<table>
<thead>
<tr>
<th>Title</th>
<th>11q13 is a susceptibility locus for hormone receptor positive breast cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Kerin, Michael J.; Miller, Nicola</td>
</tr>
<tr>
<td>Publication Date</td>
<td>2012-07</td>
</tr>
<tr>
<td>Publisher</td>
<td>Wiley</td>
</tr>
<tr>
<td>Link to publisher's version</td>
<td><a href="http://dx.doi.org/10.1002/humu.22089">http://dx.doi.org/10.1002/humu.22089</a></td>
</tr>
<tr>
<td>Item record</td>
<td><a href="http://hdl.handle.net/10379/3765">http://hdl.handle.net/10379/3765</a></td>
</tr>
<tr>
<td>DOI</td>
<td><a href="http://dx.doi.org/10.1002/humu.22089">http://dx.doi.org/10.1002/humu.22089</a></td>
</tr>
</tbody>
</table>

Some rights reserved. For more information, please see the item record link above.
11q13 Is a Susceptibility Locus for Hormone Receptor Positive Breast Cancer


Additional Supporting Information may be found in the online version of this article.

¹Contribution equally to this work. Writing Group: Diether Lambrechts, Therese Truong, Christina Justenhoven, Douglas F. Easton, Pascal Guénel, and Hiltrud Brauch

*Correspondence to: Hiltrud Brauch, Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Auerbachstr. 112, 70376 Stuttgart, Germany. E-mail: hiltrud.brauch@ikp-stuttgart.de

© 2012 WILEY PERIODICALS, INC.
Introduction

Recent genome-wide association studies (GWAS) have provided statistically robust evidence for the association of common genetic variants with breast cancer risk. In particular, variants in the gene regions of FGFR2, TOX3, MAP3K1, LSP1, SLC4A7, COX11, RAD51L1, and in chromosomal regions 8q24, 2q35, 5p12, 6q25, 1p11, and 9q21 (all MIM# 114480) were identified as susceptibility variants through GWAS [Ahmed et al., 2009; Antoniou et al., 2010; Broeks et al., 2011; Easton et al., 2009; Milne et al., 2009; Stacey et al., 2007, 2008; Thomas et al., 2009]. Typically, the variants in these loci occur commonly within the general population, but they confer only modest increases in risk with odds ratios (ORs) ranging from 1.10 to 1.43 per allele. Together these variants explain approximately 5% of the familial risk for breast cancer. Despite these relatively small risk effects, the identification of new disease susceptibility loci using GWAS may contribute critically to our understanding of the mechanisms underlying breast cancer tumorigenesis. Furthermore, some loci are more strongly associated with specific tumor subtypes; for instance, the FGFR2 rs2981582 variant is more strongly associated with estrogen receptor (ER)-positive than ER-negative disease [Broeks et al., 2011; Milne et al., 2009; Turnbull et al., 2010; Yang et al., 2011]

A recent two-stage GWAS conducted by Turnbull et al. [Turnbull et al., 2010] involving 3,659 cases with family history of breast cancer and 4,897 controls in the first stage, and 12,576 cases and 12,223 controls in the second stage, identified five novel susceptibility loci. The loci are on 11q13, 9p21, 10p15, 10q21, and 10q22 and are, respectively, close to the cyclin D1 (CCND1; MIM# 114500) and fibroblast growth factor genes (FGF3; MIM# 610706, FGF4; MIM# 104980, FGF19; MIM# 603891), the cyclin-dependent kinase inhibitors CDKN2A (MIM# 606719), and CDKN2B, (MIM# 600431), the zinc finger genes ZNF365 (MIM# 607818) and ZMIZ1 (MIM# 607159), and ANKR4D [Turnbull et al., 2010]. Although the evidence for these associations was very strong, additional analyses, involving a much larger number of well-characterized breast cancer patients, are needed to independently confirm these associations and assess whether their risks vary with respect to tumor subtype. The Breast Cancer Association Consortium (BCAC), through its global collaborative approach, has gathered more than 96,000 breast cancer cases and controls for independent replication analysis, thereby providing a unique resource for this type of study [Breast Cancer Association Consortium, 2006; Easton et al., 2007].

Materials and Methods

Study Population

Ethics Statement: Written informed consent was obtained from all study participants and the analyses were approved by the institutional review boards at each study center.

Thirty-nine case-control studies from BCAC, which were not included previously in Turnbull et al. [Turnbull et al., 2010], participated in this pooled analysis. Of these, 29 studies were conducted in Europe, 5 in North America, 3 in Asia, and 2 in Australia. All studies provided information on disease status and age at diagnosis for cases and self-reported race/ethnicity for all subjects. All but five studies (BIGGS, HUBCS, KARBAC, ORIGO) also provided age at interview for controls. Family history of breast cancer among first degree relatives was provided by 13 studies (ABCFS, BBCS, CE-CLE, CTS, ESTHER, GENICA, GESBC, KBCP, MARIE, MCBCS, SASBAC, SBCS, UCBCS). ER and PR status as well as histology of the tumor were available for a subset of cases. This histopathology information was generally abstracted from medical reports. A total of 44,662 cases and 45,502 controls of European descent and 4,076 cases and 2,573 controls of Asian descent were included in this analysis. The description of study designs and final sample sizes per study are provided in the Supp. Table S1.

Genotyping and Quality Control

The rs1011970, rs2380205, rs10995190, rs704010, and rs614367 genetic variants were genotyped by MassARRAY iPLEX Gold (Sequenom, San Diego, CA), TaqMan (Applied Biosystems, Foster City, CA), and Fluidigm technology (Fluidigm, South San Francisco, CA) (Supp. Table S1). The method used by each study is identified in Supp. Table S1. All studies included ≥2% duplicates and 93 CEPH DNAs (HAPMAPPT01, Coriell Institute for Medical Research, Camden, NJ). The average genotype completion rate per variant was 99% and all genotype completion rates per study were greater than 95% for each variant. We used a χ2-test (1df) to verify that the genotype distributions for each single nucleotide polymorphism (SNP) were consistent with those expected under Hardy–Weinberg equilibrium (HWE) within each study and separately among European and Asian control subjects. A Bonferroni
correction for multiple tests was applied for the HWE test and gave a P value of 0.0002 as the cutoff for statistical significance, based on approximately 200 independent tests carried out. There was no evidence of departure from HWE for any SNP except rs614367 in one study (PBCS), which was therefore excluded from the analysis for this variant.

### Statistical Analysis

We used unconditional logistic regression to estimate OR and 95% confidence interval (CI). OR per allele or P values for trend were calculated by assuming a log-additive model. Pooled ORs were calculated using individual-level data. Logistic regression models were adjusted for study by including study specific indicator variables. Restricting the analysis to studies for which age at interview of controls was available, additional adjustment for age made no substantial difference in the results. Europeans and Asians were analyzed separately. Subgroup analyses were performed for breast cancer defined by hormone receptor status (ER and PR) and histological subtypes (ductal, lobular, and other tumors) and by family history of breast cancer. For the analyses stratified by family history, we excluded studies with cases selected for family history of breast cancer (ABCs, CNIO-BCS, HEBCS, KARBAC, KConFab/AOCS, MBCSG, NC-BCFR; Supp. Table S1). Heterogeneity of OR across the studies or across the stratification groups was assessed using the Cochran Q test. All tests were two sided. All analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC).

### Results

We analyzed SNPs rs1011970, rs2380205, rs10995190, rs704010, and rs614367 in 49,608 breast cancer cases and 48,772 controls from 39 studies participating in BCAC. Of these women, 93% were of European descent and 7% of Asian descent (Table 1). Four of the variants, rs1011970, rs10995190, rs704010, and rs614367, were associated with overall breast cancer risk in women of European descent (P < 1 × 10^-6; Table 1, Fig. 1, and Supp. Fig. S1). Per-allele ORs for these variants were very similar to those observed in the initial study by Turnbull et al. (Table 1) [Turnbull et al., 2010]. We estimated a lower OR for homozygotes at rs1011970 (OR = 1.10 in our study vs. OR = 1.29 in Turnbull et al.) and rs10995190 (OR = 0.75 in our study vs. OR = 0.83). These differences, however, might be explained by the wide CIs around the risk estimates due to low minor allele frequencies (MAF = 0.16), respectively. Significant heterogeneity by study was only observed for the SNP rs1011970 (P heterogeneity = 0.01; Supp. Fig. 1). This heterogeneity was due to the BSUCH study in which the per-allele OR was opposite directed to the overall estimated effect. After removing BSUCH from the analysis, heterogeneity between studies was not significant (P heterogeneity = 0.25), but the association of rs1011970 with breast cancer risk was similar (OR 1.08, 95% CI 1.05–1.11) vs. OR 1.09, P = 1 × 10^-10, before and after exclusion of BSUCH, respectively). The SNP rs2380205 on 10p15 showed limited evidence for association with breast cancer risk (P = 0.06). The 95% CI limits for the per-allele OR (0.98, 95% CI 0.96–1.00) excluded the OR estimate of 0.94 previously reported by Turnbull et al. [Turnbull et al., 2010], indicating either that the original association was false positive, or that the effect size is substantially smaller than previously reported.

In women of Asian descent, none of the variants was significantly associated with breast cancer risk with the exception of a borderline association with rs704010 (Table 1). However, each of the variants exhibited much lower minor allele frequencies (MAF) in women of Asian descent (Table 1), and none of the estimated per-allele ORs differed significantly from those of European descent.

Next, subgroup analyses for breast cancer defined by hormone receptor status (ER and PR status), histopathological subtype (ductal, lobular, and other tumors), and family history of breast cancer were performed separately in women of European and Asian descent. In Europeans, SNP rs614367 was significantly associated with ER-positive (OR 1.26; 95% CI 1.06–1.79) but not with ER-negative breast cancer (OR 1.13; 95% CI 0.95–1.31; Table 1). The association was stronger for ER-positive/PR-positive (OR 1.29; 95% CI 1.00–1.67) than for ER-positive/PR-negative tumors (OR 1.12; 95% CI 0.96–1.31; Table 1). This difference was not significant (P heterogeneity = 0.26; Table 1). The per-allele OR for rs1011970 was also slightly higher for ER-positive than for ER-negative breast cancer (OR 1.13; 95% CI 1.02–1.24) vs. OR 1.07; 95% CI 1.02–1.12; Fig. 1), but this difference was not significant (P heterogeneity = 0.45). The per-allele ORs for rs2380205, rs704010, and rs10995190 did not differ by tumor receptor status (Fig. 1). There was no evidence for heterogeneity in the per-allele ORs by histopathological subtypes for any SNP. With respect to family history of breast cancer we observed that the OR of SNP rs10995190 was lower than 1 in women without family history (OR 0.83; 95% CI 0.80–0.86), whereas it was greater than 1 in women with a family history of breast cancer (OR 1.05; 95% CI 0.96–1.12; Fig. 1). No other SNP showed significant differences between women with and without family history of breast cancer (Fig. 1).

Subgroup analyses in women of Asian descent showed that the association with rs704010 was stronger for ER-negative/PR-negative breast cancer (OR 1.30; 95% CI 1.20–1.41; Fig. 2).

---

Table 1. Overall Breast Cancer Risk Effects in Women of European Descent and Asian Descent of 5 GWAS Identified Loci [Turnbull et al., 2010]

<table>
<thead>
<tr>
<th>SNP</th>
<th>Position</th>
<th>Alleles</th>
<th>MAF</th>
<th>Per-allele OR (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1011970</td>
<td>G&gt;T</td>
<td>0.16</td>
<td>1.10 (1.11–1.30)</td>
<td>3 × 10^-5</td>
<td>1.09 (1.04–1.14)</td>
</tr>
<tr>
<td>rs2380205</td>
<td>G&gt;T</td>
<td>0.44</td>
<td>0.86 (0.81–0.92)</td>
<td>8 × 10^-8</td>
<td>0.94 (0.90–0.98)</td>
</tr>
<tr>
<td>rs10995190</td>
<td>G&gt;A</td>
<td>0.16</td>
<td>0.76 (0.70–0.84)</td>
<td>6 × 10^-6</td>
<td>0.86 (0.82–0.91)</td>
</tr>
<tr>
<td>rs704010</td>
<td>G&gt;A</td>
<td>0.37</td>
<td>1.15 (1.03–1.11)</td>
<td>3 × 10^-10</td>
<td>1.07 (1.03–1.11)</td>
</tr>
<tr>
<td>rs614367</td>
<td>C&gt;T</td>
<td>0.15</td>
<td>1.30 (1.20–1.41)</td>
<td>4 × 10^-8</td>
<td>1.15 (1.10–1.20)</td>
</tr>
</tbody>
</table>

*All P values are two sided. Abbreviations: ca, cases; co, controls; MAF, minor allele frequency (second listed); OR, odds ratio; SNP, single nucleotide polymorphism.
**Figure 1.** Forest plots of stratified analysis of the five variants in European women. Except for the OR for heterozygous and homozygous effect, OR and 95% CI were derived from the per-allele model. All models are adjusted for age and study. *P* for heterogeneity was derived from the Cochran Q test. Squares represent odds ratios; size of the square represents inverse of the variance of the log odds ratio; horizontal lines represent 95% confidence intervals.
Figure 2. Forest plots of stratified analysis of the five variants in Asian women. Except for the OR for homozygous and homoyzgous effect, OR and 95% CI were derived from the per-allele model. All models are adjusted for age and study. P for heterogeneity was derived from the Cochran Q test. Squares represent odds ratios; size of the square represents inverse of the variance of the log odds ratio; horizontal lines represent 95% confidence intervals.
histopathological subtype was observed for any SNP. We did not perform analyses stratified by family history of breast cancer because the number of subjects was too small among Asian women.

To examine potential associations between the breast-cancer-risk-associated SNPs and gene expression we screened the publicly available Expression Quantitative Trait Locus (eQTL) database GENEVAR (www.sanger.ac.uk/resources/software/genevar). No associations with gene expression were observed.

Discussion

This is the largest association study in breast cancer to date and it provides independent and strong evidence for rs1011970, rs10995190, rs704010, and rs614367 being breast cancer susceptibility loci. These variants are located within the footprint of plausible candidate genes: CDKN2A/2B (rs1011970), ZMIZ1 (rs704010), ZNF365 (rs10995190), and CCND1 (rs614367) consistent with the critical role of cell cycle control, gene regulation, and cell proliferation pathways in breast tumorigenesis. Each of these genes and one of the SNPs have been reported to be linked with other diseases or phenotypes. In particular, GWAS studies identified several SNPs in 9p21 near CDKN2 that have been associated with cutaneous nevi/melanoma [Falchi et al., 2009], glioma [Shete et al., 2009; Wrensch et al., 2009], type 2 diabetes [Zeggini et al., 2007] and coronary artery disease [Harismendy et al., 2011]. One SNP in the 3’ untranslated region of CDKN2A has been linked with pancreatic cancer [Chen et al., 2007]. All 9p21 SNPs differ from the breast cancer risk SNP rs1011970 described herein, yet this SNP is in linkage disequilibrium with the glioma SNP rs4977756 (r^2 = 0.137; D’ = 1.0). Interestingly, the 9p21 interval is the second densest gene locus for predicted enhancers in the human genome and the one containing the most disease-associated variants indicating that this chromosomal region has important regulatory function [Harismendy et al., 2011]. The ZMIZ1 is known to be a recombination partner to form an ABL1 fusion gene in B-cell acute lymphoblastic leukaemia [Soler et al., 2008] and a nonsynonymous SNP of ZNF365 gene has been associated with Crohn’s disease [Haritunians et al., 2011]. Of note, the ZNF365 SNP rs10995190 now confirmed to be associated with breast cancer risk in this study has recently been associated with mammographic density which is considered one of the strongest risk factors for breast cancer [Lindstrom et al., 2011].

The strongest association with breast cancer was for SNP rs614367 in European women. The estimated OR (1.21 overall, and 1.29 for ER-positive/PR-positive breast cancer) is comparable to that reported for the FGF2 locus, the most strongly associated known common susceptibility variant for breast cancer. SNP rs614367 is located in an LD block of ~170kb on 1q13 that contains no known genes. This polymorphism lies ~130kb upstream of CCND1, encoding cyclin D1, which is known to be mutated, amplified or overexpressed in various cancers, including breast cancer [Dickson et al., 1995; Kim and Diehl, 2009]. Cyclin D1 together with cyclin-dependent kinases CDK4 and CDK6 mediate phosphorylation of the retinoblastoma protein (Rb) in the cell cycle G1 phase, leading to inactivation of pRB and commitment of mammalian cells to proceed to cell division in response to multiple signaling pathways, including tyrosine kinase and ER signaling [Lange and Yee, 2011]. If the association with rs614367 proves to be functionally related to CCND1, the stronger association of rs614367 with ER-positive disease would be consistent with the role of CCND1 as a mediator of estrogen-induced cell proliferation. There is evidence from cell line models that cyclin D1 expression together with inactivation of pRB are features of poor response to endocrine therapies [Lange and Yee, 2011]. However, it is not certain at this stage whether or not the association between rs614367 and breast cancer risk is mediated through CCNC1. Whether 11q13 genetic variation affects the role of cyclin D1 as an oncogenic driver remains to be determined, as other plausible candidates, including FGFI4 and FGFI9 located at distances of 180kb and 270kb from rs614367, respectively, might also be involved.

The absence of any general breast cancer risk effects in women of Asian descent may be attributed to much lower MAFs of the SNPs tested in this present study and, therefore, lack of statistical power. Yet, the finding of an association of rs704010 with ER-negative/PR-negative breast cancer suggests a potential relevance in this ethnic group, but much larger sample sizes will be needed for the identification of SNP associations with breast cancer risk as well as patient and tumor characteristics.

In conclusion, we confirm the association of four new breast cancer susceptibility loci, provide precise estimates of the associated risks, and provide evidence of variation in the strength of associations by hormone receptor status. We are currently following up these findings through fine-mapping approaches to identify the causal SNPs and genes. This should in turn allow further studies on the impact of the risk causing variants on gene function, and hence explain the observed associations at the molecular level.

Acknowledgments

We thank Maggie Angelakos, Judi Maskiell, Gillian Dite (ABCFS); Laura van ’t Veer, Linde Braaf, Senno Verhoef, Frans Hogervorst, Bas Bueno-de-Mesquita (ABCBS); Eileen Williams, Elaine Ryder-Mills, Kara Sargus (BCBS); Niall McInerny, Gabrielle Colleran, Andrew Rowan, Angela Jones (BIGGS); Chao Alonso, Tais Moreno, Guillermo Pita, Primitiva Menendez, Anna González-Neira (CNIO-BCS); Sylvia Rabstein, Anne Spickenheuer, Hans-Peter Fischer, Beate Pesch, Volker Harth, Christian Baich (GENICA); Ursula Elber, Tanya Koehler (GESBC); Eija Myöhänen, Helena Kemiläinen (KBCP); Heather Thorne, Eveline Niedermayr (kConFab/AOCS); D. Bowtell, A. de-Fazio, D. Gertig, A. Green, P. Webb (the AOCs Management Group); A. Green, P. Parsons, N. Hayward, P. Webb, D. Whiteman (the ACS Management Group); Gilian Peuteman, Dominic Sweerts, Thomas Van Brussel, Kathleen Corthouts (LMBC); Tracy Slinger, Elke Mutschelknauss, S. Behrens, R. Birr, W. Busch, U. Elber, B. Kaspereit, N. Knes, K. Smit (MARIE); Meera Sangaramoorthy (NC-BCFR); Meeri Otsuuka, Kari Mononen (OBCS); Julila Knight, Nyanza Wierasooriya (OFBCR); E. Krol-Warmerdam, J. Blom (ORIGO); Louise Brinton, Neonila Szeszenia-Dabrowska, Beata Pilepskina, Witold Zatonski, Pei Chao, Michael Stagner (PBCS); Sue Higham, Helen Cramp, Dan Connelly (SBCS); Irene Masunaka (UCIBCS); Bernard Peissel, Nadia Zaffaroni, Marco A. Pierotti, Monica Barile, Bernardo Bonanni, and the personnel of the Cancer Genetics Testing laboratory (MBCSG); The Breastbreakthrough Breast Cancer and the Institute of Cancer Research, the Study participants, Study staff, and the doctors, nurses, and other healthcare staff and data providers who have contributed to the Study (UKBGS).

Contract grant sponsors: Part of this work was supported by the European Community’s Seventh Framework Programme under grant agreement number 223175 (grant number HEALTH-F2-2009-223175) (COGS). The BCAC is funded by Cancer Research UK (C1287A10118 and C1287A10214). Meetings of the BCAC have been funded by the European Union COST program (BM0606). D.E.E. is a Principal Research Fellow of Cancer Research UK. The ABCFS, NC-BCFR, and OBBCR work was supported by the United States National Cancer Institute, National Institutes of Health (NIH) under RFA-CA-06-503, and through cooperative agreements with members of the Breast Cancer Family Registry (BCFR) and Principal Investigators, including Cancer Care Ontario (U01 CA69467), Cancer Prevention Institute of California (U01 CA69417), and University of Melbourne (U01 CA69638). Samples from the NC-BCFR were processed and distributed by the Coriell Institute for Medical Research. 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 BCFR, nor does mention...
of trade names, commercial products, or organizations imply endorsement by the US Government or the BCFR. The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia) and the Victorian Breast Cancer Research Consortium. J.L.H. is a National Health and Medical Research Council (NHMRC) Australia Fellow and a Victorian Breast Cancer Research Consortium Group Leader. M.C.S. is a NHMRC Senior Research Fellow and a Victorian Breast Cancer Research Consortium Group Leader. The ABCFS study was supported by the Dutch Cancer Society (grants NKI DCS 2007–3839 and 2009–4363) and the Dutch National Genomics Initiative. The ACP is funded by the Breast Cancer Research Trust. The work of the BBCC was partly funded by ELAN-Fond of the University Hospital of Erlangen. The BBCS is funded by Cancer Research UK and Breakthrough Breast Cancer and acknowledges NHS funding to the NIHR Biomedical Research Centre, and the National Cancer Research Network (NCRN). BIGGS: E.S. is supported by NIHR Comprehensive Biomedical Research Centre, Guy’s and St. Thomas’ NHS Foundation Trust in partnership with King’s College London. I.T. is supported by the Oxford Biomedical Research Centre. The BSUCH study was supported by the Dietmar–Hopp Foundation, the Helmholtz Society and the German Cancer Research Center (DKFZ). CECELIE study was funded by Fondation de France (grant 2004012618; 2007005156), Institut National du Cancer (INCa grant 2007–1 SP2; 2008–1 CP-4; 2009–1 SHS SP-04), Association pour la Recherche contre le Cancer (ARC grant 2008–1 CP-4). The CNIO-BCS was supported by the Genome Spain Foundation, the Red Tematica de Investigacion Cooperativa en Cancer and grants from the Asociacion Espanola Contra el Cancer and the Fondo de Investigacion Sanitario (PI081583 and PI081120). The CGPS was supported by the Chief Physician Johan Boserup and Lise Boserup Fund, the Danish Medical Research Council and Herlev Hospital. The ESTHER study was supported by a grant from the Baden-Wuerttemberg Ministry of Science, Research and Arts. Additional cases were recruited in the context of the VERDI study, which was supported by a grant from the German Cancer Aid (Deutsche Krebshilfe). The GENICA Network was funded by the Federal Ministry of Education and Research (BMBF), Germany, grants 01KW97975/5, 01KW9796/8, 01KW97770/1, 01KWO114; the Robert Bosch Foundation, Stuttgart; Deutsches Krebsforschungszentrum (DKFZ), Heidelberg; Evangelische Kliniken Bonn GmbH, Johannesitter Krankenhaus, Bonn; Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (lPA), Bochum, Germany. The LBMC was supported by the “Stichting tegen Kanker” (grants 232–2008 and 196–2010). The GC–HBOC was supported by Deutsche Krebshilfe (107054), the Dietmar–Hopp Foundation, the Helmholtz society; and the German Cancer Research Centre (DKFZ). The HABCS study was supported by the Rudolf Bartling Foundation and by an intramural grant from Hannover Medical School. The HERCS study has been financially supported by the Helmholtz University Central Hospital Research Fund, Academy of Finland (132473), the Finnish Cancer Society, and the Sigrid Juselius Foundation. The HM–BCS was supported by short-term fellowships from the German Academic Exchange Program (to N.B.), and the Friends of Hannover Medical School (to N.B.). The HUBCS was supported by a grant from the German Federal Ministry of Research and Education (RUS08/017). The KARCAB work was supported by the Swedish Cancer Society and the Gustav V Jubilee Foundation. KConFab is supported by grants from the National Breast Cancer Foundation; the 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 KConFab Clinical Follow Up Study was funded by the NHMRC (145684, 288704, and 454508). Financial support for the ABCFS was provided by the United States Army Medical Research and Materiel Command (DAMD17–01–1–0729), the Cancer Council of Tasmania and Cancer Foundation of Western Australia and the NHMRC (199600). G.C.T. and P.W. are supported by the NHMRC. The KBCP was supported financially by the special Government Funding (EVO) of Kuopio University Hospital grants, Cancer Fund of North Savo, the Finnish Cancer Organizations, the Academy of Finland, and by the strategic funding of the University of Eastern Finland. The MARIE study was supported by the Deutsche Krebshilfe e.V. (70–2892–BR 1), the Hamburg Cancer Society, the German Cancer Research Center, and the genotype work in part by the Federal Ministry of Education and Research (BMBF) Germany (01KHO402). MBCSG is supported by grants from Ministero della Salute (Extraordinary National Cancer Program 2006 “Alleanza contro il Cancro”, and “Progetto Tumori Femminili” to P.R.), Ministero dell’Universita’ e Ricerca (RBA03-BETH to PR), Fondazione Italiana per la Ricerca sul Cancro (Special Project “Hereditary tumors”), Associazione Italiana per la Ricerca sul Cancro (4017 and by funds from Italian citizens who allocated the 5/1000 share of their tax payment in support of the Fondazione IRCCS Istituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects “5 x 1000”). The MCBCS was supported by the NIH grants [CA122340, CA128978] and a Specialized Program of Research Excellence (SPORE) in Breast Cancer [CA116201]. MCCS is supported by Cancer Council Victoria and by NHMRC (grants 209057, 251533, 396414, 504711, and 504715). The NBCS was supported by grants from the Norwegian Research council, 155218/V40, 175240/S10 to ALBD, FUGE-NFR 181600/V11 to VNK and a Swiss Bridge Award to ALBD. The OBS was supported by research grants from the Finnish Cancer Foundation, the Sigrid Juselius Foundation, the Academy of Finland, the University of Oulu, and the Oulu University Hospital. The PBCS was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA. The SBCS was supported by Yorkshire Cancer Research and the Breast Cancer Campaign. The SEBCS was supported by the Korea Health 21 R&D Project [AO30001], Ministry of Health and Welfare, Republic of Korea. The SZBCS was supported by Grant PRZ_KBN_122/05/2004; Katarzyna Jaworska is a fellow of International Ph.D. program, Postgraduate School of Molecular Medicine, Warsaw Medical University, supported by the Polish Foundation of Science. The TWBCS is supported by the Taiwan Biobank project of the Institute of Biomedical Sciences, Academia Sinica, Taiwan. The UCIBCS component of this research was supported by the NIH [CA58866, CA92044] and the Von V Smith Foundation (IVS39420). ORIGO were funded by grants from the Dutch Cancer Society (UL1997–1505) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL CP16). The UKBGS thank Breakthrough Breast Cancer and the Institute of Cancer Research for funding. The ICR acknowledges NHS funding to the NIHR Biomedical Research Centre.

References


