | 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 | 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 × 10⁻⁶ |

Abbreviations: ER, estrogen receptor; OR, odds ratio; PRS, polygenic risk score. *OR for male breast cancer per standard deviation increase in the standardized PRS.
<table>
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<tr>
<th>PRS Group</th>
<th>No. of Controls</th>
<th>No. of Prostate Cancer Cases</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>No. of Controls</th>
<th>No. of Prostate Cancer Cases</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>No. of Controls</th>
<th>No. of Prostate Cancer Cases</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
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<td>PRS, quartile</td>
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</tr>
<tr>
<td>1st</td>
<td>328</td>
<td>26</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
<td>88</td>
<td>9</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
<td>240</td>
<td>17</td>
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<tr>
<td>2nd</td>
<td>329</td>
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<td>1.07 to 3.08</td>
<td>.026</td>
<td>94</td>
<td>14</td>
<td>1.45</td>
<td>0.59 to 3.58</td>
<td>.418</td>
<td>235</td>
<td>33</td>
<td>1.45</td>
<td>0.59 to 3.58</td>
<td>.418</td>
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<tr>
<td>3rd</td>
<td>328</td>
<td>56</td>
<td>2.23</td>
<td>1.32 to 3.76</td>
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<td>106</td>
<td>15</td>
<td>1.45</td>
<td>0.59 to 3.58</td>
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<td>222</td>
<td>40</td>
<td>2.69</td>
<td>1.41 to 5.12</td>
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<td>328</td>
<td>84</td>
<td>3.36</td>
<td>2.05 to 5.52</td>
<td>1.7 × 10⁻²</td>
<td>92</td>
<td>33</td>
<td>3.45</td>
<td>1.50 to 7.97</td>
<td>.004</td>
<td>236</td>
<td>51</td>
<td>3.26</td>
<td>1.75 to 6.06</td>
<td>1.8 × 10⁻³</td>
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<tr>
<td>Trend</td>
<td>1,313</td>
<td>212</td>
<td>1.56†</td>
<td>1.35 to 1.81</td>
<td>3.2 × 10⁻²</td>
<td>380</td>
<td>71</td>
<td>1.72†</td>
<td>1.30 to 2.29</td>
<td>1.8 × 10⁻³</td>
<td>933</td>
<td>141</td>
<td>1.49†</td>
<td>1.26 to 1.77</td>
<td>4.9 × 10⁻²</td>
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<td>Association between prostate PRS and prostate cancer by Gleason score</td>
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<tr>
<td>Controls</td>
<td>1,313</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>380</td>
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<td>933</td>
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<td>—</td>
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<tr>
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<td>53</td>
<td>1.44†</td>
<td>1.10 to 1.87</td>
<td>.008</td>
<td>—</td>
<td>26</td>
<td>1.26†</td>
<td>0.81 to 1.94</td>
<td>.306</td>
<td>—</td>
<td>27</td>
<td>1.64†</td>
<td>1.17 to 2.31</td>
<td>.004</td>
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<td>102</td>
<td>1.67†</td>
<td>1.37 to 2.04</td>
<td>4.7 × 10⁻²</td>
<td>—</td>
<td>21</td>
<td>2.01†</td>
<td>1.23 to 3.29</td>
<td>.005</td>
<td>—</td>
<td>81</td>
<td>1.59†</td>
<td>1.29 to 1.97</td>
<td>2.0 × 10⁻²</td>
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<tr>
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<td>57</td>
<td>1.49†</td>
<td>1.13 to 1.97</td>
<td>.004</td>
<td>—</td>
<td>24</td>
<td>2.09†</td>
<td>1.37 to 3.17</td>
<td>.001</td>
<td>—</td>
<td>33</td>
<td>1.18†</td>
<td>0.82 to 1.68</td>
<td>.370</td>
</tr>
<tr>
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<tr>
<td>Gleason score ≥ 7</td>
<td></td>
<td>7</td>
<td>1.19†</td>
<td>0.81 to 1.75</td>
<td>.372</td>
<td>1.60†</td>
<td>0.89 to 2.90</td>
<td>.118</td>
<td>0.99†</td>
<td>0.59 to 1.66</td>
<td>.960</td>
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</tbody>
</table>

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 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 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.4,9,24 Propective 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.20–22 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.\(^4^0\) 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,\(^4^1\) 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.\(^4^2\)-\(^4^4\) 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.\(^4^5\)

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.

**Administrative support:** Antonis C. Antoniou

**Provision of study materials or patients:** Melissa Southey, Ramunas Janavicius, Yuan Chun Ding, Paolo Radice, Karin Kast, Kathleen B.M. Claes, Heli Nevanlinna, Gord Glendon, Sook-Yee Yoon, Katherine L. Nathanson, Antonis C. Antoniou


**Data analysis and interpretation:** Julie Lecarpentier, Valentina Silvestri, Karoline B. Kuchenbaecker, Ali Amin Al Olama, Rita K. Schmutzler, Antonis C. Antoniou, Laura Ottini

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

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

**AUTHOR CONTRIBUTIONS**

Conception and design: Georgia Chenevix-Trench, Rita K. Schmutzler, Antonis C. Antoniou, Laura Ottini

**REFERENCES**


8. Thompson D, Easton DF: Breast Cancer Linkage Consortium: Cancer incidence in BRCA1

Affiliations
Julie Lecarpentier, Karoline B. Kuchenbaecker, Daniel Barrowdale, Joe Dennis, Lesley McGuffog, Goska Leslie, Andrew Lee, Ali Amin Al Olama, Jonathan P. Tyrer, Debra Frost, Steve Ellis, Douglas F. Easton, and Antonius C. Antoniou, University of Cambridge; Karoline B. Kuchenbaecker, The Wellcome Trust Sanger Institute, Hinxton; Marc Tischkowitz, Addenbrooke’s Treatment Centre, Addenbrooke’s Hospital, Cambridge; D. Gareth Evans, Manchester University, Central Manchester University Hospitals NHS Foundation Trust, Manchester; Alex Henderson, Newcastle Upon Tyne Hospitals NHS Trust, Newcastle upon Tyne; Carole Brewer, Royal Devon and Exeter Hospital, Exeter; Diana Eccles, Southampton University Hospitals NHS Trust, Southampton; Jackie Cook, Sheffield Children’s Hospital, Sheffield; Kai-ren Ong, Birmingham Women’s Hospital Healthcare NHS Trust, Edgbaston, Birmingham; Lisa Walker, Churchill Hospital, Oxford; Lucy E. Siddall, Great Ormond Street Hospital for Children NHS Trust; Shirley Hodgson, St George’s, University of London; Louise Izatt, Guy’s and St Thomas’ NHS Foundation Trust; Ros Eeles, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust; Nick Orr, The Institute of Cancer Research, London; Mary E. Porteous, Western General Hospital, Edinburgh; Rosemarie Davidson, South Glasgow University Hospitals, Glasgow; Julian Adlard, Chaple Allerton Hospital, Leeds, United Kingdom; Valentina Silvestri, Pietro Rizzolo, Anna Sara Navazio, Virginia Valentini, Veronica Zelli, and Laura Ottini, Sapienza University of Rome; Angelo Toss, Veronica Medici, and Laura Cortesi, University of Modena and Reggio Emilia, Modena; Ines Zanna and
Domenico Palli, Cancer Research and Prevention Institute, Florence; Paolo Radice, Siranoush Manoukian, Bernard Peissel, and Jacopo Azzollini, Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Nazionale Tumori (INT); Paolo Peterlongo, Italian Foundation for Cancer Research Institute of Molecular Oncology (IFOM), Milan; Alessandra Viel and Giulia Cini, CRO Aviano, National Cancer Institute, Aviano; Giuseppe Damante, University of Udine, Udine; Stefania Tommasi, Istituto Nazionale Tumori “Giovanni Paolo II”, Barì; Elisa Alducci, Silvia Tognazzo, and Marco Montagna, Veneto Institute of Oncology IOV - IRCCS, Padua; Maria A. Caligo, University and University Hospital of Pisa, Pisa, Italy; Penny Soucy and Jacques Simard, Centre Hospitalier Universitaire de Québec Research Center and Laval University, Quebec City, Quebec; Anna Marie Mulligan and Irene L. Andrulis, University of Toronto; Gord Glendon and Irene L. Andrulis, Mount Sinai Hospital, Toronto, Ontario, Canada; Melissa Southey, Ian Campbell, Paul James, and Gillian Mitchell, University of Melbourne, Parkville, Victoria; Amanda B. Spurdle, Helene Holland, and Georgia Chenevix-Trench, QIMR Berghofer Medical Research Institute, Brisbane, Queensland; Ian Campbell, Paul James, and Gillian Mitchell, Peter MacCallum Cancer Centre, East Melbourne, New South Wales, Australia; Esther M. John, Cancer Prevention Institute of California, Fremont; Linda Steele, Yuan Chun Ding, Susan L. Neuhausen, and Jeffrey N. Weitzel, City of Hope, Duarte, CA; Thomas A. Conner and Saundra S. Buys, Huntsman Cancer Institute; David E. Goldgar, University of Utah School of Medicine, Salt Lake City, UT; Andrew K. Godwin, University of Kansas Medical Center, Kansas City; Priyanka Sharma, University of Kansas Medical Center, Westwood, KS; Timothy R. Rebbeck, Harvard TH Chan School of Public Health and Dana Farber Cancer Institute, Boston, MA; Joseph Vijai, Mark Robson, Anne Lincoln, Jacob Musinsky, Pragna Gaddam, and Kenneth Offit, Memorial Sloan Kettering Cancer Center, New York, NY; Jennifer T. Proud and Mark H. Greene, National Cancer Institute, Bethesda, MD; Amanda Ewart Toland and Leigha Senter, The Ohio State University, Columbus, OH; Dezheng Huo, Sarah M. Nielsen, and Olufumilayo I. Olopade, University of Chicago Medical Center, Chicago, IL; Katherine L. Nathanson and Susan M. Domchek, University of Pennsylvania, Philadelphia; Christa Lorenchick and Rachel C. Jankowitz, University of Pittsburgh Medical Center, Pittsburgh, PA; Fergus J. Couch, Mayo Clinic, Rochester, MN; Ramunas Janavicius, State Research Institute Innovative Medicine Center, Vilnius, Lithuania; Thomas V.O. Hansen, Rigshospitalet, Copenhagen University Hospital, Copenhagen; Anders Bojesen and Henriette Roed Nielsen, Vejle Hospital, Vejle; Anne-Bine Skytte, Lone Sunde, and Uffe Birk Jensen, Aarhus University Hospital, Aarhus; Inge Sokilde Pedersen, Aalborg University Hospital, Aalborg; Lotte Krogh, Torben A. Kruse, and Mads Thomassen, Odense University Hospital, Odense, Denmark; Ana Osorio, National Cancer Research Centre and Spanish Network on Rare Diseases; Miguel de la Hoya, Vanesa Garcia-Barberan, Trinidad Caldes, and Pedro Perez Segura, Hospital Clinico San Carlos, El Instituto de Investigación Sanitaria del Hospital Clinico San Carlos, Madrid; Judith Balmana, University Hospital, Vall d’Hebron; Sara Gutiérrez-Enriquez and Orland Diez, Vall d’Hebron Institute of Oncology; Orland Diez, University Hospital Vall d’Hebron; Alex Teule, Jesús Del Valle, Lidia Felubadalo, Miquel Angel Pujana, and Conxi Lazaro, Bellvitge Biomedical Research Institute, Catalan Institute of Oncology, Barcelona; Angel Izquierdo, Esther Darder, and Joan Brunet, Institut d’Investigació Biomèdica de Girona, Catalan Institute of Oncology, Girona, Spain; Florentia Fostira, National Centre for Scientific Research "Demokritos", Athens, Greece; Ute Hamann, German Cancer Research Center (DKFZ); Christian Sutter, University Hospital Heidelberg, Heidelberg; Alfonsin Meindl, Klinikum rechts der Isar, Technical University Munich; Nina Ditsch, Ludwig-Maximilian University, Munich; Andrea Gehrig, University Würzburg, Würzburg; Bernd Dworniczak, University of Münster, Münster; Christoph Engel, University of Leipzig; Dorothea Wand, University Hospital, Leipzig; Dieter Niederacher, University Hospital Düsseldorf, Heinrich-Heine University, Düsseldorf; Doris Steinemann, Hannover Medical School, Hannover; Eric Hahnen, Jan Hauke, Kerstin Rhiem, Barbara Wappenschmidt, and Rita K. Schmutzler, University Hospital Cologne, Cologne; Karin Kast, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden; Norbert Arnold, University Hospital of Schleswig-Holstein, Christian-Albrechts University Kiel, Kiel; Shan Wang-Gohrke, University Hospital Ulm, Ulm, Germany; Christine Lasset, Francesca Damiola, and Laure Barjhoux, Centre Léon Bérard; Sylvie Mazoyer, University of Lyon, Lyon; Dominique Stoppa-Lyonnet and Muriel Belotti, Institut Curie, Paris, France; Mattias Van Heetvelde, Bruce Poppe, Kim De Leeerneer, and Kathleen B.M. Claes, Ghent University, Gent, Belgium; Johanna I. Kiöski, Sofia Khan, and Heli Nevanlinna, University of Helsinki; Johanna I. Kiöski, Kristiina Aittomäki, Sofia Khan, and Heli Nevanlinna, Helsinki University Hospital, Helsinki, Finland; Christi J. van Asperen, Leiden University Medical Center, Leiden, the Netherlands; Tibor Vaszko, Miklos Kasler, and Edith Ohal, National Institute of Oncology, Budapest, Hungary; Adalgeir Arason, Bjarni A. Agnarsson, Oskar Th. Johannsson, and Rosa B. Barkardottir, Landspítali University Hospital and Biomedical Centre, University of Iceland, Reykjavik, Iceland; Manuel R. Teixeira and Pedro Pinto, Portuguese Oncology Institute; Manuel R. Teixeira, Porto University, Porto, Portugal; Jong Won Lee, Ulsan College of Medicine and Asan Medical Center; Min Hyuk Lee and JiHyoun Lee, Soochunhyang University and Hospital; Sung-Won Kim and Eunyoung Kang, Daerim St Mary's Hospital; Sue Kyung Park, Seoul National University College of Medicine, Seoul; Zisun Kim, Soochunhyang University Bucheon Hospital, Bucheon, Korea; Yun Y. Tan, Andreas Berger, and Christian F. Singer, Medical University of Vienna, Vienna, Austria; Sook-Yee Yoon and Soo-Hwang Teo, Sime Darby Medical Centre, Subang Jaya, Malaysia; and Anna von Wachenfeldt, Karolinska University Hospital, Stockholm, Sweden.

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 la Science et de l'Innovation du Québec through Genome Québec, the Quebec Breast Cancer
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, 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 N02-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, Basser 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 or ascopubs.org/jco/site/ifc.

Julie Lecarpentier
No relationship to disclose

Valentina Silvestri
No relationship to disclose

Karoline B. Kuchenbaecker
No relationship to disclose

Daniel Barrowdale
Stock or Other Ownership: GlaxoSmithKline

Joe Dennis
No relationship to disclose

Lesley McGuffog
No relationship to disclose

Penny Soucy
No relationship to disclose

Goska Leslie
No relationship to disclose

Piera Rizzolo
No relationship to disclose

Anna Sara Navazio
No relationship to disclose

Virginia Valentini
No relationship to disclose

Veronica Zelli
No relationship to disclose

Andrew Lee
No relationship to disclose

Ali Amin Al Olama
No relationship to disclose

Jonathan P. Tyrer
No relationship to disclose

Melissa Southey
No relationship to disclose

Esther M. John
No relationship to disclose

Thomas A. Conner
No relationship to disclose

David E. Goldgar
No relationship to disclose

Saundra S. Buys
No relationship to disclose

Ramunas Janavicius
No relationship to disclose

Linda Steele
No relationship to disclose

Yuan Chun Ding
No relationship to disclose

Susan L. Neuhausen
No relationship to disclose

Thomas V.O. Hansen
No relationship to disclose

Ana Osorio
No relationship to disclose

Jeffrey N. Weitzel
No relationship to disclose

Angela Toss
No relationship to disclose

Veronica Medici
No relationship to disclose

Laura Cortesi
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Domenico Palli
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Giulia Cini
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Giuseppe Damante
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Stefania Tommasi
No relationship to disclose

Paolo Peterlongo
No relationship to disclose

Florentia Fostira
No relationship to disclose

Ute Hamann
No relationship to disclose

D. Gareth Evans
Honorable: AstraZeneca

Alex Henderson
Honorable: Novartis

Carole Brewer
No relationship to disclose
Diana Eccles  
Honoraria: AstraZeneca  
Consulting or Advisory Role: AstraZeneca

Jackie Cook  
No relationship to disclose

Kai-ren Ong  
No relationship to disclose

Lisa Walker  
No relationship to disclose

Lucy E. Side  
No relationship to disclose

Mary E. Porteous  
No relationship to disclose

Rosemarie Davidson  
No relationship to disclose

Shirley Hodgson  
No relationship to disclose

Debra Frost  
No relationship to disclose

Julian Adlard  
No relationship to disclose

Louise Izatt  
No relationship to disclose

Ros Eedes  
No relationship to disclose

Steve Ellis  
No relationship to disclose

Marc Tischkowitz  
No relationship to disclose

Andrew K. Godwin  
Research Funding: Deciphera Pharmaceuticals (Inst)

Alfons Meindl  
No relationship to disclose

Andrea Gehrig  
No relationship to disclose

Bernd Dworniczak  
No relationship to disclose

Christian Sutter  
No relationship to disclose

Christoph Engel  
No relationship to disclose

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

Karim 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 Damiola  
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

Vanesa Garcia-Barberan  
No relationship to disclose

Trinidad Caldes  
No relationship to disclose

Pedro Perez Segura  
No relationship to disclose

Johanna I. Kiiski  
No relationship to disclose

Kristiina Aittomäki  
No relationship to disclose

Soﬁa Khan  
No relationship to disclose

Heli Nevanlinna  
No relationship to disclose
Polygenic Risk Scores in Male BRCA1 and BRCA2 Mutation Carriers

Christi J. van Asperen
Research Funding: AstraZeneca (Inst)

Tibor Vaszko
No relationship to disclose

Miklos Kasler
No relationship to disclose

Edith Olah
No relationship to disclose

Judith Balmana
No relationship to disclose

Sara Gutierrez-Enriquez
No relationship to disclose

Orland Diez
No relationship to disclose

Alex Teule
No relationship to disclose

Angel Izquierdo
No relationship to disclose

Esther Darder
No relationship to disclose

Joan Brunet
No relationship to disclose

Jesús Del Valle
Speakers’ Bureau: AstraZeneca

Lidia Feliubadalo
Speakers’ Bureau: AstraZeneca

Miquel Angel Pujana
Research Funding: Roche (Inst), Astellas Pharma (Inst)

Conxi Lazaro
No relationship to disclose

Adalgeir Arason
No relationship to disclose

Bjarni A. Agnarsson
No relationship to disclose

Oskar Th. Johannsson
Consulting or Advisory Role: Tesaro
Travel, Accommodations, Expenses: Roche, Novartis

Rosa B. Barkardottir
No relationship to disclose

Elisa Alducci
No relationship to disclose

Silvia Tognazzo
No relationship to disclose

Marco Montagna
No relationship to disclose

Manuel R. Teixeira
No relationship to disclose

Pedro Pinto
No relationship to disclose

Amanda B. Spurdle
No relationship to disclose

Helene Holland
No relationship to disclose

Jong Won Lee
No relationship to disclose

Min Hyuk Lee
No relationship to disclose

Jihyoun Lee
No relationship to disclose

Sung-Won Kim
No relationship to disclose

Eunyoung Kang
No relationship to disclose

Zisun Kim
No relationship to disclose

Priyanka Sharma
Consulting or Advisory Role: Abbvie
Research Funding: GlaxoSmithKline, Novartis, Celgene, Cosmo Biosciences (I)
Travel, Accommodations, Expenses: Abbvie

Timothy R. Rebbeck
No relationship to disclose

Joseph Vijai
No relationship to disclose

Mark Robson
Honoraria: AstraZeneca
Consulting or Advisory Role: McKesson, AstraZeneca
Research Funding: AstraZeneca (Inst), AbbVie (Inst), Myriad Genetics (Inst), Medivation (Inst), Tesaro (Inst)
Travel, Accommodations, Expenses: AstraZeneca

Anne Lincoln
No relationship to disclose

Jacob Musinsky
No relationship to disclose

Pragna Gaddam
No relationship to disclose

Yen Y. Tan
No relationship to disclose

Andreas Berger
No relationship to disclose

Christian F. Singer
No relationship to disclose

Jennifer T. Loud
No relationship to disclose

Mark H. Greene
No relationship to disclose

Anna Marie Mulligan
No relationship to disclose

Gord Glendon
No relationship to disclose

Irene L. Andrulis
No relationship to disclose

Amanda Ewart Toland
No relationship to disclose
Leigha Senter
Consulting or Advisory Role: Clovis Oncology, MyGeneCounsel
Anders Bojesen
No relationship to disclose
Henriette Roed Nielsen
No relationship to disclose
Anne-Bine Skytte
No relationship to disclose
Lone Sunde
No relationship to disclose
Uffe Birk Jensen
No relationship to disclose
Inge Sokilde Pedersen
No relationship to disclose
Lotte Krogh
No relationship to disclose
Torben A. Kruse
No relationship to disclose
Maria A. Caligo
No relationship to disclose
Sook-Yee Yoon
Research Funding: AstraZeneca
Soo-Hwang Teo
Honoraria: AstraZeneca
Consulting or Advisory Role: AstraZeneca
Research Funding: AstraZeneca (Inst)
Anna von Wachenfeldt
No relationship to disclose
Dezheng Huo
No relationship to disclose
Sarah M. Nielsen
No relationship to disclose
Olufunmilayo I. Olopade
No relationship to disclose
Katherine L. Nathanson
No relationship to disclose
Susan M. Domchek
Research Funding: AstraZeneca (Inst), Clovis Oncology (Inst), AbbVie (Inst), PharmaMar (Inst)
Christa Lorenchick
No relationship to disclose
Rachel C. Jankowitz
Consulting or Advisory Role: Advaxis, bioTheranostics
Ian Campbell
No relationship to disclose
Paul James
No relationship to disclose
Gillian Mitchell
Honoraria: AstraZeneca
Consulting or Advisory Role: AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca
Nick Orr
No relationship to disclose
Sue Kyung Park
No relationship to disclose
Mads Thomassen
No relationship to disclose
Kenneth Offit
No relationship to disclose
Fergus J. Couch
Travel, Accommodations, Expenses: Ambry Genetics
Jacques Simard
No relationship to disclose
Douglas F. Easton
No relationship to disclose
Georgia Chenevix-Trench
No relationship to disclose
Rita K. Schmutzler
No relationship to disclose
Antonis C. Antoniou
No relationship to disclose
Laura Ottini
No relationship to disclose
Acknowledgment

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 Griskievicius. **CBCS** (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-CCGCRN** (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 Centres, Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Hospices Civils de Lyon–Centre Léon Bérard, Equipe Génétique du cancer du sein, Centre de Rechercheen Cancérologie de Lyon: Olga Sinilnikova (deceased), Sylvie Mazoyer, Francesca Damiai, Laure Barjhoux, Carole Verny-Pierre, Mélanie Léone, Nadia Bouthry-Krzyza, Alain Calender, Sophie Giraud; and Service de Génétique Oncologique, Institut Curie, Paris: Dominique Stoppa-Lyonnet, Marion Gauthier-Villars, Bruno Buecher, Claude Houdayer, Etienne Rouleau, Lisa Golmard, Agnès Collet, Virginie Moncoutier, Muriel Belotti, Antoine de Pauw, Camille Elan, Catherine Nogues, Emmanuelle Fourme, Anne-Marie Birot; Institut Gustave Roussy, Villejuif: Brigitte Bressac-de-Pailletter, Olivier Caron, Marine Guillaud-Batalli; 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 Vuar, Laurent Castera; Institut Paoli Calmettes, Marseille: Hagay Sobol, Violaine Bourdon, Tetsuro Noguchi, Audrey Remenieras, François Eisinger; CHU Arnaud-de-Villeneuve, Montpellier: Isabelle Couper, Pascal Pujol; Centre Oscar Lambret, Lille: Jean-Philippe Peyrat, Joëlle Fournier, Françoise Révillion, Philippe Vennin (deceased), Claude Adenis; Centre Paul Strauss, Strasbourg: Danièle Muller, Jean-Pierre Fricker; Institut Bergonié, Bordeaux: Emmanuelle Barouk-Simonet, Françoise Bonnet, Virginie Bubien, Nicolas Sevenet, Michel Longy; Institut Claudius Regaud, Toulouse: Yves-Jean Bignon, Nancy Uhrhammer; Centre Léon Bérard, Lyon: Christine Lasset, Valérie Bonadona, Sandrine Handallou; Centre François Baclesse, Caen: Agnès Hardouin, Pascaline Berthet, Dominique Vuar, Laurent Castera; Institut Paoli Calmettes, Marseille: Hagay Sobol, Violaine Bourdon, Tetsuro Noguchi, Audrey Remenieras, François Eisinger; CHU Arnaud-de-Villeneuve, Montpellier: Isabelle Couper, Pascal Pujol; Centre Oscar Lambret, Lille: Jean-Phillipe Peyrat, Joëlle Fournier, Françoise Révillion, Philippe Vennin (deceased), Claude Adenis; Centre Paul Strauss, Strasbourg: Danièle Muller, Jean-Pierre Fricker; Institut Bergonié, Bordeaux: Emmanuelle Barouk-Simonet, Françoise Bonnet, Virginie Bubien, Nicolas Sevenet, Michel Longy; Institut Claudius Regaud, Toulouse: Yves-Jean Bignon, Rosine Guimand, Laurence Gladiev, Viviane Filleul; CHU Grenoble: Dominique Leroux, Hélène Dreyfus, Christine Reibischung, Magalie Peysselon; CHU Dijon: Fanny Coron, Laurence Faivre; CHU St-Etienne: Fabienne Prieur, Marine Lebrun, Caroline Kientz; HôtelDieu Centre Hospitalier, Chambéry: Sandra Fert Ferrer; Centre Antoine Lacassagne, Nice: Marc Fréray; CHU Limoges: Laurence Vénat-Bouvet; CHU Nantes: Capucine Delnatte; CHU Bretonneau, Tours: Isabelle Mortemousque; Groupe Hospitalier Pitié-Salpêtrière, Paris: Florence Coullet, Chrystelle Colas, Florent Soubré, Mathilde Warcoin; CHU Vandoeuvre-les-Nancy: Johanna Sokolowska, Myriam Bronner; CHU Besançon: Marie-Agnès Collonge-Rame, Alexandre Damet; 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 Grombez. **HCSC** (Hospital Clinico San Carlos): We acknowledge Alicia Tosar and Paula Diaeux for their technical assistance. **HEBCS** (Helsinki Breast Cancer Study): We thank Taru A. Muraen, Carl Blomqvist, MD, Kirstimari Aaltonen, MD, Irja Erkkila, RN, and Virpi Palola, RN, for their help with the HBECS data and samples. **Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON)**: HEBON consists of the following collaborating centers: Coordinating center: Netherlands Cancer Institute, Amsterdam: M.A. Rookus, F.B.L. Hogervorst, F.E. van Leeuwen, S. Verhoef, M.K. Schmidt, N.S. Russell, J.L. de Lange, R. Wijnands; Erasmus Medical Center: J.M. Collée, A.M.W. van den Ouweland, M.J. Hoonoing, C. Seyneve, C.H.M. van Deurzen, I.M. Obdeijn; Leiden University Medical Center: C.J. van Asperen, J.T. Wijnen, R.A.E.M. Tollenaa, P. Devilee, T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center: C.M. Ketts, A.R. Mensenkamp; University Medical Center Utrecht: M.G.E.M. Ausems, R.B. van der Luijt, C.C. van der Pol; Amsterdam Medical Center: C.M. Aalfs, T.A.M. van Os; Vrije Universiteit Medical Center: C.M. Kets, A.R. Mensenkamp; University Medical Center Groningen: J.C. Oosterwijk, A.H. van der Hout, M.J. Mourits, G.H. de Bock; The Netherlands Foundation for the Detection of Hereditary Tumours, Leiden: H.F. Vanen; The Netherlands Comprehensive Cancer Organization (IKNL): S. Siesling, J. Verloop; The Dutch Pathology Registry (PALGA): L.I.H. Overbeek. HEBON thanks the registration teams of IKNL and PALGA for part of the data collection. **HUNBOCS** (Molecular Genetic Studies of Breast- and Ovarian Cancer in Hungary): We thank the Hungarian Breast and Ovarian Cancer Study Group members (Janos Papp, Aniko Bozsik, Judit Franko, Maria Balogh, Gabriella Domokos, Judit Ferenczi, Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary) and the clinicians and patients for their contributions to this study. **HVH** (University Hospital Vall d’Hebron): We thank the Cellex Foundation for providing research facilities and equipment. **ICO** (Institut Català d’Oncologia): We thank the ICO Hereditary Cancer Program team led by Gabriel Capella, MD. **INHERIT** (International Hereditary Breast Cancer Study): We thank Martine Dumont, MD, Martine Tranchant and Stéphane Dubois for QC, sample management and skillful assistance. J.S. is Chair holder of the Canada Research Chair in Oncogenetics. J.S. and P.S. were part of the QC and Genotyping coordinating group of iCOGS and Oncoarray (BCAC and CIMBA). **IPOBICS** (Portuguese Oncology Institute-Porto ...
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 Överholm, 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.