



Aalborg Universitet

AALBORG UNIVERSITY  
DENMARK

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

EMBRACE; GEMO Study Collaborators; HEBON; KConFab Investigators

*Published in:*

Journal of clinical oncology : official journal of the American Society of Clinical Oncology

*DOI (link to publication from Publisher):*

[10.1200/JCO.2016.69.4935](https://doi.org/10.1200/JCO.2016.69.4935)

*Creative Commons License*

CC BY 4.0

*Publication date:*

2017

*Document Version*

Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

*Citation for published version (APA):*

EMBRACE, GEMO Study Collaborators, HEBON, & KConFab Investigators (2017). Prediction of Breast and Prostate Cancer Risks in Male BRCA1 and BRCA2 Mutation Carriers Using Polygenic Risk Scores. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 35(20), 2240-2250. <https://doi.org/10.1200/JCO.2016.69.4935>

### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- ? Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- ? You may not further distribute the material or use it for any profit-making activity or commercial gain
- ? You may freely distribute the URL identifying the publication in the public portal ?

### Take down policy

If you believe that this document breaches copyright please contact us at [vbn@aub.aau.dk](mailto:vbn@aub.aau.dk) providing details, and we will remove access to the work immediately and investigate your claim.



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

Julie Lecarpentier, Valentina Silvestri, Karoline B. Kuchenbaecker, Daniel Barrowdale, Joe Dennis, Lesley McGuffog, Penny Soucy, Goska Leslie, Piera Rizzolo, Anna Sara Navazio, Virginia Valentini, Veronica Zelli, Andrew Lee, Ali Amin Al Olama, Jonathan P. Tyrer, Melissa Southey, Esther M. John, Thomas A. Conner, David E. Goldgar, Saundra S. Buys, Ramunas Janavicius, Linda Steele, Yuan Chun Ding, Susan L. Neuhausen, Thomas V.O. Hansen, Ana Osorio, Jeffrey N. Weitzel, Angela Toss, Veronica Medici, Laura Cortesi, Ines Zanna, Domenico Palli, Paolo Radice, Siranoush Manoukian, Bernard Peissel, Jacopo Azzollini, Alessandra Viel, Giulia Cini, Giuseppe Damante, Stefania Tommasi, Paolo Peterlongo, Florentia Fostira, Ute Hamann, D. Gareth Evans, Alex Henderson, Carole Brewer, Diana Eccles, Jackie Cook, Kai-ren Ong, Lisa Walker, Lucy E. Side, Mary E. Porteous, Rosemarie Davidson, Shirley Hodgson, Debra Frost, Julian Adlard, Louise Izatt, Ros Eeles, Steve Ellis, Marc Tischkowitz, EMBRACE, Andrew K. Godwin, Alfons Meindl, Andrea Gehrig, Bernd Dworkniczak, Christian Sutter, Christoph Engel, Dieter Niederacher, Doris Steinemann, Eric Hahnen, Jan Hauke, Kerstin Rhiem, Karin Kast, Norbert Arnold, Nina Ditsch, Shan Wang-Gohrke, Barbara Wappenschmidt, Dorothea Wand, Christine Lasset, Dominique Stoppa-Lyonnet, Muriel Belotti, Francesca Damiola, Laure Barjhoux, Sylvie Mazoyer, GEMO Study Collaborators, Mattias Van Heetvelde, Bruce Poppe, Kim De Leeneer, Kathleen B.M. Claes, Miguel de la Hoya, Vanesa Garcia-Barberan, Trinidad Caldes, Pedro Perez Segura, Johanna I. Kiiski, Kristiina Aittomäki, Sofia Khan, Heli Nevanlinna, Christi J. van Asperen, HEBON, Tibor Vaszko, Miklos Kasler, Edith Olah, Judith Balmaña, Sara Gutiérrez-Enríquez, Orland Diez, Alex Teulé, Angel Izquierdo, Esther Darder, Joan Brunet, Jesús Del Valle, Lidia Feliubadalo, Miquel Angel Pujana, Conxi Lazaro, Adalgeir Arason, Bjarni A. Agnarsson, Oskar Th. Johannsson, Rosa B. Barkardottir, Elisa Alducci, Silvia Tognazzo, Marco Montagna, Manuel R. Teixeira, Pedro Pinto, Amanda B. Spurdle, Helene Holland, KConFab Investigators, Jong Won Lee, Min Hyuk Lee, Jihyoun Lee, Sung-Won Kim, Eunyoung Kang, Zisun Kim, Priyanka Sharma, Timothy R. Rebbeck, Joseph Vijai, Mark Robson, Anne Lincoln, Jacob Musinsky, Pragna Gaddam, Yen Y. Tan, Andreas Berger, Christian F. Singer, Jennifer T. Loud, Mark H. Greene, Anna Marie Mulligan, Gord Glendon, Irene L. Andrulis, Amanda Ewart Toland, Leigha Senter, Anders Bojesen, Henriette Roed Nielsen, Arne-Bine Skytte, Lone Sunde, Uffe Birk Jensen, Inge Sokilde Pedersen, Lotte Krogh, Torben A. Kruse, Maria A. Caligo, Sook-Yee Yoon, Soo-Hwang Teo, Anna von Wachenfeldt, Dezheng Huo, Sarah M. Nielsen, Olufunmilayo I. Olopade, Katherine L. Nathanson, Susan M. Domchek, Christa Lorenchick, Rachel C. Jankowitz, Ian Campbell, Paul James, Gillian Mitchell, Nick Orr, Sue Kyung Park, Mads Thomassen, Kenneth Offit, Fergus J. Couch, Jacques Simard, Douglas F. Easton, Georgia Chenevix-Trench, Rita K. Schmutzler, Antonis C. Antoniou, and Laura Ottini

Author affiliations and support information (if applicable) appear at the end of this article.

Published at [jco.org](http://jco.org) on April 27, 2017.

J.L. and V.S. contributed equally to this work as co-first authors.

R.K.S., A.C.A., and L.O. contributed equally to this work as co-last authors.

The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the BCFR. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Corresponding author: Laura Ottini, MD, Department of Molecular Medicine, Sapienza University of Rome, Viale Regina Elena, 324, 00161, Rome, Italy; e-mail: [laura.ottini@uniroma1.it](mailto:laura.ottini@uniroma1.it).

© 2017 by American Society of Clinical Oncology. Licensed under the Creative Commons Attribution 4.0 License.



0732-183X/17/3520w-2240w/\$20.00

### ASSOCIATED CONTENT



See accompanying Editorial on page 2224



Data Supplement  
DOI: <https://doi.org/10.1200/JCO.2016.69.4935>

DOI: <https://doi.org/10.1200/JCO.2016.69.4935>

### A B S T R A C T

#### Purpose

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

#### Materials and Methods

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

#### Results

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

#### Conclusion

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

*J Clin Oncol* 35:2240-2250. © 2017 by American Society of Clinical Oncology. Licensed under the Creative Commons Attribution 4.0 License: <http://creativecommons.org/licenses/by/4.0/>

## INTRODUCTION

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

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,<sup>11,12</sup> and their combined effects have been shown to have significant implications for risk stratification and targeted prevention.<sup>13-15</sup> By contrast, only two male breast cancer susceptibility SNPs have been identified to date,<sup>16</sup> but there is some evidence that suggests that common variants that are associated with female breast cancer may influence male breast cancer risk.<sup>17-19</sup>

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<sup>20-22</sup>; 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.<sup>23</sup> Pathogenic variants were defined as previously described.<sup>24</sup> All participating studies have been approved by local ethical review committees.

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

genotyping: 265 with breast cancer, 212 with prostate cancer, 43 with both diseases, and 1,469 unaffected.

**Genotyping and Quality Control**

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

**Statistical Methods**

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

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

PRSs were standardized to have mean 0 and variance 1 (Data Supplement). We evaluated associations with quartiles of PRS on the basis of the PRS distribution in controls. Absolute age-specific cumulative risks of developing breast or prostate cancer at different percentiles of PRS were calculated using published methods<sup>33</sup> (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.<sup>12,22,28-31,34</sup> 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.<sup>11,14,32,35-38</sup> Log-OR estimates from published population-based studies were used according to the approach above.<sup>11,32</sup> This PRS included 103 (71 genotyped, 32 imputed) SNPs (Data Supplement).

## RESULTS

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

### Breast Cancer PRSs

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

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

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

### Prostate Cancer PRS

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

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

We observed significant associations between prostate cancer PRS with both low ( $< 7$ ) and high ( $\geq 7$ ) 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

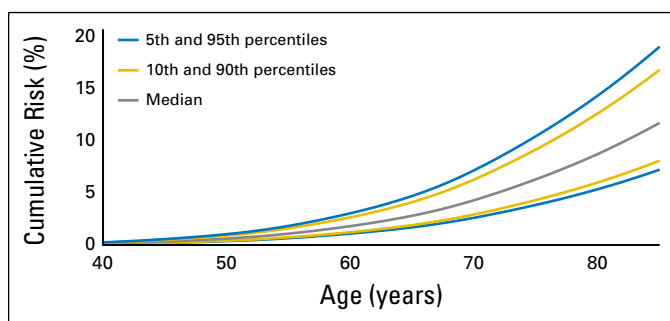
| Quartile               | All Samples     |                            |       |              |                      | <i>BRCA1</i> Samples |                            |       |              |                      | <i>BRCA2</i> Samples |                            |       |              |        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

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

**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

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

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



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

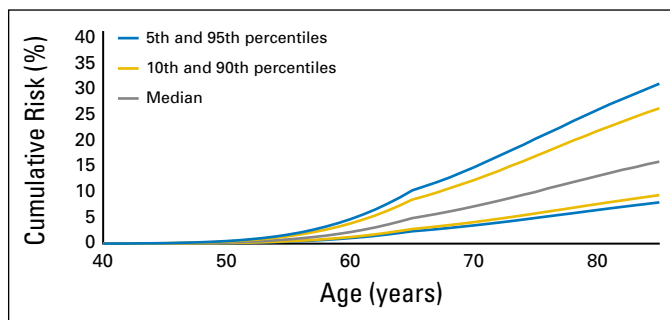
We have demonstrated that the combined effects of known breast cancer susceptibility SNPs modify breast cancer risk for male mutation carriers and, separately, that the combined effects of known prostate cancer susceptibility SNPs modify prostate cancer risk for male mutation carriers.

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.

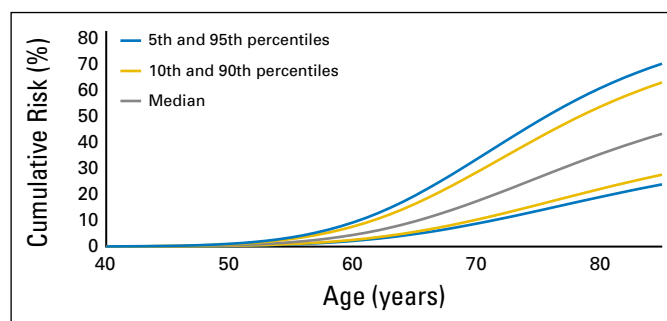
We estimated an OR for breast cancer of 1.36 per SD increase in the overall breast cancer PRS. No study in the general population has assessed this exact PRS yet, but Mavaddat et al<sup>15</sup> estimated an OR for female breast cancer of 1.55 for a PRS based on a subset of SNPs in females. Although 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<sup>15</sup> 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.<sup>14</sup>

Overall, our results indicate that population-based breast and prostate cancer PRSs are predictive of cancer risk for male



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



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

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.<sup>23</sup>

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.<sup>4,9</sup> 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.<sup>39</sup> 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.<sup>40</sup> 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,<sup>41</sup> to include genetic risk assessment by PRSs in study protocols to assess the impact of cancer risk stratification in male mutation carriers. Recently, it has been suggested that polygenic risk-stratified screening can reduce overdiagnosis in the general population.<sup>42-44</sup> 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.<sup>45</sup>

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

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org](http://jco.org).

#### AUTHOR CONTRIBUTIONS

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

**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

**Collection and assembly of data:** Valentina Silvestri, Daniel Barrowdale, Joe Dennis, Lesley McGuffog, Penny Soucy, Goska Leslie, Piera Rizzolo, Anna Sara Navazio, Virginia Valentini, Veronica Zelli, Andrew Lee, Ali Amin Al Olama, Jonathan P. Tyrer, Melissa Southey, Esther M. John, Thomas A. Conner, David E. Goldgar, Sandra S. Buys, Ramunas Janavicius, Linda Steele, Yuan Chun Ding, Susan L. Neuhausen, Thomas V.O. Hansen, Ana Osorio, Jeffrey N. Weitzel, Angela Toss, Veronica Medici, Laura Cortesi, Ines Zanna, Domenico Palli, Paolo Radice, Siranoush Manoukian, Bernard Peissel, Jacopo Azzollini, Alessandra Viel, Giulia Cini, Giuseppe Damante, Stefania Tommasi, Paolo Peterlongo, Florentia Fostira, Ute Hamann, D. Gareth Evans, Alex Henderson, Carole Brewer, Diana Eccles, Jackie Cook, Kai-ren Ong, Lisa Walker, Lucy E. Side, Mary E. Porteous, Rosemarie Davidson, Shirley Hodgson, Debra Frost, Julian Adlard, Louise Izatt, Ros Eeles, Steve Ellis, Marc Tischkowitz, Andrew K. Godwin, Alfons Meindl, Andrea Gehrig, Bernd Dworniczak, Christian Sutter, Christoph Engel, Dieter Niederacher, Doris Steinemann, Eric Hahnen, Jan Hauke, Kerstin Rhiem, Karin Kast, Norbert Arnold, Nina Ditsch, Shan Wang-Gohrke, Barbara Wappenschmidt, Dorothea Wand, Christine Lasset, Dominique Stoppa-Lyonnet, Muriel Belotti, Francesca Damiola, Laure Barjhoux, Sylvie Mazoyer, Mattias Van Heetvelde, Bruce Poppe, Kim De Leeneer, Kathleen B.M. Claes, Miguel de la Hoya, Vanesa Garcia-Barberan, Trinidad Caldes, Pedro Perez Segura, Johanna I. Kiiski, Kristiina Aittomäki, Sofia Khan, Heli Nevanlinna, Christi J. van Asperen, Tibor Vaszko, Miklos Kasler, Edith Olah, Judith Balmaña, Sara Gutiérrez-Enríquez, Orland Diez, Alex Teulé, Angel Izquierdo, Esther Darder, Joan Brunet, Jesús Del Valle, Lidia Feliubadaló, Miquel Angel Pujana, Conxi Lazaro, Adalgeir Arason, Bjarni A. Agnarsson, Oskar Th. Johannsson, Rosa B. Barkardóttir, Elisa Alducci, Silvia Tognazzo, Marco Montagna, Manuel R. Teixeira, Pedro Pinto, Amanda B. Spurdle, Helene Holland, Jong Won Lee, Min Hyuk Lee, Jihyoun Lee, Sung-Won Kim, Eunyoung Kang, Zisun Kim, Priyanka Sharma, Timothy R. Rebbeck, Joseph Vijai, Mark Robson, Anne Lincoln, Jacob Musinsky, Pragna Gaddam, Yen Y. Tan, Andreas Berger, Christian F. Singer, Jennifer T. Loud, Mark H. Greene, Anna Marie Mulligan, Gord Glendon, Irene L. Andrulis, Amanda Ewart Toland, Leigha Senter, Anders Bojesen, Henriette Roed Nielsen, Anne-Bine Skytte, Lone Sunde, Uffe Birk Jensen, Inge Sokilde Pedersen, Lotte Krogh, Torben A. Kruse, Maria A. Caligo, Sook-Yee Yoon, Soo-Hwang Teo, Anna von Wachenfeldt, Dezheng Huo, Sarah M. Nielsen, Olufunmilayo I. Olopade, Katherine L. Nathanson, Susan M. Domchek, Christa Lorenchick, Rachel C. Jankowitz, Ian Campbell, Paul James, Gillian Mitchell, Nick Orr, Sue Kyung Park, Mads Thomassen, Kenneth Offit, Fergus J. Couch, Jacques Simard, Douglas F. Easton, Georgia Chenevix-Trench, Rita K. Schmutzler, Antonis C. Antoniou, Laura Ottini

**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

#### REFERENCES

1. Castro E, Eeles R: The role of BRCA1 and BRCA2 in prostate cancer. *Asian J Androl* 14: 409-414, 2012
2. Rizzolo P, Silvestri V, Tommasi S, et al: Male breast cancer: Genetics, epigenetics, and ethical aspects. *Ann Oncol* 24:viii75- viii82, 2013 (suppl 8)

3. Kote-Jarai Z, Leongamornlert D, Saunders E, et al: BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: Implications for genetic testing in prostate cancer patients. *Br J Cancer* 105:1230-1234, 2011
4. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al: Germline BRCA1 mutations increase prostate cancer risk. *Br J Cancer* 106:1697-1701, 2012
5. Basham VM, Lipscombe JM, Ward JM, et al: BRCA1 and BRCA2 mutations in a population-based

study of male breast cancer. *Breast Cancer Res* 4:R2, 2002

6. Cancer Research UK: Cancer incidence for common cancers. <http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/>
7. Breast Cancer Linkage Consortium: Cancer risks in BRCA2 mutation carriers. *J Natl Cancer Inst* 91:1310-1316, 1999
8. Thompson D, Easton DF; Breast Cancer Linkage Consortium: Cancer incidence in BRCA1



- mutation carriers. *J Natl Cancer Inst* 94:1358-1365, 2002
9. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al: Cancer risks in *BRCA2* families: Estimates for sites other than breast and ovary. *J Med Genet* 42:711-719, 2005
  10. Tai YC, Domchek S, Parmigiani G, et al: Breast cancer risk among male *BRCA1* and *BRCA2* mutation carriers. *J Natl Cancer Inst* 99:1811-1814, 2007
  11. Al Olama AA, Kote-Jarai Z, Berndt SI, et al: A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nat Genet* 46:1103-1109, 2014
  12. Michailidou K, Beesley J, Lindstrom S, et al: Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nat Genet* 47:373-380, 2015
  13. Pashayan N, Duffy SW, Chowdhury S, et al: Polygenic susceptibility to prostate and breast cancer: Implications for personalised screening. *Br J Cancer* 104:1656-1663, 2011
  14. Amin Al Olama A, Benlloch S, Antoniou AC, et al: Risk analysis of prostate cancer in PRACTICAL, a multinational consortium, using 25 known prostate cancer susceptibility loci. *Cancer Epidemiol Biomarkers Prev* 24:1121-1129, 2015
  15. Mavaddat N, Pharoah PD, Michailidou K, et al: Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst* 107:djv036, 2015
  16. Orr N, Lemnrau A, Cooke R, et al: Genome-wide association study identifies a common variant in *RAD51B* associated with male breast cancer risk. *Nat Genet* 44:1182-1184, 2012
  17. Orr N, Cooke R, Jones M, et al: Genetic variants at chromosomes 2q35, 5p12, 6q25.1, 10q26.13, and 16q12.1 influence the risk of breast cancer in men. *PLoS Genet* 7:e1002290, 2011
  18. Ottini L, Silvestri V, Saieva C, et al: Association of low-penetrance alleles with male breast cancer risk and clinicopathological characteristics: Results from a multicenter study in Italy. *Breast Cancer Res Treat* 138:861-868, 2013
  19. Silvestri V, Rizzolo P, Scarnò M, et al: Novel and known genetic variants for male breast cancer risk at 8q24.21, 9p21.3, 11q13.3 and 14q24.1: Results from a multicenter study in Italy. *Eur J Cancer* 51:2289-2295, 2015
  20. Gaudet MM, Kuchenbaecker KB, Vijai J, et al: Identification of a *BRCA2*-specific modifier locus at 6p24 related to breast cancer risk. *PLoS Genet* 9:e1003173, 2013
  21. Couch FJ, Wang X, McGuffog L, et al: Genome-wide association study in *BRCA1* mutation carriers identifies novel loci associated with breast and ovarian cancer risk. *PLoS Genet* 9:e1003212, 2013
  22. Bojesen SE, Pooley KA, Johnatty SE, et al: Multiple independent variants at the *TERT* locus are associated with telomere length and risks of breast and ovarian cancer. *Nat Genet* 45:371-384, 384e1-2, 2013
  23. Silvestri V, Barrowdale D, Mulligan AM, et al: Male breast cancer in *BRCA1* and *BRCA2* mutation carriers: Pathology data from the Consortium of Investigators of Modifiers of *BRCA1/2*. *Breast Cancer Res* 18:15, 2016
  24. Rebbeck TR, Mitra N, Wan F, et al: Association of type and location of *BRCA1* and *BRCA2* mutations with risk of breast and ovarian cancer. *JAMA* 313:1347-1361, 2015
  25. Dunning AM, Michailidou K, Kuchenbaecker KB, et al: Breast cancer risk variants at 6q25 display different phenotype associations and regulate *ESR1*, *RMND1* and *CCDC170*. *Nat Genet* 48:374-386, 2016
  26. Couch FJ, Kuchenbaecker KB, Michailidou K, et al: Identification of four novel susceptibility loci for oestrogen receptor negative breast cancer. *Nat Commun* 7:11375, 2016
  27. Michailidou K, Hall P, Gonzalez-Neira A, et al: Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet* 45:353-361, 361e1-2, 2013
  28. Lin WY, Camp NJ, Ghousaini M, et al: Identification and characterization of novel associations in the *CASP8/ALS2CR12* region on chromosome 2 with breast cancer risk. *Hum Mol Genet* 24:285-298, 2015
  29. Ghousaini M, Edwards SL, Michailidou K, et al: Evidence that breast cancer risk at the 2q35 locus is mediated through *IGFBP5* regulation. *Nat Commun* 4:4999, 2014
  30. French JD, Ghousaini M, Edwards SL, et al: Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. *Am J Hum Genet* 92:489-503, 2013
  31. Meyer KB, O'Reilly M, Michailidou K, et al: Fine-scale mapping of the *FGFR2* breast cancer risk locus: Putative functional variants differentially bind *FOXA1* and *E2F1*. *Am J Hum Genet* 93:1046-1060, 2013
  32. Amin Al Olama A, Dadaev T, Hazelett DJ, et al: Multiple novel prostate cancer susceptibility signals identified by fine-mapping of known risk loci among Europeans. *Hum Mol Genet* 24:5589-5602, 2015
  33. Antoniou AC, Beesley J, McGuffog L, et al: Common breast cancer susceptibility alleles and the risk of breast cancer for *BRCA1* and *BRCA2* mutation carriers: implications for risk prediction. *Cancer Res* 70:9742-9754, 2010
  34. Kuchenbaecker KB, McGuffog L, Barrowdale D, et al: Evaluation of polygenic risk scores for breast and ovarian cancer risk prediction in *BRCA1* and *BRCA2* mutation carriers. *J Natl Cancer Inst* (in press)
  35. Eeles RA, Olama AA, Benlloch S, et al: Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet* 45:385-391, 391e1-2, 2013
  36. Kote-Jarai Z, Olama AA, Giles GG, et al: Seven prostate cancer susceptibility loci identified by a multi-stage genome-wide association study. *Nat Genet* 43:785-791, 2011
  37. Gudmundsson J, Sulem P, Manolescu A, et al: Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet* 39:631-637, 2007
  38. Eeles RA, Kote-Jarai Z, Giles GG, et al: Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet* 40:316-321, 2008
  39. National Comprehensive Cancer Network: NCCN guidelines genetic/familial high-risk assessment: Breast and ovarian, version 2.2016. <http://www.nccn.org>
  40. National Institute for Clinical Excellence (NICE): Familial breast cancer: Classification, care and managing breast cancer and related risks in people with a family history of breast cancer (CG164). <https://www.nice.org.uk/guidance/cg164>
  41. Bancroft EK, Page EC, Castro E, et al: Targeted prostate cancer screening in *BRCA1* and *BRCA2* mutation carriers: Results from the initial screening round of the IMPACT study. *Eur Urol* 66:489-499, 2014 [Erratum: *Eur Urol* 67:e126, 2015]
  42. Pashayan N, Pharoah PD, Schleutker J, et al: Reducing overdiagnosis by polygenic risk-stratified screening: Findings from the Finnish section of the ERSPC. *Br J Cancer* 113:1086-1093, 2015
  43. Pashayan N, Duffy SW, Neal DE, et al: Implications of polygenic risk-stratified screening for prostate cancer on overdiagnosis. *Genet Med* 17:789-795, 2015
  44. Grönberg H, Adolfsen J, Aly M, et al: Prostate cancer screening in men aged 50-69 years (STHLM3): A prospective population-based diagnostic study. *Lancet Oncol* 16:1667-1676, 2015
  45. Macinnis RJ, Antoniou AC, Eeles RA, et al: A risk prediction algorithm based on family history and common genetic variants: Application to prostate cancer with potential clinical impact. *Genet Epidemiol* 35:549-556, 2011

### 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 Antonis 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, Rome; **Angela 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”, 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 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 **Sandra 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 **Olufunmilayo 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**, **Vanessa Garcia-Barberan**, **Trinidad Caldes**, and **Pedro Perez Segura**, Hospital Clinico San Carlos, El Instituto de Investigación Sanitaria del Hospital Clínico San Carlos, Madrid; **Judith Balmaña**, University Hospital, Vall d’Hebron; **Sara Gutiérrez-Enríquez** and **Orland Diez**, Vall d’Hebron Institute of Oncology; **Orland Diez**, University Hospital Vall d’Hebron; **Alex Teulé**, **Jesús Del Valle**, **Lidia Feliubadalo**, **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; **Alfons 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 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 Leeneer**, and **Kathleen B.M. Claes**, Ghent University, Ghent, 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 Olah**, 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**, 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; **Yen 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 Fondation 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. BFOCC-LT (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 Families Professorship. CNIO (Spanish National Cancer Centre) was partially supported by Spanish Association against Cancer (AECC08), RTICC 06/0020/1060, FISPI08/1120, Mutua Madrileña Foundation (FMMA), 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-CCGCRN) 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 CONSTIT 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 “5x1000”) 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 Toscano 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 Funding 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. 5U01-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, parlons-en!” Award; the Canadian 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. RD12/00369/0006 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 91109024, 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 Regional Development FEDER Funds: FIS PI12/02585 to O.D. and FIS PI13/01711 to S.G.-E. S.G.-E. is funded by Miguel Servet contract (ISCIII). ICO (Institut Català d'Oncologia) contract grant sponsor: Asociación Española Contra el Cáncer, Spanish Health Research Fund; Carlos III Health Institute; Catalan Health Institute and Autonomous Government of Catalonia; Contract Grants No.: ISCIIRETIC RD06/0020/1051, RD12/0036/008, PI10/01422, PI10/00748, PI13/00285, PIE13/00022, 2009SGR290, and 2014SGR364. The ILUH group was supported by the Icelandic Association “Walking for Breast Cancer Research” and by the Landspítali University Hospital Research Fund. INHERIT (INterdisciplinary HHealth Research Internal Team BReast CAnceR susceptibility) was supported by the Canadian Institutes of Health Research for the “CIHR Team in Familial Risks of Breast Cancer” program Grant No. CRN-87521 and the Ministry of Economic Development, Innovation and Export Trade Grant No. PSR-SIIRI-701. IOVBHOCs (Istituto Oncologico Veneto Hereditary Breast and Ovarian Cancer Study) was supported by Ministero della Salute and “5x1000” Istituto Oncologico Veneto grant. IPOBCS (Portuguese

Oncology Institute-Porto Breast Cancer Study) was supported by Liga Portuguesa Contra o Cancro. kConFab (Kathleen Cuninghams 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 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, Bassett Research Center for BRCA. University of Pittsburgh Magee-Women's Hospital was supported by Frieda G. and Saul F. Shapira BRCA-Associated Cancer Research Program; Hackers for Hope Pittsburgh. Victorian Familial Cancer Trials Group (VFCTG) was supported by Victorian Cancer Agency, Cancer Australia, National Breast Cancer Foundation.

#### ***Prior Presentation***

Presented at the 2015 Annual Meeting of the American Society of Human Genetics, October 6-10, 2015, Baltimore, MD.



**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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

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

**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

**Sandra 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**

No relationship to disclose

**Ines Zanna**

No relationship to disclose

**Domenico Palli**

No relationship to disclose

**Paolo Radice**

No relationship to disclose

**Siranoush Manoukian**

No relationship to disclose

**Bernard Peissel**

No relationship to disclose

**Jacopo Azzollini**

No relationship to disclose

**Alessandra Viel**

No relationship to disclose

**Giulia Cini**

No relationship to disclose

**Giuseppe Damante**

No relationship to disclose

**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**

**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 Eeles**

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**Karin Kast****Honoraria:** AstraZeneca**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

**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 Balmaña**  
No relationship to disclose

**Sara Gutiérrez-Enríquez**  
No relationship to disclose

**Orland Diez**  
No relationship to disclose

**Alex Teulé**  
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, bioTherapeutics

**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 Similnikova. *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 Griškevičius. *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. Similnikova, 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 Recherche en Cancérologie de Lyon: Olga Similnikova (deceased), Sylvie Mazoyer, Francesca Damiola, 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 Fourme, Anne-Marie Birot; Institut Gustave Roussy, Villejuif: Brigitte Bressac-de-Paillerets, 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 Castera; Institut Paoli Calmettes, Marseille: Hagay Sobol, Violaine Bourdon, Tetsuro Noguchi, Audrey Remenieras, François Eisinger; CHU Arnaud-de-Villeneuve, Montpellier: Isabelle Coupier, Pascal Pujol; Centre Oscar Lambret, Lille: Jean-Philippe Peyrat, Joëlle Fournier, Françoise Révillion, Philippe Vennin (deceased), Claude Adenis; Centre Paul Strauss, Strasbourg: Danièle Muller, Jean-Pierre Fricker; Institut Bergonié, Bordeaux: Emmanuelle Barouk-Simonet, Françoise Bonnet, Virginie Bubien, Nicolas Sevenet, Michel Longy; Institut Claudius Regaud, Toulouse: Christine Toulas, Rosine Guimbaud, Laurence Gladieff, Viviane Feillel; CHU Grenoble: Dominique Leroux, Hélène Dreyfus, Christine Rebuschung, 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 Frénay; CHU Limoges: Laurence Vénat-Bouvet; CHU Nantes: Capucine Delnatte; CHU Bretonneau, Tours: Isabelle Mortemousque; Groupe Hospitalier Pitié-Salpêtrière, Paris: Florence Coulet, Chrystelle Colas, Florent Soubrier, Mathilde Warcoïn; CHU Vandoeuvre-les-Nancy: Johanna Sokolowska, Myriam Bronner; CHU Besançon: Marie-Agnès Collonge-Rame, Alexandre Damette; Creighton University, Omaha, NE: Henry T. Lynch, Carrie L. Snyder. *G-FAST* (Ghent University Hospital): B.P. is a senior clinical investigator of FWO. We acknowledge the technical support of Ilse Coenen 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 Erkkilä, RN, and Virpi Palola, RN, for their help with the HEBCS 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. Hooning, C. Seynaeve, C.H.M. van Deurzen, I.M. Obdeijn; Leiden University Medical Center: C.J. van Asperen, J.T. Wijnen, R.A.E.M. Tollenaar, 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-García, 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. Vasen; 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* (INterdisciplinary HEalth 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 Oncoarray (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'Connor 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-Askmal, 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.