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Published in: Journal of Clinical Oncology

Document Version: Publisher's PDF, also known as Version of record

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


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 risk prediction.

Materials and Methods

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

Results

In male carriers of BRCA1/2 mutations, PRS that was based on 88 female breast cancer susceptibility variants was associated with breast cancer risk (odds ratio per standard deviation of PRS, 1.36; 95% CI, 1.19 to 1.56; \( P = 8.6 \times 10^{-5} \)). 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; \( P = 3.2 \times 10^{-8} \)). Large differences in absolute cancer risks were observed at the extremes of the PRS distribution. For example, prostate cancer risk by age 80 years at the 5th and 95th percentiles of the PRS varies from 7% to 26% for carriers of BRCA1 mutations and from 19% to 61% for carriers of BRCA2 mutations, respectively.

Conclusion

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

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INTRODUCTION

Germline mutations in BRCA1 and, predominantly, BRCA2 are associated with increased risks in men of developing breast and prostate cancers.1,2 BRCA1/2 mutations account for approximately 10% of male breast cancer and 2% of prostate cancer cases.3,4 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.5,6 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.7-10

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

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

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

MATERIALS AND METHODS

Samples

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

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

Genotyping and Quality Control

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

Statistical Methods

Association Analyses. We evaluated associations of SNPs with risks of breast and prostate cancer simultaneously using multinomial logistic regression. The control group in this analysis was defined as the set of samples without a breast or prostate cancer diagnosis. Breast and prostate cancer cases were defined on the basis of age at diagnosis, whichever occurred first. If breast and prostate cancer occurred at the same time, individuals were treated as patients with breast cancer. Thus, of 1,802 samples, 277 were defined as patients with breast cancer, 212 as patients with prostate cancer, and 1,313 as controls. Analyses were adjusted for the first three principal components, age at breast or prostate cancer for patient-cases and age at interview for controls, and gene (BRCA1 or BRCA2). A robust variance approach—clustering of family membership—was used to adjust for related individuals. Additional logistic regression analyses were carried out to assess associations separately with breast or prostate cancer risk (Data Supplement). We also performed a set of sensitivity analyses by considering patient cases with both breast and prostate cancer as a separate group in a multinomial logistic regression model (Data Supplement). Analysis was performed in R (version 3.2.3; R Foundation, Vienna, Austria) and STATA software (version 13.1; STATA, College Station, TX; Computing Resource Center, Santa Monica, CA). Polygenic Risk Scores. Assuming a log-additive model for the joint effects of SNPs, we constructed polygenic risk scores (PRSs) by summing the number of alleles across SNPs that were weighted by their estimated per-allele log-odds ratios (ORs) in published 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.12,22,24-31,34 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 genotyped, 32 imputed) SNPs (Data Supplement).

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

Breast Cancer PRSs

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

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

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

Prostate Cancer PRS

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

There was a highly significant association between the prostate cancer PRS and prostate cancer risk for male carriers of BRCA1/2 mutations (OR for prostate cancer per SD increase, 1.56; 95% CI, 1.35 to 1.81; $P = 3.2 \times 10^{-7}$; Table 2). Associations remained significant when analyses were performed separately for carriers of BRCA1 and BRCA2 mutations (BRCA1: OR, 1.72; 95% CI, 1.30 to 2.29; $P = 1.8 \times 10^{-4}$; BRCA2: OR, 1.49; 95% CI, 1.26 to 1.77; $P = 4.9 \times 10^{-6}$). There was an increasing risk of prostate cancer with increasing PRS quartiles. When compared with the 1st quartile, OR for prostate cancer for men in the 2nd quartile was 1.82 (95% CI, 1.07 to 3.08; $P = .026$), for men in the 3rd quartile, 2.23 (95% CI, 1.32 to 3.76; $P = .003$), and for men in the 4th quartile, 3.36 (95% CI, 2.05 to 5.52; $P = 1.7 \times 10^{-6}$).

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

Discriminatory Ability

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

Predicted Risks of Male Breast and Prostate Cancer by PRS Percentile

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

Discussion

We performed the first GWAS, to our knowledge, in male carriers of BRCA1/2 mutations to identify common variants that modify the risks of breast and prostate cancer in these men. Although we analyzed the largest series of male mutation carriers available, this study is underpowered to detect associations with individual low-risk SNPs.
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>All Samples</th>
<th>BRCA1 Samples</th>
<th>BRCA2 Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Controls</td>
<td>No. of Breast Cancer Cases</td>
<td>OR</td>
</tr>
<tr>
<td>Overall PRS</td>
<td>329</td>
<td>43</td>
<td>1.00</td>
</tr>
<tr>
<td>1st</td>
<td>328</td>
<td>56</td>
<td>1.28</td>
</tr>
<tr>
<td>2nd</td>
<td>327</td>
<td>76</td>
<td>1.72</td>
</tr>
<tr>
<td>3rd</td>
<td>329</td>
<td>102</td>
<td>2.35</td>
</tr>
<tr>
<td>4th</td>
<td>329</td>
<td>102</td>
<td>2.35</td>
</tr>
<tr>
<td>Trend</td>
<td>1,313</td>
<td>277</td>
<td>1.36*</td>
</tr>
<tr>
<td>ER-positive PRS</td>
<td>1st</td>
<td>328</td>
<td>41</td>
</tr>
<tr>
<td>2nd</td>
<td>329</td>
<td>56</td>
<td>1.36</td>
</tr>
<tr>
<td>3rd</td>
<td>328</td>
<td>82</td>
<td>1.95</td>
</tr>
<tr>
<td>4th</td>
<td>328</td>
<td>98</td>
<td>2.37</td>
</tr>
<tr>
<td>Trend</td>
<td>1,313</td>
<td>277</td>
<td>1.36*</td>
</tr>
<tr>
<td>ER-negative PRS</td>
<td>1st</td>
<td>329</td>
<td>52</td>
</tr>
<tr>
<td>2nd</td>
<td>327</td>
<td>67</td>
<td>1.39</td>
</tr>
<tr>
<td>3rd</td>
<td>329</td>
<td>78</td>
<td>1.61</td>
</tr>
<tr>
<td>4th</td>
<td>328</td>
<td>80</td>
<td>1.60</td>
</tr>
<tr>
<td>Trend</td>
<td>1,313</td>
<td>277</td>
<td>1.19*</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>PRS Group</th>
<th>No. of Controls</th>
<th>No. of Prostate Cancer Cases</th>
<th>OR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Controls</strong></td>
<td><strong>No. of Prostate Cancer Cases</strong></td>
<td><strong>OR 95% CI</strong></td>
<td><strong>P</strong></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer PRS, quartile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>328</td>
<td>26</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>2nd</td>
<td>329</td>
<td>47</td>
<td>1.82</td>
<td>1.07 to 3.08</td>
</tr>
<tr>
<td>3rd</td>
<td>328</td>
<td>56</td>
<td>2.23</td>
<td>1.32 to 3.76</td>
</tr>
<tr>
<td>4th</td>
<td>328</td>
<td>84</td>
<td>3.36</td>
<td>2.05 to 5.52</td>
</tr>
<tr>
<td>Trend</td>
<td>1,313</td>
<td>212</td>
<td>1.56†</td>
<td>1.35 to 1.81</td>
</tr>
<tr>
<td>Association between prostate PRS and prostate cancer by Gleason score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>1,313</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gleason score &lt; 7</td>
<td>—</td>
<td>53</td>
<td>1.44†</td>
<td>1.10 to 1.87</td>
</tr>
<tr>
<td>Gleason score ≥ 7</td>
<td>—</td>
<td>102</td>
<td>1.67†</td>
<td>1.37 to 2.04</td>
</tr>
<tr>
<td>Gleason score missing</td>
<td>—</td>
<td>57</td>
<td>1.49†</td>
<td>1.13 to 1.97</td>
</tr>
<tr>
<td>Case only analysis:</td>
<td>1.19†</td>
<td>0.81 to 1.75</td>
<td>.372</td>
<td>1.60†</td>
</tr>
</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 al estimated an OR for female breast cancer of 1.55 for a PRS based on a subset of SNPs in females. Although the present estimate in males is not significantly different from that observed in females, it is somewhat lower. A lower OR may be a result of certain breast cancer SNPs that were included in the PRS that are not associated with male breast cancer risk, or individual SNPs may have smaller ORs for male breast cancer than female breast cancer. Alternatively, the estimate of Mavaddat et al 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.

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.

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. 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. 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
To account for both breast and prostate cancer risk in male mutation carriers, we provide a prostate cancer risk assessment based on the BRCA1/2 polygenic risk score. We also consider recent evidence suggesting that polygenic risk assessment by PRSs in study protocols may 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.

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.

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 Antonios 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. Side, 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, Chapel Allerton Hospital, Leeds, United Kingdom; Valentina Silvestri, Piera Rizzolo, Anna Sara Navazio, Virginia Valentini, Veronica Zelli, and Laura Ottini, Sapienza University of Rome; Angela Toss, Veronica Medici, and Laura Cortesi, University of Modena and Reggio Emilia, Modena; Ines Zanna and

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Domenico Palli, Cancer Research and Prevention Institute, Florence; Paolo Radice, Siranoush Manoukian, Bernard Peissel, and Jacopo Azzolini, 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 Tommassi, Istituto Nazionale Tumori “Giovanni Paolo II”, Bari; 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 Quebec Research Center and Laval University, Quebec City, Quebec; Anna Marie Mulligan and Irene L. Andrilus, University of Toronto; Gord Glendon and Irene L. Andrilus, Mount Sinai Hospital, Toronto, Ontario, Canada; Melissa Southey, Ian Campbell, Paul James, and Gillian Mitchell, University of Melbourne, Parkville, Victoria; Amanda B. Spurtle, Helene Holland, and Georgina 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. Loud 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 O. 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 Institute, Vilnius, Lithuania; Thomas V.O. Hansen, Rigshospitalet, Copenhagen University Hospital, Copenhagen; Anders Bojesen and Henriette Roed Nielsen, Veje Hospital, Veje; Anne-Bine Skytte, Lone Sunde, and Uffe Birk Jansen, 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; Alfonso Meindl, Klinikumrechts 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 Riheim, 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 Leeener, and Kathleen B.M. Claes, Ghent University, Gent, Belgium; Johanna I. Kiiski, Sofia Khan, and Heli Nevanlinna, University of Helsinki; Johanna I. Kiiski, 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, Landsdæli 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 Jihyou Lee, Soonchunhyang 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, Soonchunhyang 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 l’Économie, de la Science et de l’Innovation du Québec through Genome Québec, the Quebec Breast Cancer
Foundation for the PERSPECTIVE project, the US National Institutes of Health (NIH; Grant No. 1U19-CA148065 for the Discovery, Biology and Risk of Inherited Variants in Breast Cancer [DRIVE] project; Grant No. X01-HG007492 to the Centre for Inherited Disease Research), Cancer Research UK (C1287/A16563), Odense University Hospital Research Foundation (Denmark), the National R&D Program for Cancer Control, Ministry of Health and Welfare (Republic of Korea) (1420190), the Breast Cancer Research Foundation, the National Health and Medical Research Council (Australia), and German Cancer Aid (110837); CIMBA data management and data analysis were supported by Cancer Research UK Grants No. C12292/A20861 and C12292/A11174. A.C.A. is a Cancer Research UK Senior Cancer Research Fellow; G.C.-T. is an NHMRC Senior Principal Research Fellow; J.L. has been financially supported by the Fondazione ARC Grant No. SAE20131200623; the PERSPECTIVE project was supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the Ministère de l’Économie, de la Science et de l’Innovation du Québec through Genome Québec, and the Quebec Breast Cancer Foundation. Also supported by the Ministère de l’Économie, Innovation et Exportation du Québec Grant No. PSR-SIIRI-701. The Breast Cancer Family Registry (BCFR) was supported by Grant No. UM1-CA164920 from the National Cancer Institute. BFBOCC-IT (Baltic Familial Breast Ovarian Cancer Consortium Lithuanian section) was supported by Lithuania Research Council of Lithuania (Grant No. SEN-18/2015). BRICOH (Beckman Research Institute of the City of Hope) S.L.N. is partially supported by the Morris and Horowitz Foundations Professorship. CNIO (Spanish National Cancer Centre) was partially supported by Spanish Association against Cancer (AECC08), RTICC 06/0020/1060, FISP108/1120, Mutua Madrileña Foundation (FMM), and SAF2010-20493. A.O. is supported by Spanish Ministry of Economy and Competitiveness (MINECO) SAF2014-57680-R. The City of Hope Clinical Cancer Genomics Community Research Network (COH-CGGCRN) was supported in part by Grant No. RC4CA153828 (principal investigator, J.W.) from the National Cancer Institute and the Office of the Director, NIH. The CONSIT team was supported by the Italian Association of Cancer Research to P.P. (IG12821), P.R. (IG15547), and L.O. (IG16933), and from Italian citizens who allocated the 5 × 1,000 share of their tax payment in support of the Fondazione IRCCS Istituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects “5×1000”) to S.M. Supported by Sapienza University of Rome (post-doc annual research grant “Avvio alla ricerca” 2016) to V.S. Supported by the ITT (Istituto Toscana Tumori) triennial grant 2010 to D.P. DEMOKRITOS was supported by the European Union (European Social Fund) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework Research Program of the General Secretariat for Research and Technology; SYN11_10_19 NBCA. Investing in knowledge society through the European Social Fund. The DKFZ study was supported by the DKFZ. EMBRACE was supported by Cancer Research UK Grants No. C1287/A10118 and C1287/A11990. D.G.E. is supported by an NIH Research (NIHR) grant to the Biomedical Research Centre, Manchester. The investigators at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust are supported by an NIHR grant to the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. R.E. is supported by Cancer Research UK Grant No. C5047/A8385. R.E. is also supported by NIHR support to the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. FCCC (Fox Chase Cancer Center) is supported by The University of Kansas Cancer Center (Grant No. P30-CA168524) and the Kansas Bioscience Authority Eminent Scholar Program. A.K.G. was funded by Grants No. SU01-CA113916 and R01-CA140323, and by the Chancellors Distinguished Chair in Biomedical Sciences Professorship. The German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) was supported by the German Cancer Aid (Grant No. 110837; to R.K.S.). GEMO (Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers) was supported by the Ligue Nationale contre le Cancer; the Association “Le cancer du sein, parloins-en!” Award; The Association of Institutes of Health Research for the “CIHR Team in Familial Risks of Breast Cancer” program and the French National Institute of Cancer. Genetic Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers (GEMO) study: National Cancer Genetics Network UNICANCER Genetic Group, France. Ghent University Hospital (G-FAST): M.V.H. obtained funding from IWT. HCSC (Hospital Clinico San Carlos) was supported by Grants No. RD12/0036/0006 and 15/00059 from ISCIII (Spain), partially supported by European Regional Development FEDER funds. HEBCS (Helsinki Breast Cancer Study) was supported by the Helsinki University Hospital Research Fund, Academy of Finland (266528), the Finnish Cancer Society and the Sigrid Juselius Foundation. The HEBON study is supported by the Dutch Cancer Society Grants No. NKI1998-1854, NKI2004-3088, NKI2007-3756, the Netherlands Organization of Scientific Research Grant No. NWO 9110902, the Pink Ribbon Grants No. 110005 and 2014-187.WO76, the BBMRI Grant No. NWO 184.021.007/CP46 and the Transcan grant JTC 2012 Cancer 12-054. Hungarian Breast and Ovarian Cancer Study (HUNBOCS) was supported by Hungarian Research Grants No. KTIA-OTKA CK-80745 and OTKA K-112228. HVH (University Hospital Vall d’Hebron) was supported by Spanish Instituto de Salud Carlos III funding, an initiative of the Spanish Ministry of Economy and Innovation partially supported by European Research Grants No. KTIA-OTKA CK-80745 and OTKA K-112228.
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, Basser Research Center for BRCA. University of Pittsburgh Magee-Women’s Hospital was supported by Frieda G. and Saul F. Shapiro 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.
Polygenic Risk Scores in Male BRCA1 and BRCA2 Mutation Carriers

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.

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Ute Hamann  No relationship to disclose
D. Gareth Evans  Honoraria: AstraZeneca
Alex Henderson  Honoraria: 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 Ede
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
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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

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 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. Kiiksi
No relationship to disclose

Kristiina Aittomäki
No relationship to disclose

Sofia Khan
No relationship to disclose

Heli Nevanlinna
No relationship to disclose
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
Jesus 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. Bardardottir
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  
Honouraria: 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  
Honouraria: 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
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. **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 Damiali, Laure Barjhoux, Carole Verny-Pierre, Mélanie Léone, Nadia Boutry-Kryza, 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 Fournier, Anne-Marie Birot; Institut Gustave Roussey, Villejuif: Brigitte Bressac-de-Pailerets, 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 Vaur, Laurent Castéra; Institut Paoli Calmettes, Marseille: Hagay Sobol, Violaine Bourdon, Tetsuro Noguchi, Audrey Remenieras, François Eisinger; CHU Arnaud-de-Villeneuve, Montpellier: Isabelle Coupiere, 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; Institute Bergonié, Bordeaux: Emmanuelle Barouk-Simonet, Françoise Bonnet, Virginie Bubien, Nicolas Sevenet, Michel Longy; Institut Claudius Regaud, Toulouse: Christine Toula, Rosine Guillaud, Laurence Gladieff, Viviane Feillel; CHU 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 Cert Ferrer; Centre Antoine Lacassagne, Nice: Marc Frénay; CHU Limoges: Laurence Vénat-Bouvet; CHU Nantes: Capucine Delnasse; CHU Bretonneau, Tours: Isabelle Moritemouques; Groupe Hospitalier Pitié-Salpêtrière, Paris: Florence Couteau, Chrystelle Colas, Florent Soubrier, Mathilde Warcho; 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** (Gent University Hospital): B.P. is a senior clinical investigator of FWO. We acknowledge the technical support of Ilse Coeneen Brecht Crombez. **HCSC** (Hospital Clinico San Carlos): We acknowledge Alicia Tosar and Paula Diaque for their technical assistance. **HEBCS** (Helsinki Breast Cancer Study): We thank Taru A. Muranen, Carl Blomqvist, MD, Kirsimari Aaltonen, MD, Irja Bubien, RN, and Virpi Paloma, RN, for their help with the HEBCS data and samples. **Hereditary Breast and Ovarian Cancer Research Group Netherlands** (HERBON): HERBON 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. Hooning, C. Seynaeve, C.H.M. van de Urzen, I.M. Obdeijn; Leiden University Medical Center: C.J. van Asperen, J.T. Wijnen, R.A.E.M. Tollenar, P. Devilee, T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center: C.M. Kets, 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: J.J.P. Gille, Q. Waisfisz, H.E.J. Meijers-Heijboer; University Hospital Maastricht: E.B. Gómez-Garcia, M.J. Blok; 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. Vassen; The Netherlands Comprehensive Cancer Organization (IKNL): S. Siesling, J. Verloopen; The Dutch Pathology Registry (PALGA): L.I.H. Overbeek. HERBON 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 Breast Cancer Program team led by Gabriel Capella, MD. **INHERIT** (INterdisciplinary HEarth Research Internal Team BReast CAncer susceptibility): 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 Oncarray (BCAC and CIMBA). **IPOBCS** (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 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.